Project
M5250C

Protocol
M525101-21

A Phase II Study of Nemolizumab in Patients with Systemic Sclerosis

Single-arm multiple-dose study

Protocol

Version 3.0

Maruho Co., Ltd.

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List of Definitions of Abbreviations and Technical Terms

Acronym/Abbreviation/ Technical term	Full text/Definition
ACR-CRISS	American College of Rheumatology Combined Response Index in diffuse cutaneous Systemic Sclerosis
ADL	Activities of daily living
AE	Adverse events
AIDS	Acquired immunodeficiency syndrome
ALB	Albumin
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma/serum concentration-time curve
$AUC_{0\text{-}28day}$	Area under the serum concentration-time curve 0-28day
AUC_{last}	Area under the serum concentration-time curve from zero to last observed concentration time point
A/G ratio	Albumin-Globulin ratio
BLQ	Below the lower limit of quantification
CBA	Cell-based assay
CK	Creatine kinase
C_{max}	Maximum concentration in plasma/serum
COVID-19	Coronavirus disease 2019
CREA	Creatinine
CRP	C reactive protein
CTCAE	Common terminology criteria for adverse events
CyTOF	Cytometry by time of flight
D-Bil	Direct bilirubin
DCS	Dual chamber syringe
dcSSc	Diffuse cutaneous SSc
DLco	Diffusing capacity of lung for carbon monoxide
ECG	Electrocardiogram
ECL	Electro Chemi Luminescence
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
EULAR	European League Against Rheumatism
FAS	Full analysis set
FACIT-Fatigue	Functional assessment of chronic illness therapy-Fatigue
FEV_1	Forced expiratory volume in one second
FSSG	Frequency Scale for the Symptoms of GERD
FU	Follow up
FVC	Forced vital capacity
GCP	Good clinical practice

Acronym/Abbreviation/ Technical term	Full text/Definition
γ-GT	γ-Glutamyl transpeptidase
HAQ-DI	Health assessment questionnaire disability index
Hb	Hemoglobin
HBc antibody	Hepatitis B core antibody
HBs antigen	Hepatitis B surface antigen
HBV	Hepatitis B virus
hCG	human chorionic gonadotrophin
HCV	Hepatitis C virus
HDL-C	High-density lipoprotein cholesterol
HIV	Human immunodeficiency virus
HRCT	High-resolution computed tomography
Ht	Hematocrit
IL	Interleukin
IL-31RA	Interleukin-31 receptor A
IP	Investigational product
IRB	Institutional review board
JCOG	Japan clinical oncology group
KL-6	Krebs von den lungen-6
lcSSc	Limited cutaneous SSc
LDH	Lactic acid dehydrogenase
LDL-C	Low density lipoprotein cholesterol
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA/J	Medical dictionary for regulatory activities / Japanese edition
mRSS	Modified rodman total skin thickness score
nemolizumab	Humanized anti-human interleukin-receptor A (IL-31RA) monoclonal antibody
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
PAH	Pulmonary arterial hypertension
PGA	Physician’s global assessment
Plt	Platelet
PT	Preferred term
PtGA	Patient’s global assessment
QFT-3G	QuantiFERON-TB Gold
RBC	Red blood cell
SAE	Serious adverse event
SP-D	Surfactant protein D
SOC	System organ class
SSc	Systemic sclerosis
TARC	Thymus and activation-regulated chemokine

Acronym/Abbreviation/ Technical term	Full text/Definition
T-Bil	Total-bilirubin
TC	Total cholesterol
TG	Triglyceride
TLC	Total lung capacity
t_{max}	Time to reach the maximum concentration in plasma/serum
TP	Total protein
T-SPOT	T-SPOT®.TB
UA	Uric acid
UN	Urea nitrogen
VAS	Visual analogue scale
WBC	White blood cell

Protocol Synopsis

1. Study objectives

1.1 Primary Objective

To exploratorily evaluate the efficacy of nemolizumab in systemic sclerosis (SSc) patients with moderate to severe skin thickening

1.2 Secondary Objective

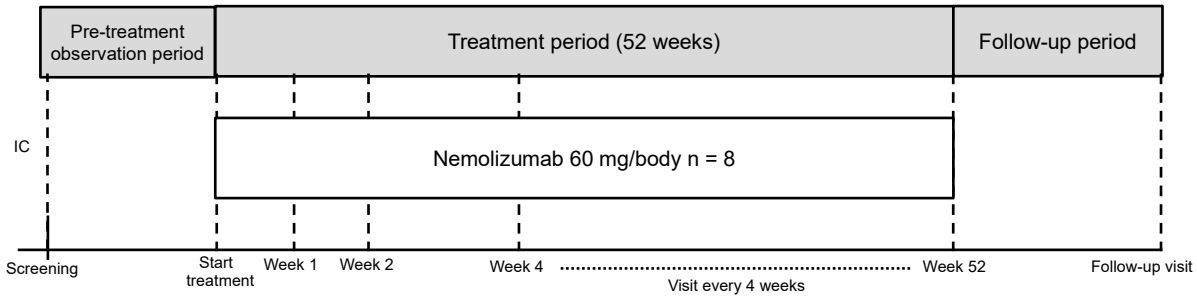
To evaluate the safety and pharmacokinetics of nemolizumab in SSc patients with moderate to severe skin thickening

2. Study Design

This is a phase II, single-arm, multiple-dose study consisting of a pre-treatment observation period (1-4 weeks) and a treatment period (52 weeks). The pre-treatment observation period is from the day of screening to the day of study treatment initiation, and participants will visit the site a total of twice, for screening and for study treatment initiation. Treatment period is from the day of study treatment initiation and every 4 weeks thereafter. Participants having received study treatment will be followed up 84 days after the day of the last dose of study treatment. Follow-up period is from Visit17 (Week 52) or the day of discontinuation visit to the day of follow-up visit.

Study phase: Phase II
Study type: Open-label, single-arm, multiple-dose study
Participants: SSc patients with moderate to severe skin thickening
Target Sample Size: 8 participants

Figure 2-1: Study Schema



1) Pre-treatment observation period

The investigator or subinvestigator will make observations and assessments at the screening visit specified in Table 4-1 after obtaining informed consent from the participant.

2) Treatment period

The investigator or subinvestigator will administer the investigational product (IP) (nemolizumab, 60 mg/body) every 4 weeks (Q4W) at visits until Week 48 after making observations and assessments on the day of study treatment initiation specified in Table 4-1. In addition, the investigator or subinvestigator will make perform observations and assessments at each visit specified in Table 4-1.

3） Follow-up period

All participants having received the IP will be scheduled to visit for follow-up 12 weeks after the day of the last dose of study treatment (the day of follow-up visit). On the day of the follow-up visit, the investigator or subinvestigator will evaluate the safety and efficacy after completion of study treatment for all participants.

3. Target Indication and Inclusion and Exclusion Criteria for Patients

3.1 Target Indication

SSc

3.2 Inclusion Criteria

Participants must meet all of the following criteria for study entry:

Inclusion Criteria	Assessment timing		
	Day of Informed Consent	Day of Screening	Day of treatment start
1） Patients aged 20 to 70 years at the time of informed consent	X	–	–
2） Patients meeting the classification criteria for SSc in ACR and EULAR 2013	X	–	–
3） Patients with systemic sclerosis who have moderate to severe skin thickening, with mRSS of 10 to 22 on both the screening and treatment initiation dates	–	X	X
4） Patients considered by the investigator or subinvestigator to be competent to perform the protocol-specified self-assessment	X	X	X

3.3 Exclusion Criteria

Participants who meet any of the following criteria will be excluded from study entry:

Exclusion Criteria	Confirmation timing		
	Day of informed consent	Day of Screening	Day of treatment start
1） Patients complicated with diseases considered inappropriate for participation in clinical trials, such as serious* cardiac/hepatic/renal/pulmonary/hematologic disease *Refer to the Criteria for Seriousness Classification of Adverse Drug Reactions. (PAB/SD Notification No.80 by the Director of Safety Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare dated June 29, 1992) and the Common Terminology Criteria for Adverse Events v 5.0 Japanese JCOG version (CTCAE v 5.0-JCOG).	X	X	X
2） Patients complicated with congestive heart failure [New York Heart Association (NYHA) Functional Class III or IV]	X	X	X
3） Patients having any of the following complications or concomitant/concurrent diseases: a） Severe chronic pulmonary disease (including %FVC < 60%, or %DLco < 40% on the day of screening, calculated from the New Reference Values for Spirometry in Japanese adults calculated with the LMS	X	X	X

Exclusion Criteria	Confirmation timing		
	Day of informed consent	Day of Screening	Day of treatment start
Method (the Japanese Respiratory Society)" b) Serious complications associated with SSc other than interstitial lung disease* (e.g., renal crisis) * Interstitial lung disease is excluded if it falls under Item a) of 3) c) Poorly controlled asthma that requires steroids (systemic), intravenous infusion of aminophylline, subcutaneous injection of adrenaline 0.1%, oxygen inhalation, or antibody drugs d) Diseases to affect the assessment of SSc			
4) Patients with a history of malignant tumor, who are receiving no treatment and have had no recurrence /relapse for ≥5 years at the time of informed consent, or patients with a history of radical treatment for cervical intraepithelial neoplasia at the time of informed consent may be included in the study	X	X	X
5) Patients with Immune deficiency (e.g., congenital immunodeficiency, AIDS, or HIV).	X	X	X
6) Patients with a history or current hypersensitivity (including anaphylaxis) to immunoglobulin products (plasma-derived preparations or genetic recombinant monoclonal antibodies)	X	X	X
7) Patients weighing < 30.0 kg or > 120 kg on the day of study treatment initiation	–	–	X
8) Patients whose laboratory test values on the day of screening meet any of the following criteria: a) AST or ALT > 2 times the upper limit of normal b) Serum creatinine ≥2.0 mg/dL c) WBC <3000 cells/μL	–	–	X
9) Patients infected with hepatitis B virus (HBV) or hepatitis C virus (HCV) (Positive for HBs antigen or HBc antibody on the day of screening, positive for anti-HCV antibody on the day of screening) The allowed exceptions are as follows: ・ Patients confirmed not to be infected with HBV at the time of the HBV-DNA test performed before study treatment initiation in the case of negative for HBs antigen and positive for HBc antibody in the hepatitis B test performed on the day of screening. ・ Patients confirmed not to be infected with HCV at the time of the HCV-RNA test performed before study treatment initiation in the case of positive for anti-HCV antibody in the hepatitis C test performed on the day of screening	–	–	X
10) Patients with latent or active tuberculosis based on the result of the screening TB test. The allowed exception is patients deemed not to be infected with tuberculosis according to the "Guidelines for the use of interferon-γ release assay (Prevention Committee of the Japanese Society for Tuberculosis).	–	–	X
11) Patients with either of the following infectious diseases: ・ Recurrent/chronic infections or other active infections	X	X	X

Exclusion Criteria		Confirmation timing		
		Day of informed consent	Day of Screening	Day of treatment start
deemed by the investigator to possibly aggravated by participating in the study. ・ Infections (including skin infections) requiring systemic antibiotics, antivirals, or antifungals within 7 days prior to the day of study treatment initiation.				
12) Patients who have received oral steroids (> 10 mg/day of prednisolone or equivalent), dosage of receiving oral steroids have been changed (from ≤ 10 mg/day of prednisolone or equivalent), or newly treated with oral steroids, within 14 days before the day of study treatment initiation		–	–	X
13) Patients who have received any of the following therapies within the indicated period prior to the day of study treatment initiation		–	(X)*	X
a) Within 365 days	Cyclophosphamide			
b) Within 120 days or 5 times the elimination half-life of the drug, whichever is longer	Antibody drugs			
c) Within 28 days	・ Live vaccines ・ The following systemic medications: – Antifibrotic drugs (e.g., pirfenidone, nintedanib) – Immunosuppressants (e.g., cyclosporine, tacrolimus, azathioprine, mycophenolate mofetil, mizoribine, sulfasalazine, leflunomide, methotrexate, hydroxychloroquine, D-penicillamine, sirolimus) – Tyrosine kinase inhibitors (e.g., imatinib) – JAK inhibitors (e.g., tofacitinib, upadacitinib) – Endothelin receptor agonists (e.g., bosentan, ambrisentan, macitentan) – Phosphodiesterase-5 inhibitors (e.g., sildenafil, tadalafil) – Prostaglandin analogue (e.g., alprostadil, epoprostenol) – Riociguat ・ Injections of corticosteroids (excluding joint injections) ・ Phototherapy			

Exclusion Criteria	Confirmation timing		
	Day of informed consent	Day of Screening	Day of treatment start
・ High-dose intravenous immunoglobulin therapy			
14） Patients who are within 120 days from the end of participation in other clinical trials or post-marketing clinical studies (i.e., the last day of administration of another IP or post-marketing clinical study drug) until the day of study treatment initiation, or participating in other clinical trials or post-marketing clinical studies	–	(X)*	X
15） Women who are pregnant, breastfeeding, possibly pregnant, or unwilling to use appropriate contraception measures as instructed by the investigator during the study period	X	X	X
16） Patients who meet any of the following criteria: a） Having not met eligibility for participation when participating in this study in the past d） Having previously received nemolizumab (including placebo)	X	X	X
17） Patients with confirmed or suspected COVID-19	–	X	X
18） Patients with a history of confirmed or suspected COVID-19 excluding those meeting any of the following criteria: • At least 20 days after the onset of symptoms and at least 72 hours after the resolution of symptoms. • Confirmed not to carry SARS-Cov-2.	–	X	X
19） Patients found to have close contacts with COVID-19 patients within 14 days before the day of study treatment initiation	–	–	X
20） Other patients who are considered ineligible for the study by the investigator	X	X	X

*The exclusion criteria will be assessed with the expected date of study treatment initiation as the starting point.

4. Schedule of Study Procedures and Assessments

Table 4-1 Schedule of Study Procedures and Assessments

Visit	1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17/ discont	FU
Visit name	IC day	Screening	Treatment initiation	W 1	W 2	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 52 or discont	FU[J]
Reference day	-	-14	1	8	15	29	57	85	113	141	169	197	225	253	281	309	337	365/ discont	Day of last dose +84
Visit window	-	-16/+9	-	±2	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7/ day of discon+14	±7
Screening/management																			
Informed consent	X[a]																		
Physician examinations	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient Background	X	X	X																
Body weight		X	X			X	X	X	X	X	X	X	X	X	X	X	X		
Registration		X 1st	X 2nd															X Time of discont	
Efficacy evaluation																			
mRSS[b]		X	X			X		X			X			X				X	X
Respiratory function test[C]		X						X			X							X	
Chest HRCT[d]		X									X							X	
Severity classification of the lung		X									X							X	

Visit	1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17/ discont	FU
Visit name	IC day	Screening	Treatment initiation	W 1	W 2	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 52 or discont	FU[j]
ACR-CRISS								X			X							X	
Number of digital ulcers		X	X					X			X			X				X	
Physician's Global Assessment			X					X			X			X				X	
HAQ-DI			X					X			X			X				X	
FACIT-Fatigue			X					X			X			X				X	
FSSG			X					X			X			X				X	
Patient's Global Assessment			X					X			X			X				X	
Safety evaluation																			
Vital signs		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Echocardiography		X									X							X	
Electrocardiogram		X									X							X	
Photography[e]			X																
Laboratory tests																			
Hematology Blood chemistry TARC Urinalysis		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy[f] and TB[g] tests		X																	
Hepatitis B and C tests[h]		X						(X)			(X)			(X)			(X)		(X)
Antinuclear antibodies test			X																
PK analysis and immunogenicity																			

Visit	1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17/ discont	FU
Visit name	IC day	Screening	Treatment initiation	W 1	W 2	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 52 or discont	FU[j]
Serum nemolizumab concentrations			X	X	X	X	X	X	X	X	X			X				X	X
Anti-nemolizumab antibody assay			X								X			X				X	X
Biomarkers																			
IL-31			X			X	X	X	X	X	X			X				X	
KL-6, SP-D, NT-proBNP			X			X		X			X			X				X	
Exploratory biomarkers			X					X			X							X	
Investigational product administration																			
Administration[i]			X			X	X	X	X	X	X	X	X	X	X	X	X		
Others																			
Comprehensive measurement of autoantibodies			X								X							X	
CyTOF measurement			X								X							X	
Adverse Events		→																	
Concomitant medications and therapies		→																	

[a] To be obtained before the observation/tests for the study, and may be obtained on the same day as the day of screening
[b] In principle, the same investigator or subinvestigator will evaluate each participant throughout the study.
[c] If the %FVC decreases by ≥ 15% from baseline, %FVC will be measured again within 1 month.
[d] If having been performed within 1 month of the specified timepoint, not necessary to be performed at the specified timepoint, and the results within 1 month will be substituted.

[e] Not to be performed if refused by the participant.
If any of the following treatment-emergent adverse events occurs, photographs of the affected skin areas of the adverse event should be taken while the event (at least once) is occurring and at the final outcome evaluation, in addition to the scheduled visit (i.e., the day of study treatment initiation).
• Atopic dermatitis
• Adverse events with skin symptoms of edematous erythema or scaling
• Any other adverse event for which the investigator or subinvestigator considers that photography is necessary.

[f] To be performed on female participants excluding those who never become pregnant.

[g] May be conducted on another day after the day of screening before the day of study treatment initiation

[h] • Hepatitis B
The participants who test negative for HBs antigen and positive for HBc antibody will undergo HBV-DNA measurement before the day of study treatment initiation. The participants enrolled through HBV-DNA measurement will undergo HBV-DNA measurement once every three months.
•
Hepatitis C
The participants who test positive for the anti-HCV antibody will undergo HCV-RNA measurement before the day of study treatment initiation. The participants enrolled through HCV-RNA measurement will undergo HCV-RNA measurement once every three months.

i To be administered after all observation/tests are performed. If the IP cannot be administered within the window indicated, the next dose should be administered 14 days or later after the day of the previous dose.

[j] Participants who discontinued the study will visit the site 84 days (±7 days) after the day of the last dose of study treatment for observation/tests at FU shown in Table 4-1. Participants discontinued the study before study treatment initiation need not to undergo observation/tests scheduled on the day of visit for discontinuation.

5. Treatment Method

5.1 Method of Administration

The investigator or subinvestigator will slowly administer the IP, nemolizumab (one DCS [0.6 ml]) subcutaneously to the upper arm, abdomen, or thigh of the participants. The IP may be administered by a person qualified to administer it under the instruction of the investigator or subinvestigator.

5.2 Treatment Period

52 weeks

All participants who have received at least one dose of the IP will visit the site 12 weeks after the day of the last dose of study treatment for follow-up.

5.3 Concomitant Medications and Therapies

5.3.1 Restricted Concomitant Medications

The following medications may be continued at a stable dose if used for at least 14 days before the day of study treatment initiation. However, the dose may be reduced at the discretion of the investigator or subinvestigator, and after dose reduction, the dose may be increased up to that used at the day of study treatment initiation.

・Oral steroids (≤ 10 mg/day of prednisolone or equivalent)

5.3.2 Prohibited Concomitant Medications and Therapies

Concomitant use of medications and therapies listed below is prohibited in this study.

- From the day of study treatment initiation to Week 52 or to the physical examination on the day of visit for discontinuation

1） The following systemic medications:
   a） Antifibrotic drugs (e.g., pirfenidone, nintedanib)
   b） Immunosuppressants (e.g., cyclophosphamide, cyclosporine, tacrolimus, azathioprine, mycophenolate mofetil, mizoribine, sulfasalazine, leflunomide, methotrexate, hydroxychloroquine, D-penicillamine, sirolimus)
   c） Tyrosine kinase inhibitors (e.g., imatinib)
   d） JAK inhibitors (e.g., tofacitinib, upadacitinib)
   e） Endothelin receptor agonists (e.g., bosentan, ambrisentan, macitentan)
   f） Phosphodiesterase-5 inhibitors (e.g., sildenafil, tadalafil)
   g） Prostaglandin analogues (e.g., alprostadil, epoprostenol)
   h） Riociguat
2） Injections of corticosteroids (excluding joint injections)
3） Phototherapy
4） High-dose intravenous immunoglobulin therapy
5） Antibody drugs
6） Live vaccines

- From the day of study treatment initiation to the day of follow-up visit

1） Other drugs and medical devices under development

6. Study Discontinuation of Individual Participants

6.1 Discontinuation Criteria

1) Use of other antibody drugs by Week 52 visit
2) Use of live vaccines by Week 52 visit
3) The investigator or subinvestigator determined that an adverse event which would prevent the continuation of the study has occurred.
4) The participant is found to fail to meet any of the inclusion criteria or to meet any of the exclusion criteria.
5) The participant is found to be pregnant.
6) The investigator or subinvestigator has determined that the participant should be withdrawn from the study due to inadequate response to the IP.
7) The participant requests to withdraw from the study.
8) The participant no longer visits the medical institution, and the study cannot be continued.
9) The participant has died.
10) The sponsor has determined the participant discontinuation from the study due to significant protocol deviations.
11) The sponsor has prematurely terminated the study.
12) The investigator or subinvestigator has determined to withdraw the participant from the study for any other reasons.

7. Efficacy Evaluation

7.1 Primary Endpoint

Change from baseline in mRSS at Week 24

7.2 Other Endpoints

1) Change from baseline in mRSS at Week 52
2) Change from baseline in HAQ-DI at Week 52
3) Change from baseline in HAQ-DI at Week 24
4) Change from baseline in %FVC at Week 52
5) Change from baseline in %FVC at Week 24
6) Change from baseline in DLco at Week 52
7) Change from baseline in DLco at Week 24
8) Change from baseline in PGA at Week 52
9) Change from baseline in PGA at Week 24
10) Change from baseline in PtGA at Week 52
11) Change from baseline in PtGA at Week 24
12) ACR-CRISS at Week 52
13) ACR-CRISS at Week 24
14) Change from baseline in the number of digital ulcers at Week 52
15) Change from baseline in the number of digital ulcers at Week 24
16) Time-course change in the following items:
    a) HAQ-DI
    b) FACIT-Fatigue
    c) FSSG
    d) FVC

e) %FVC
f) DLco
g) %DLco
h) TLC
i) FEV_1
j) Severity evaluation of lung lesion
k) PGA
l) PtGA
m) ACR-CRISS
n) The number of digital ulcers

8. Safety Evaluation

8.1 Assessments for Safety Evaluations

1) Adverse events
   a) Symptoms and signs
   b) Abnormal laboratory test values
   c) Abnormal vital signs
   d) Abnormal electrocardiograms
2) Laboratory test values
3) Vital signs
4) Electrocardiogram
5) Echocardiography

9. Target Sample Size

8 participants

10. Study Period

December 2021 to November 2024

Table of Contents

1. Introduction

1.1 Background of Development

1.1.1 Pathophysiology and epidemiology of systemic sclerosis

Systemic scleroderma (SSc) is a systemic autoimmune disease characterized by fibrosis and vasculopathy of skin and various internal organs such as lung and classified as a connective tissue disease. Skin fibrosis, a common symptom in patients with SSc, is considered to be excessive deposition of the extracellular matrix mainly composed of collagen. [1)] In Japan, SSc is designated as an intractable disease; according to the information of the Japan Intractable Diseases Information Center, the number of SSc patients is about 20,000. [2)] The male-to-female ratio of patients is 1:12 and is more prevalent in women between the ages of 30 and 50 years.

SSc is classified as either diffuse cutaneous systemic scleroderma (dcSSc) in which skin thickening extends to the proximal extremities (i.e. the upper arms and the thighs) or the trunk or limited cutaneous systemic scleroderma (lcSSc) in which skin thickening is limited to the distal extremities (i.e. the forearms and the lower legs) and the face.[3)] In dcSSc patients, as skin thickening progresses, visceral involvement such as in the lungs, gastrointestinal tract, kidneys, and heart, and joint flexion contracture progress. In dcSSc in particular, it is widely recognized that the degree of skin thickening correlates with that of fibrotic lesions in internal organs, and higher severity of skin thickening has been reported to be associated with higher rates of visceral involvement including in the lungs and lower survivals. [4), 5), 6)] In addition, fibrosis of internal organs, as well as skin thickening, develops at an early stage, in which slight tissue damage accumulates and progresses to irreversible organ damage. Therefore, treatment should be initiated as early as possible, especially in patients in whom the condition is predicted to become severe. In lcSSc patients, on the other hand, skin thickening progresses slowly and are not eligible for aggressive treatment. However, lcSSc with the possibility of rapid and widespread progression of skin thickening may be eligible for treatment.[7)]

1.1.2 Therapeutic treatment of systemic sclerosis and its issues

The etiology of SSc has not been clarified, and the main treatment methods are symptomatic treatments and disease-modifying drugs that inhibit disease progression. The progression and sites of involvement of SSc are different for each patient, and accordingly, the treatment method is selected based on the symptom of each patient.

Diagnostic Criteria, Severity Classification and Guidelines of Systemic Sclerosis[7)] state that oral corticosteroids are thought to be empirically valid for patients with progressing skin thickening at an early stage but that they have risk factors for inducing renal crisis. Cyclophosphamide is the most recommended treatment option for both skin thickening and interstitial lung disease in patients with SSc; however, it has a problem of difficulty in long-term administration because of its carcinogenicity, immunosuppression, and side effects of drug such as hemorrhagic cystitis. Other drugs for SSc symptoms are prostacyclin, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors for the treatment of pulmonary hypertension, calcium channel blockers for the treatment of cardiac involvement, intravenous prostaglandin E1 or prostacyclin for the treatment of disturbed blood flow in the fingers, and proton pump inhibitors for the treatment of reflux esophagitis. However, due to limited efficacy or safety issues of these therapeutic agents, the disease burden remains high and there is a great unmet medical need.

1.1.3 Summary description and significance of the development of nemolizumab

Nemolizumab is a monoclonal antibody that recognizes interleukin-31 receptor A (IL-31RA) in humans, which competitively inhibits the binding of interleukin-31 (IL-31) to its receptor, thereby blocking subsequent signal transduction into the cells. Nemolizumab was initially developed by [redacted] Co., Ltd.; the worldwide development and marketing rights, except in Japan and Taiwan,

were granted to [redacted] in 2016, while the development and marketing rights in the field of skin diseases in Japan were granted to [redacted]

IL-31 is a cytokine produced mainly from activated T cells. IL-31 is present at higher levels in serum in SSc than in healthy individuals; IL-31 positive cells were identified in inflammatory infiltrates in fibrotic lesions in the skin and lungs[8)]. Moreover, an *in vitro* study with dermal fibroblasts from healthy individuals showed IL-31 increased collagen production in these cells, and IL-31 administration to mice induced skin and lung fibrosis in an *in vivo* study, suggesting that IL-31 induces skin and lung fibrosis via inducing collagen production in fibroblasts[8)].These results indicate that IL-31 is a key cytokine involved in the development of SSc, and therefore, nemolizumab is expected to inhibit the progression of or ameliorate of skin and pulmonary fibrosis in SSc.

From the above, nemolizumab is considered to be a possible new treatment option for SSc. Thus, this study has been developed to explore the efficacy and safety of nemolizumab in SSc patients.

1.2 Guidelines, Consultation with Pharmaceuticals and Medical Devices Agency (PMDA), etc., Referenced for Study Planning

This study has been planned in reference to the “Diagnostic criteria, severity classification and guidelines of systemic sclerosis.”

2. Study objectives

2.1 Primary Objective

To exploratorily evaluate the efficacy of nemolizumab in systemic sclerosis (SSc) patients with moderate to severe skin thickening

2.2 Secondary Objective

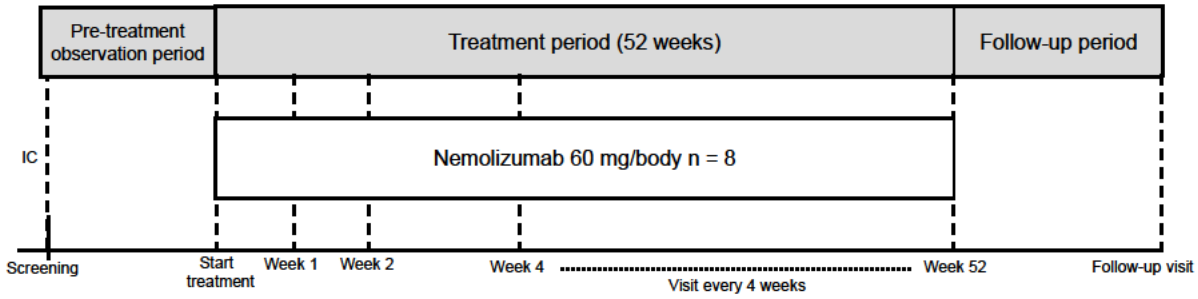
To evaluate the safety and pharmacokinetics of nemolizumab in SSc patients with moderate to severe skin thickening

3. Study Design

This is a phase II, single-arm, multiple-dose study consisting of a pre-treatment observation period (1-4 weeks) and a treatment period (52 weeks). The pre-treatment observation period is from the day of screening to the day of study treatment initiation, and participants will visit the site a total of twice, for screening and for study treatment initiation. The treatment period is from the day of study treatment initiation to Visit 17 (Week 52), during which participants will visit a total of 15 times: Week1,2 and 4, and every four weeks thereafter. Participants having received study treatment will be followed up 84 days after the day of the last dose of study treatment. Follow-up period is from Visit17 (Week 52) or the day of discontinuation visit to the day of follow-up visit.

Study phase: Phase II
Study type: Open-label, single-arm, multiple-dose study
Participants: SSc patients with moderate to severe skin thickening
Target Sample Size: 8 participants

Figure 3-1: Study Schema



1) Pre-treatment observation period
The investigator or subinvestigator will make observations and assessments at the screening visit specified in Table 9-1 after obtaining informed consent from the participant.

2) Treatment period
The investigator or subinvestigator will administer the investigational product (IP) (nemolizumab, 60 mg/body) every 4 weeks (Q4W) at visits until Week 48 after making observations and assessments on the day of study treatment initiation specified in Table 9-1. In addition, the investigator or subinvestigator will make perform observations and assessments at each visit specified in Table 9-1.

3) Follow-up period

All participants having received the IP will be scheduled to visit for follow-up 12 weeks after the day of the last dose of study treatment (the day of follow-up visit). On the day of the follow-up visit, the investigator or subinvestigator will evaluate the safety and efficacy after completion of study treatment for all participants.

4. Target Indication and Inclusion and Exclusion Criteria for Participants

The investigator or subinvestigator will ensure before enrollment that all inclusion criteria are met and none of the exclusion criteria are met.

4.1 Target Indication

SSc

4.2 Inclusion Criteria

Participants must meet all of the following criteria for study entry:

Inclusion Criteria	Assessment timing		
	Day of Informed Consent	Day of Screening	Day of treatment start
1) Patients aged 20 to 70 years at the time of informed consent	X	–	–
2) Patients meeting the classification criteria for SSc in ACR and EULAR 2013	X	–	–
3) Patients with systemic sclerosis who have moderate to severe skin thickening, with mRSS of 10 to 22 on both the screening and treatment initiation dates	–	X	X
4) Patients considered by the investigator or subinvestigator to be competent to perform the protocol-specified self-assessment	X	X	X

・ Rationale for inclusion criteria

1)	Established for safety consideration and to select patients with a sufficient capacity for judgment
2)	Established to standardize the diagnostic criteria for SSc for participants
3)	Established to include only patients with moderate to severe symptoms who are considered to be target patients for this drug.
4)	Established to select patients who can comply with the protocol-specified activities.

4.3 Exclusion criteria

Participants who meet any of the following criteria will be excluded from study entry:

Exclusion Criteria	Confirmation timing		
	Day of informed consent	Day of Screening	Day of treatment start
1) Patients complicated with diseases considered inappropriate for participation in clinical trials, such as serious* cardiac/hepatic/renal/pulmonary/hematologic disease *Refer to the Criteria for Seriousness Classification of Adverse Drug Reactions. (PAB/SD Notification No.80 by the Director	X	X	X

Exclusion Criteria	Confirmation timing		
	Day of informed consent	Day of Screening	Day of treatment start
of Safety Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare dated June 29, 1992) and the Common Terminology Criteria for Adverse Events v 5.0 Japanese JCOG version (CTCAE v 5.0-JCOG).			
2) Patients complicated with congestive heart failure [New York Heart Association (NYHA) Functional Class III or IV]	X	X	X
3) Patients having any of the following complications or concomitant/concurrent diseases: a) Severe chronic pulmonary disease (including %FVC < 60%, or %DLco < 40% on the day of screening, calculated from the New Reference Values for Spirometry in Japanese adults calculated with the LMS Method (the Japanese Respiratory Society)" b) Serious complications associated with SSc other than interstitial lung disease* (e.g., renal crisis) * Interstitial lung disease is excluded if it falls under Item a) of3) c) Poorly controlled asthma that requires steroids (systemic), intravenous infusion of aminophylline, subcutaneous injection of adrenaline 0.1%, oxygen inhalation, or antibody drugs d) Diseases to affect the assessment of SSc	X	X	X
4) Patients with a history of malignant tumor, who are receiving no treatment and have had no recurrence /relapse for ≥5 years at the time of informed consent, or patients with a history of radical treatment for cervical intraepithelial neoplasia at the time of informed consent may be included in the study	X	X	X
5) Patients with Immune deficiency (e.g., congenital immunodeficiency, AIDS, or HIV).	X	X	X
6) Patients with a history or current hypersensitivity (including anaphylaxis) to immunoglobulin products (plasma-derived preparations or genetic recombinant monoclonal antibodies)	X	X	X
7) Patients weighing < 30.0 kg or > 120 kg on the day of study treatment initiation	–	–	X
8) Patients whose laboratory test values on the day of screening meet any of the following criteria: a) AST or ALT > 2 times the upper limit of normal b) Serum creatinine ≥2.0 mg/dL c) WBC <3000 cells/μL	–	–	X
9) Patients infected with hepatitis B virus (HBV) or hepatitis C virus (HCV) (Positive for HBs antigen or HBc antibody on the day of screening, positive for anti-HCV antibody on the day of screening) The allowed exceptions are as follows: ・ Patients confirmed not to be infected with HBs at the time of the HBV-DNA test performed before study treatment initiation in the case of negative for HBs antigen and positive for HBc antibody in the hepatitis B test	–	–	X

Exclusion Criteria		Confirmation timing		
		Day of informed consent	Day of Screening	Day of treatment start
performed on the day of screening. ・ Patients confirmed not to be infected with HCV at the time of the HCV-RNA test performed before study treatment initiation in the case of positive for anti-HCV antibody in the hepatitis C test performed on the day of screening				
10) Patients with latent or active tuberculosis based on the result of the screening TB test. The allowed exception is patients deemed not to be infected with tuberculosis according to the "Guidelines for the use of interferon-γ release assay (Prevention Committee of the Japanese Society for Tuberculosis).		–	–	X
11) Patients with either of the following infectious diseases: ・ Recurrent/chronic infections or other active infections deemed by the investigator to possibly aggravated by participating in the study ・ Infections (including skin infections) requiring systemic antibiotics, antivirals, or antifungals within 7 days prior to the day of study treatment initiation.		X	X	X
12) Patients who have received oral steroids (> 10 mg/day of prednisolone or equivalent), dosage of receiving oral steroids have been changed (from ≤ 10 mg/day of prednisolone or equivalent), or newly treated with oral steroids, within 14 days before the day of study treatment initiation		–	–	X
13) Patients who have received any of the following therapies within the indicated period prior to the day of study treatment initiation		–	(X)*	X
a) Within 365 days	Cyclophosphamide			
b) Within 120 days or 5 times the elimination half-life of the drug, whichever is longer	Antibody drugs			
c) Within 28 days	i. Live vaccines ii. The following systemic medications: – Antifibrotic drugs (e.g., pirfenidone, nintedanib) – Immunosuppressants (e.g., cyclosporine, tacrolimus, azathioprine, mycophenolate mofetil, mizoribine, sulfasalazine, leflunomide, methotrexate, hydroxychloroquine, D-penicillamine, sirolimus) – Tyrosine kinase inhibitors (e.g., imatinib)			

Exclusion Criteria		Confirmation timing		
		Day of informed consent	Day of Screening	Day of treatment start
	– JAK inhibitors (e.g., tofacitinib, upadacitinib) – Endothelin receptor agonists (e.g., bosentan, ambrisentan, macitentan) – Phosphodiesterase-5 inhibitors (e.g., sildenafil, tadalafil) – Prostaglandin analogue (e.g., alprostadil, epoprostenol) – Riociguat iii. Injections of corticosteroids (excluding joint injections) iv. Phototherapy v. High-dose intravenous immunoglobulin therapy			
14) Patients who are within 120 days from the end of participation in other clinical trials or post-marketing clinical studies (i.e., the last day of administration of another IP or post-marketing clinical study drug) until the day of study treatment initiation, or participating in other clinical trials or post-marketing clinical studies		–	(X)*	X
15) Women who are pregnant, breastfeeding, possibly pregnant, or unwilling to use appropriate contraception measures as instructed by the investigator during the study period		X	X	X
16) Patients who meet any of the following criteria: a) Having not met eligibility for participation when participating in this study in the past b) Having previously received nemolizumab (including placebo)		X	X	X
17) Patients with confirmed or suspected COVID-19		–	X	X
18) Patients with a history of confirmed or suspected COVID-19 excluding those meeting any of the following criteria: • At least 20 days after the onset of symptoms and at least 72 hours after the resolution of symptoms. • Confirmed not to carry SARS-Cov-2.		–	X	X
19) Patients found to have close contacts with COVID-19 patients within 14 days before the day of study treatment initiation		–	–	X
20) Other patients who are considered ineligible for the study by the investigator		X	X	X

*The exclusion criteria will be assessed with the expected date of study treatment initiation as the starting point.

・ Rationale for exclusion criteria

1) to 6), 8) to 11), 15), and 17) to 19)	Established considering the safety of participants
7)	Since the dose in this study is 60 mg/body, the upper body weight limit was set not to be lower than the dose (0.5 mg/kg) proven effective in the studies conducted to date in patients with atopic dermatitis, in view of efficacy. The lower

	limit of body weight was set to ensure the safety of participants so that the exposure does not exceed that at the maximum dose (2.0 mg/kg) confirmed to be tolerated after repeated administration of IP.
12)	Established considering the impact on the efficacy of the IP and to ensure the safety of the participants.
13) a), b), c) ii), iii), v),14)	Established considering the impact on the efficacy and safety evaluation of the IP. The period was considered necessary for washout based on the duration of treatment effect and half-live of each drug and therapy.
13) c), i)	Established considering the impact on the safety evaluation of the IP. The period was considered necessary for washout based on the duration of treatment effect and half-live of each drug
13) c), iv)	Established considering the impact on the efficacy evaluation of the IP. The period was considered necessary for washout based on the duration of treatment effect and half-live of each therapy.
16)	1) Established to exclude patients ineligible for this study 2) Established to exclude the impact on the evaluation of efficacy and safety
20)	Established as a general criterion to exclude patients considered ineligible for this study by the investigator or subinvestigator.

5. Study Discontinuation of Individual Participants

The investigator or subinvestigator will withdraw the participant signing informed consent from the study and take appropriate measures if participant meets any of the following discontinuation criteria before observation/tests at Visit 17 (Week 52). Even if the participant requests withdrawal from the study, the participant's data will be used.

5.1 Discontinuation criteria

1) Use of other antibody drugs by Week 52 visit
2) Use of live vaccines by Week 52 visit
3) The investigator or subinvestigator determined that an adverse event which would prevent the continuation of the study has occurred.
4) The participant is found to fail to meet any of the inclusion criteria or to meet any of the exclusion criteria.
5) The participant is found to be pregnant.
6) The investigator or subinvestigator has determined that the participant should be withdrawn from the study due to inadequate response to the IP.
7) The participant requests to withdraw from the study.
8) The participant no longer visits the medical institution, and the study cannot be continued
9) The participant has died.
10) The sponsor has determined the participant discontinuation from the study due to significant protocol deviations.

The sponsor has prematurely terminated the study.
The investigator or subinvestigator has determined to withdraw the participant from the study for any other reasons.

・ Rationale for discontinuation criteria

1) to 3), 5)	Established considering the safety of the participants
4)	Established because the participants are considered ineligible for the study
6)	Established to reduce disadvantages for the participants

7)	Established because it is considered the rights of participants
8) to 11)	Established for contingencies
12)	Established to allow participant discontinuation from the study at the discretion of the investigator or subinvestigator.

5.2 Procedure for Discontinuation

5.2.1 Discontinuation before Enrollment

1) For the participant not led to enrollment because of not satisfying the inclusion criteria, meeting any of the exclusion criteria or other reasons, the investigator or subinvestigator will explain the reason to withdraw the participant from the study, take appropriate action for the participant. The investigator or subinvestigator will ascertain and record the date of discontinuation and the reason for discontinuation in the source documents. A visit for discontinuation and observation/tests scheduled on the day of visit for discontinuation will not be performed.
2) The investigator, subinvestigator, or CRC will record the data for the items described in Section 19.1.2 in the CRF.

5.2.2 Discontinuation after Enrollment

1) The investigator or subinvestigator will explain the reason to withdraw the participant from the study and take appropriate action, ascertain and record the reason for discontinuation in the source documents.
2) The investigator or subinvestigator will perform the observation/tests scheduled on the day of visit for discontinuation. When determining to discontinue the study on a day other than the day of the visit, the investigator or subinvestigator will instruct the participant to come to the study site as early as possible. However, if the day of visit for discontinuation is on or after 77 days from the last dose of study treatment.
3) The investigator, subinvestigator, or CRC will record the data of the items described in Section 19.1.1 in the CRF.

5.3 Handling of Participants Who Fail to Visit the Study Site

5.3.1 Participants Discontinuing Study Site Visit Between the Day of Informed Consent and the Day of Enrollment

When a participant discontinues visiting the study site after the day of informed consent but before enrollment, the investigator or subinvestigator will perform follow-up of the participant through contact with him/her by telephone, letter or other means to record the method and the result of follow-up, reason(s) for not visiting with the date of such information obtained, presence or absence of adverse events, and other information obtained in the source document.

5.3.2 Participants Discontinuing Study Site Visit in the Period after the Enrollment up to Visit 17 (Week 52)

If a participant discontinues visiting the study site after assigned to treatment, the investigator or subinvestigator will identify the whereabouts of the participant as far as possible and encourage him/her to visit the study site. If the participant dose not visit the study site, the investigator or subinvestigator will perform follow-up of the participant through contact with him/her by telephone, letter, or other means to document the method of follow-up, reason(s) for not visiting with the date of such information obtained, presence or absence of adverse events, and other information obtained.

5.3.3 Participants Discontinuing Study Site Visit during the Follow-up Period

The participant who cannot visit the study site within the window of the follow-up visit will be encouraged to visit the study site on the nearest day to the window. If the participant does not visit the study site, the investigator or subinvestigator will perform follow up of the participant through contact with him/her by telephone, letter, and other means to document the method of follow-up, reason(s) for not visiting with the

date of such information obtained, the presence or absence of adverse events, and other information obtained.

6. Participant Enrollment

6.1 Informed Consent

The investigator or subinvestigator will fully explain the study to participants who are considered eligible for the study and obtain written consent before the procedures for the study (see Section 27.4 for the method and points to note for obtaining informed consent).
The investigator or subinvestigator will record the participant information on the participant screening log and provide the participant identification code. The participant identification will be AF001-XXX and will be coded in order of informed consent acquisition. Each participant will use the same participant identification code from informed consent to completion of the study.

6.2 Notification when the Participant is Treated by Another Doctor

The investigator or subinvestigator will ask participants whether or not they are being treated by another doctor. When a participant is being treated by another doctor, the investigator or subinvestigator will notify the doctor of his/her participation in the study after obtaining his/her consent. In addition, the investigator or subinvestigator will record this notification to the doctor in the medical record, etc.

6.3 Enrollment Procedure of Participants

1) For first and second registration.
   For participants considered eligible for the study on the day of screening and on the day of study treatment initiation, the investigator or subinvestigator will enter the necessary information in the source documents, and then fill out a registration form and fax it to the sponsor. The registration form should be filled out and faxed after the source documents have been prepared, which can be performed by the CRC.

2) For discontinuation before assigned to treatment
   For participants discontinued from the study after informed consent but before second registration, the investigator or subinvestigator will enter the necessary information in the source documents, and then fill out a registration form and fax it to the sponsor. The registration form should be filled out and faxed after the source documents have been prepared, which can be performed by the CRC.

3) Correction of entries in the source documents
   When an error is found in the information registered, the investigator or subinvestigator will correct the data in the source document and enter the necessary information in a registration form as needed, and then fax it to the sponsor to correct such data. The registration form should be filled out and faxed after the source documents have been corrected, which can be performed by the CRC.

7. Investigational Product

7.1 Name, Dosage Form, and Strength of the IP

Name, dosage form, and strength of the IPs are indicated in Table 7-1.

Table 7-1 Name, dosage form and strength of investigational product

Name of investigational product	Formulation	Active ingredient and strength (Per DCS)	Storage condition (Before preparation)
Nemolizumab	Injection (DCS)	nemolizumab 75 mg (lyophilized) Nemolizumab is overfilled to ensure injectable nemolizumab 60 mg from one DCS in consideration of the loss of the prepared drug solution during administration. The active ingredient level after preparation is 100 mg/mL.	2°C to 8°C Protection from light

7.2 Packaging and Labeling

7.2.1 Packaging

One DCS of the IP is contained in a small box.

7.2.2 Labeling

The small box is labeled with a statement for clinical study use only, the name and address of the sponsor, identification number, lot number, and storage method.

7.3 Storage and Management of Investigational Products

The investigational product manager at each study site will store and manage the IPs according to the "Operating Procedure for Investigational Product Management" prepared by the sponsor and other procedures specified at each site.

8. Treatment Method

8.1 Dispensing of Investigational Products

The investigator or subinvestigator will dispense one DCS of the IP at the following visits:
<Dispensing visits>
Day of study treatment initiation, Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48

8.2 Preparation of Investigational Products

The investigator or subinvestigator, the investigational product manager or the person in charge of preparation of the IP will prepare injection solutions of IPs according to the "Standard Operating Procedure for Investigational Product Management."

8.3 Method of Administration

On the days of administration (see Table 9-1: Schedule), the investigator or subinvestigator will subcutaneously inject one DCS (0.6-mL) of nemolizumab slowly to the participant either in the upper arm, abdomen, or thigh. The IP may be administered by a person qualified to administer it under the instruction of the investigator or subinvestigator.

・ Precautions
  - The IP will be administered after all observation/tests scheduled at the visit have been completed.
  - The IP will be administered within the window of the specified visit. However, if the IP cannot be administered within the window, the next dose should be administered 14 days or later after the

previous dose.

- If the participant's body weight is lower than 30.0 kg on the day of administration, the IP must not be administered.

・ Rationale for selection>

1） Dosage: 60 mg/body Q4W

A phase III study in Japanese patients with atopic dermatitis has demonstrated the long-term safety of nemolizumab 60 mg/body Q4W. This study has been designed to exploratorily evaluate the efficacy of nemolizumab in SSc patients at 60 mg/body Q4W which has shown the long-term efficacy in SSc patients.

2） Treatment Period

The treatment period has been set at 52 weeks because long-term observation is required to evaluate the efficacy of nemolizumab on skin thickening in SSc patients in an exploratory manner.

3） Day of Follow-up Visit

Considering the serum elimination half-life after a single dose of nemolizumab ranges from 12.6 to 14.6 days in patients with atopic dermatitis, the day of follow-up visit has been set to collect information such as the occurrence of adverse events on the day of 5 times the elimination half-life (84 days ± 7 days) from the day of the last dose.

8.4 Concomitant Medications and Therapies

8.4.1 Restricted Concomitant Medications

The following medications may be continued at a stable dose if used for at least 14 days before the day of study treatment initiation. However, the dose may be reduced at the discretion of the investigator or subinvestigator, and after dose reduction, the dose may be increased up to that used at the day of study treatment initiation.

・Oral steroids (≤ 10 mg/day of prednisolone or equivalent)

8.4.2 Duration and Method of Inspection

The investigator or subinvestigator will collect the information of concomitant medications/therapies by interviewing participants according to Section.9.3.2

8.4.3 Prohibited Concomitant Medications and Therapies

Concomitant use of medications and therapies listed below is prohibited in this study.

- From the day of study treatment initiation to Week 52 or to the physical examination on the day of visit for discontinuation

1） The following systemic medications:

a） Antifibrotic drugs (e.g., pirfenidone, nintedanib)

b） Immunosuppressants (e.g., cyclophosphamide, cyclosporine, tacrolimus, azathioprine, mycophenolate mofetil, mizoribine, sulfasalazine, leflunomide, methotrexate, hydroxychloroquine, D-penicillamine, sirolimus)

c） Tyrosine kinase inhibitors (e.g., imatinib)

d） JAK inhibitors (e.g., tofacitinib, upadacitinib)

e） Endothelin receptor agonists (e.g., bosentan, ambrisentan, macitentan)

f） Phosphodiesterase-5 inhibitors (e.g., sildenafil, tadalafil)

g） Prostaglandin analogues (e.g., alprostadil, epoprostenol)
h） Riociguat

2） Injections of corticosteroids (excluding joint injections)
3） Phototherapy
4） High-dose intravenous immunoglobulin therapy
5） Antibody drugs
6） Live vaccines

・ Rationale for selection

1) 2) 4) 5)	Established considering the impact on the efficacy of the IP and the safety of participants
3)	Established considering the impact on the efficacy evaluation of the IP
6)	Established considering the safety of participants

- From the day of study treatment initiation to the day of follow-up visit

1） Other drugs and medical devices under development

・ Rationale for selection

1)	Established considering the safety of participants and the impact on the efficacy of the IP.

8.4.4 Instructions to participants

The investigator or subinvestigator will examine the implementation status of the treatment of SSc at each visit and give instructions to the participants on treatment of SSc according to the therapeutic guidance specified in Sections 8.4.1 and 8.4.3.

9. Study Procedures and Assessments and the Schedule

9.1 Schedule of Study Procedures and Assessments

Observation, tests and sample collection will be performed according to the schedule shown in Table 9-1.

Table 9-1: Schedule

Visit	1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17/ discont	FU
Visit name	IC day	Screening	Treatment initiation	W 1	W 2	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 52 or discont	FU[j]
Reference day	-	-14	1	8	15	29	57	85	113	141	169	197	225	253	281	309	337	365/ discont	Day of last dose +84
Visit window	-	-16/+9	-	±2	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7/ day of discon+14	±7
Screening/management																			
Informed consent	X[a]																		
Physical examinations	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Demographics	X	X	X																
Body weight		X	X			X	X	X	X	X	X	X	X	X	X	X	X		
Registration		X 1st	X 2nd															X Time of discont	
Efficacy evaluation																			
mRSS[b]		X	X			X		X			X			X				X	X
Respiratory function test[C]		X						X			X							X	
Chest HRCT[d]		X									X							X	

Visit	1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17/ discont	FU
Visit name	IC day	Screening	Treatment initiation	W 1	W 2	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 52 or discont	FU[j]
Severity classification of the lung		X									X							X	
ACR-CRISS								X			X							X	
Number of digital ulcers		X	X					X			X			X				X	
Physician's Global Assessment			X					X			X			X				X	
HAQ-DI			X					X			X			X				X	
FACIT-Fatigue			X					X			X			X				X	
FSSG			X					X			X			X				X	
Patient's Global Assessment			X					X			X			X				X	
Safety evaluation																			
Vital signs		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Echocardiography		X									X							X	
Electrocardiogram		X									X							X	
Photography[e]			X																
Laboratory tests																			
Hematology Blood chemistry TARC Urinalysis		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy[f] and TB[g] tests		X																	
Hepatitis B and C tests[h]		X						(X)			(X)			(X)			(X)		(X)
Antinuclear antibodies test			X																

Visit	1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17/ discont	FU
Visit name	IC day	Screening	Treatment initiation	W 1	W 2	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 52 or discont	FU[j]
PK analysis and immunogenicity																			
Serum nemolizumab concentrations			X	X	X	X	X	X	X	X	X			X				X	X
Anti-nemolizumab antibody assay			X								X			X				X	X
Biomarkers																			
IL-31			X			X	X	X	X	X	X			X				X	
KL-6, SP-D, NT-proBNP			X			X		X			X			X				X	
Exploratory biomarkers			X					X			X							X	
Investigational product administration																			
Administration[i]			X			X	X	X	X	X	X	X	X	X	X	X	X		
Others																			
Comprehensive measurement of autoantibodies			X								X							X	
CyTOF measurement			X								X							X	
Adverse Events		→																	
Concomitant medications and therapies		→																	

[a] To be obtained before the observation/tests for the study, and may be obtained on the same day as the day of screening
[b] In principle, the same investigator or subinvestigator will evaluate each participant throughout the study.
[c] If the %FVC decreases by ≥ 15% from baseline, %FVC will be measured again within 1 month.
[d] If having been performed within 1 month of the specified timepoint, not necessary to be performed at the specified timepoint, and the results within 1 month will be substituted.

[e] Not to be performed if refused by the participant.
If any of the following treatment-emergent adverse events occurs, photographs of the affected skin areas of the adverse event should be taken while the event (at least once) is occurring and at the final outcome evaluation, in addition to the scheduled visit (i.e., the day of study treatment initiation). The photography on the scheduled visit (day of study treatment initiation) will be performed according to Section 9.3.5.4
• Atopic dermatitis
• Adverse events with skin symptoms of edematous erythema or scaling
• Any other adverse event for which the investigator or subinvestigator considers that photography is necessary.

[f] To be performed on female participants excluding those who never become pregnant.

[g] May be conducted on another day after the day of screening before the day of study treatment initiation

[h] • Hepatitis B
The participants who test negative for HBs antigen and positive for HBc antibody will undergo HBV-DNA measurement before the day of study treatment initiation. The participants enrolled through HBV-DNA measurement will undergo HBV-DNA measurement once every three months.
• Hepatitis C
The participants who test positive for anti-HCV antibody will undergo HCV-RNA measurement before the day of study treatment initiation. The participants enrolled through HCV-RNA measurement will undergo HCV-RNA measurement once every three months.

i To be administered after all observation/tests are performed. If the IP cannot be administered within the window indicated, the next dose should be administered 14 days or later after the day of the previous dose.

[j] Participants who discontinued the study will visit the site 84 days (±7 days) after the day of the last dose of study treatment for observation/tests at FU shown in Table 4-1. Participants discontinued the study before study treatment initiation need not to undergo observation/tests scheduled on the day of visit for discontinuation.

9.2 Definition of the Days of Observation, Tests, and Sample Collection

The days of observation, tests, and sample collection will be defined as follows. Table 9-1 shows the visit window of the assessment day.

9.2.1 Day of Informed Consent

The day when informed consent is obtained from the participant is defined as the day of informed consent.

9.2.2 Day of screening

The day of screening is defined as the day of first registration after completion of protocol-specified assessments. The day of informed consent may be the same day as the day of screening.
All observation/tests scheduled for the day of screening must be performed on the same day. The tuberculosis test may be performed after the day of screening; however, the test result should be reviewed before the day of study treatment initiation.

9.2.3 Day of Study Treatment Initiation

The day of study treatment initiation is defined as the day when the participant is enrolled after completion of protocol-specified assessments. All assessments scheduled for the day of study treatment initiation must be performed on the same day.
The day of study treatment initiation is Day 1, and the day before the day of study treatment initiation is Day -1.

9.2.4 Day of Assessment (Weeks 1, 2, 4, 8, 12, through 52)

Week 1 through Week 52 are days when participants visit the study site for protocol-specified observation/tests.

9.2.5 Day of Study Treatment

The day of study treatment is defined as the day when the IP is administered to the participant according to the schedule of Table 9-1 after the protocol-specified assessments are implemented.

9.2.6 Day of Discontinuation

The day of discontinuation is defined as the day when the investigator or subinvestigator determines to withdraw the participant from the study.

9.2.7 Day of Discontinuation Visit

The day of visit for discontinuation is defined as the day when the protocol-specified observation/tests scheduled for discontinuation are performed for the participant who is determined to be withdrawn from the study after study treatment initiation and visit the study site for the procedure.

9.2.8 Day of Follow-up Visit

The day of follow-up visit is defined as the day when the protocol-specified observation/tests are performed for the participant who visits the study site 84 days (±7 days) after the day of the last dose of study treatment.

9.3 Observation, Tests and Sample Collection

9.3.1 Participant Demographics

The investigator or subinvestigator will perform following assessments on the day of informed consent, the day of screening and the day of study treatment initiation.

1） Assessments on the day of informed consent
- Primary disease (diagnosis)
- Time of onset of primary disease
- Classification of primary disease (diffuse cutaneous SSc [dcSSc] or limited cutaneous SSc [lcSSc])
- Main therapy given for SSc in the past
- Date of birth
- Sex
- Complication (any disease which is ongoing at the time of informed consent)
- Race
- Inclusion and exclusion criteria (see “4. Target Indication and Inclusion and Exclusion Criteria for Participants”)

2） Assessments on the day of screening
- Inclusion and exclusion criteria (see “4. Target Indication and Inclusion and Exclusion Criteria for Participants”)
- Height

3） Assessments on the day of study treatment initiation
- Inclusion and exclusion criteria (see “4. Target Indication and Inclusion and Exclusion Criteria for Participants”)

9.3.2 Prior and Concomitant Medications and Therapies
9.3.2.1 Prior and concomitant medications
The investigator or subinvestigator will review the following medications for each participant:

1） Medications intended to treat SSc
- Used from 28 days before the day of study treatment initiation to the physical examination at the follow-up visit

2） Medications intended to treat adverse events

a） Medications intended to treat adverse events of special interest defined in Section 11.6 :
Used from the day of study treatment initiation (after initiating study treatment) to the final outcome evaluation.

b） Medications intended to treat adverse events except for 1):
Used from the day of study treatment initiation (after initiating study treatment) to the physical examination at the follow-up visit.

3） All concomitant medications other than 1), and 2)
- Used from the day of study treatment initiation (after initiating study treatment) to Week 52 or the day of discontinuation visit.

Information to be obtained	Presence or absence of concomitant medications, and the drug name, dosage, drug use classification, start and end dates of use, and indication for use of each concomitant medication
Notes	The following information is not required to be collected: ・Diagnostic agents, infusions, fluid replacement, nutritional agents, disinfectants, anesthetics for surgery, laxatives and suppository for barium examination (unless these drugs were used for treatment or are included in the prohibited concomitant medications) ・Dosage of 3) ・Among medications of 1), those newly used in participants who discontinued

	from the study on or after the physical examination at the discontinuation visit.

9.3.2.2 Prior and concomitant therapies

The investigator or subinvestigator will collect the data of the following therapies:

1) Therapies to treat SSc
   - Performed from 28 days before the day of study treatment initiation to the physical examination at the follow-up visit.
2) Concomitant therapies intended to treat adverse events
   a) Concomitant therapies intended to treat adverse events of special interest defined in Section 11.6
      - Performed from the day of study treatment initiation (after initiating study treatment) to the final outcome evaluation.
   b) Concomitant therapies intended to treat adverse events except for 1)
      - Performed from the day of study treatment initiation (after initiating study treatment) to the physical examination at the follow-up visit.
   c) Prohibited concomitant therapies
      - Performed from the day of study treatment initiation (after initiating study treatment) to Week 52 or the day of discontinuation visit.

Information to be obtained	Presence or absence of therapy, and the name of therapy, site to which concomitant therapy is applied, start and end dates of application and purpose of use of concomitant therapy
Notes	Among therapies of 1), those newly performed to participants who discontinued from the study on or after the physical examination at the discontinuation visit are not required.

9.3.3 Body Weight

The investigator or subinvestigator will measure the body weight of participants at the following timepoints:

Data to be obtained	Body weight
Time points	Day of screening, Day of study treatment initiation, Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48
Notes	・On the days of study treatment, measurement will be performed, and the results will be reviewed before administration of IP. ・Participants weighing less than 30.0 kg on the day of study treatment are not allowed to receive study treatment.

9.3.4 Efficacy Evaluation

9.3.4.1 Evaluation of Skin Findings

The investigator or subinvestigator will perform the following assessments:

Assessment	mRSS
Time points	Day of screening, Day of study treatment initiation, Week 4, 12, 24, and 36, Week 52 or Day of discontinuation visit, Day of follow-up visit
Notes	・On the day of study treatment, assessment will be performed before the treatment. ・mRSS assessment will be performed by a skilled physician experienced in scoring skin sclerosis. ・In principle, the same investigator or subinvestigator will perform assessment throughout the study period for each participant in order to minimize inter-assessor variability.

9.3.4.2 Respiratory function test

Spirometry will be performed according to the separately specified procedure.

Assessment	• Forced vital capacity (FVC) and %FVC • Diffusing capacity of lung for carbon monoxide (DLco) and % DLco • Total lung capacity (TLC) and forced expiratory volume in one second (FEV_1)
Time points	Day of screening, Week 12, and 24, Week 52 or Day of discontinuation visit
Notes	• If the %FVC decreases by ≥ 15% from baseline, %FVC will be measured again within 1 month to examine whether the %FVC decreases by ≥ 15% from baseline or not.

9.3.4.3 Chest HRCT

HRCT will be performed according to the regulations or procedures or the test manual of the study site.

Time points	• Day of screening, Week 24, Week 52 or Day of discontinuation visit
Notes	If having been performed within 1 month of the specified timepoint, it is not necessary to be performed at the specified timepoints, and the results within 1 month will be substituted.

9.3.4.4 Severity of pulmonary lesions

The investigator or subinvestigator will evaluate the severity of pulmonary lesions based on the results of respiratory function test and chest HRCT according to 10.1.4 .

Time points	Day of screening, Week 24, Week 52 or Day of discontinuation visit

9.3.4.5 ACR-CRISS

The investigator or subinvestigator will assess whether the participant fall under the following criteria:

Evaluations	• Onset of scleroderma renal crisis • Interstitial lung disease with a decline in %FVC ≥15% (requiring reconfirmation within 1 month), and %FVC of 80% or less • Onset of left ventricular failure requiring treatment (defined as left ventricular ejection fraction ≤45%) * • Onset of pulmonary arterial hypertension requiring right heart catheterization * *Caused by SSc
Time points	Week 12 and 24, Week 52 or Day of discontinuation visit

9.3.4.6 The Number of Digital Ulcers

The investigator or subinvestigator will count the number of digital ulcers.

Time points	• Day of screening, Day of study treatment initiation, Week 12, 24 and 36, Week 52 or Day of discontinuation visit
Notes	• In principle, the same investigator or subinvestigator will perform assessment throughout the study period for each participant in order to minimize inter-assessor variability.

9.3.4.7 Patient-reported outcome

The participants will perform the following assessments:

Evaluations	HAQ-DI, FACIT-Fatigue and FSSG
Time points	Day of study treatment initiation, Week 12, 24, and 36, Week 52 or Day of discontinuation visit
Notes	・ The participants will perform each assessment before receiving the examination and evaluation by the physician at the above visits. ・ The investigator or subinvestigator must not attend the assessments by the participants.

9.3.4.8 Global improvement rating

9.3.4.8.1 Patient's Global Assessment (PtGA)

The participants will assess the overall condition of SSc using a visual analog scale (VAS).

Time points	Day of study treatment initiation, Week 12, 24, and 36, Week 52 or Day of discontinuation visit
Notes	・ The participants will perform each assessment before receiving the examination and evaluation by the physician at the above visits. ・ The investigator or subinvestigator must not attend the assessments by the participants.

9.3.4.8.2 Physician's Global Assessment (PGA)

The investigator or subinvestigator will assess the overall condition of SSc of each participant using a VAS.

Time points	Day of study treatment initiation, Week 12, 24, and 36, Week 52 or Day of discontinuation visit
Notes	・ In principle, the same investigator or subinvestigator will perform assessment throughout the study period for each participant in order to minimize inter-assessor variability.

9.3.5 Safety Evaluation

9.3.5.1 Vital signs

The investigator or subinvestigator will perform the following measurements:

Measurements	Body temperature, pulse rate, and blood pressure (systolic/diastolic)
Time points	Day of screening, Day of study treatment initiation, Week 1, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48, Week 52 or Day of discontinuation visit, Day of follow-up visit
Notes	・ On the day of study treatment, measurements will be performed, and the results will be reviewed before the treatment. ・ The vital signs will be measured at rest in the sitting position.

9.3.5.2 ECG

The investigator or subinvestigator will perform the following measurements:

Measurements	PR interval, QRS interval, QT interval, heart rate and presence or absence of abnormalities
Time points	Day of screening, Week 24, Week 52 or Day of discontinuation visit

Notes	・ On the day of study treatment, measurements will be performed, and the results will be reviewed before the treatment. ・ The same electrocardiograph will be used for each participant at each measurement whenever possible. ・ ECG will be performed at rest in the supine position.

9.3.5.3 Echocardiography

Echocardiography will be performed according to the regulations, procedures, or the test manual of the study site.

Time points	Day of screening, Week 24, Week 52 or Day of discontinuation visit
Notes	・ On the day of study treatment, measurements will be performed, and the results will be reviewed before the treatment.

9.3.5.4 Photography

The investigator or subinvestigator will perform photography according to the separately specified procedure.

Sites to be Photographed	1） Anterior and dorsal views of the upper body (excluding the face) 2） Skin appearance of adverse events
Time points	1） Day of study treatment initiation 2） Duration of the following adverse events (at least once occurrence) after study treatment initiation and at the final outcome evaluation: ・ Atopic dermatitis ・ Adverse events with skin symptoms accompanied by edematous erythema or scaling ・ Any other adverse event for which the investigator or subinvestigator considers that photography is necessary.
Notes	1) and 2): ・ The photos will be retained by the study site and collected by the sponsor. When personal information can be identified from the photos, the photos must be collected with the personal information being masked. ・ Photography will not be performed if refused by the participant.

9.3.6 Laboratory tests

Laboratory tests will be performed at the central laboratory. The investigator or subinvestigator will collect blood and urine samples from participants before study treatment initiation and submit them to the central laboratory. Tuberculosis test may be performed in an in-hospital laboratory.

1） Hematology and serum chemistry tests
2） Immunological tests (thymus and activation-regulated chemokines [TARC])
3） Urinalysis

Time points	Day of screening, Day of study treatment initiation, Week 1, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48, Week 52 or Day of discontinuation visit, Day of follow-up visit
Notes	1) 2) and 3): ・ On the day of study treatment, blood and urine will be collected before the treatment. ・ The test result should be reviewed before the next study treatment. 1) and 2): ・ When aggregation or coagulation is observed in “Plt” because of a reason other than manual technique, blood will be collected into a blood collecting tube containing 3.2% sodium citrate in addition to a conventional blood collection tube from the next visit.

4） Pregnancy test

Time points	Day of screening
Notes	・ The test will be performed on female participants. However, those who are considered unable to become pregnant (e.g., menopausal women* and women who have had total hysterectomy) will be excluded. *: Defined as those who are amenorrhea for at least 12 months without any medical reason.

5） Tuberculosis test

Time points	Day of screening
Notes	・ If the test cannot be performed on the day of screening, it may be performed on another day after the day of screening but before study treatment initiation. In such cases, the rest results should be reviewed before administration of IP on the day of study treatment initiation.

6） Hepatitis B and C tests

Time points	a） Day of screening b） Week 12, 24, 36 and 48, Day of follow-up visit
Notes	a） The participants who test negative for HBs antigen and positive for HBc antibody on the day of screening will undergo HBV-DNA measurement before the day of study treatment initiation. The participants who test positive for anti-HCV antibody on the day of screening will undergo HCV-RNA measurement before the day of study treatment initiation. b） The participants enrolled through HBV-DNA measurement before the day of study treatment initiation will undergo HBV-DNA measurement once every three months. The participants enrolled through HCV-RNA measurement before the day of study treatment initiation will undergo HCV-RNA measurement once every three months.

7） Antinuclear antibodies test

Time points	Day of study treatment initiation
Notes	・ Blood will be collected before administration of IP on the day of study treatment initiation

Table 9-2: Clinical Laboratory Assessments

Laboratory tests	Parameters
Hematology	Hb, Ht, Plt, RBC, WBC, differential leukocyte count, MCV, MCH, and MCHC
Serum chemistry	Na, K, Cl, UN, CREA, Ca, T-Bil, D-Bil, TP, ALB, ALT (GPT), AST (GOT), ALP, P, LDH, CK, UA, TC, LDL-C, HDL-C, TG, A/G ratios, γ-GTs, and CRP
Immunology	TARC
Urinalysis	Protein, occult blood, urinary sugar, and urobilinogen
Pregnancy	Urine hCG
Tuberculosis	Interferon gamma release assay (Central measurement: T-SPOT, in-house examination: T-SPOT or QFT-3G)
Hepatitis B and C	HBs antigen, HBc antibody, HBV-DNA, Anti-HCV antibody, and HCV-RNA
Antinuclear antibodies	Anti-Scl-70 antibodies, anti-centromere antibodies, and anti-RNA polymerase-III antibodies

9.3.7 Pharmacokinetics

The investigator or subinvestigator will collect blood samples for central measurement of serum drug concentrations.

To be measured	Serum concentration of nemolizumab
Time points	Day of study treatment initiation, Week 1, 2, 4, 8, 12, 16, 20, 24, and 36, Week 52 or Day of discontinuation visit, Day of follow-up visit
Notes	• On the day of study treatment, blood will be collected before the treatment.

9.3.8 Immunogenicity

The investigator or subinvestigator will collect blood samples for central measurement of serum anti-nemolizumab antibodies and neutralizing antibodies.

To be measured	Serum anti-nemolizumab antibodies and neutralizing antibodies
Time points	Day of study treatment initiation, Week 24 and 36, Week 52 or Day of discontinuation visit, Day of follow-up visit
Notes	• On the day of study treatment, blood will be collected before the treatment.

9.3.9 Biomarker measurement

The investigator or subinvestigator will collect blood samples for central measurement of serum biomarkers.

To be measured	1) IL-31 2) KL-6, SP-D, NT-proBNP 3) Exploratory biomarkers
Time points	1) Day of study treatment initiation, Week 4, 8, 12, 16, 20, 24, and 36, Week 52 or Day of discontinuation visit 2) Day of study treatment initiation, Week 4, 12, 24, and 36, Week 52 or Day of discontinuation visit 3) Day of study treatment initiation, Week 12 and 24, Week 52 or Day of discontinuation visit
Notes	1) 2) 3) :

	On the day of study treatment, blood will be collected before the treatment

9.3.10 Comprehensive measurement of autoantibodies

The investigator or subinvestigator will collect blood samples for comprehensive measurement of autoantibodies. The measurement will be performed centrally.

Time points	Day of study treatment initiation, Week 24, Week 52 or Day of discontinuation visit
Notes	• On the day of study treatment, blood will be collected before the treatment.

9.3.11 CyTOF measurement

The investigator or subinvestigator will collect blood samples for central measurement of CyTOF.

Time points	Day of study treatment initiation, Week 24, Week 52 or Day of discontinuation visit
Notes	• On the day of study treatment, blood will be collected before the treatment.

9.3.12 Assessment of Adverse Events

The investigator or sub-investigator will assess the adverse events according to the procedure described in "11.4 Review and reporting of adverse events."

9.3.13 Investigation of Malfunction of DCS

The investigator or subinvestigator will investigate malfunction of DCS according to "11.11 Malfunctions of DCS."

9.3.14 Amount of Blood and Urine Samples to be Collected

In principle, the amounts of blood and urine samples to be collected on each assessment day will follow Table 9-3 unless additional tests are required.

Table 9-3: Amount of blood and urine samples to be collected

1)		Day of screening*	Day of treatment initiation	Week 1	Week 2	Week 4	Week 8, 16 and 20	Week 12**	Week 24**, and Week 52 or Day of discontinuation visit	Week 28, 32, 40, 44 and 48**	Week 36	FU**
Amount of blood collected	Laboratory tests	17 mL	6 mL	6 mL	-	6 mL	6 mL	6 mL	6 mL	6 mL	6 mL	6 mL
	Serum nemolizumab concentration	-	3 mL	3 mL	3 mL	3 mL	3 mL	3 mL	3 mL	-	3 mL	3 mL
	Anti-nemolizumab antibody	-		-	-	-	-	-		-	-	
	Antinuclear antibodies test	-	6 mL	-	-	-	-	-	-	-	-	-
	Biomarker measurement	-	12 mL	-	-	9 mL	3 mL	12 mL	12 mL	-	9 mL	-
	Comprehensive measurement of autoantibodies	-	5 mL	-	-	-	-	-	5 mL	-	-	-
	CyToF measurement	-	5 mL	-	-	-	-	-	5 mL	-	-	-
Total amount of blood collected		17 mL	37 mL	9 mL	3 mL	18 mL	12 mL	21 mL	31 mL	6 mL	18 mL	9 mL
Amount of urine collected		10 mL	10 mL	10 mL	-	10 mL	10 mL	10 mL	10 mL	10 mL	10 mL	10 mL

* : The participants found to require measurement of HBV-DNA or HCV-RNA as a result of the hepatitis B and hepatitis C tests performed on the day of screening will need an additional 5 mL of blood to be drawn before the day of study treatment initiation.

** : The participants enrolled through HBV-DNA or HCV-RNA will need an additional 5 mL of blood to be drawn on Week 12, 24, 36 and 48, and on the day of follow up visit.

10. Efficacy Evaluation

10.1 Efficacy Assessments

10.1.1 Assessment of Skin Findings

1) Modified Rodnan Total Skin Thickness Score (mRSS)

The investigator or subinvestigator will assess the degree of skin thickening for each of 17 sites (fingers of both hands, dorsum of both hands, both forearms, both upper arms, face, anterior chest, abdomen, both thighs, both lower legs, and dorsum of both feet) with a 4-point scale from 0 to 3 according to Table 10-1 on each specified day of assessment. Total score will be 0 to 51.

Table 10-1 Scoring the degree of skin thickening by two-step pinching method

Score	Skin thickening	Broad pinching	Slight pinching	Skin thickness when pinched broadly
0	Normal	Possible	Possible	Not thick
1	Mild	Possible	Possible	Thick
2	Moderate	Possible	Impossible	Thicker
3	Severe	Impossible	Impossible	–

10.1.2 Respiratory Function Test

Spirographic examinations, including the flow-volume curve, lung volume measurements, and diffusing lung capacity for carbon monoxide (DL_{CO}) will be performed on each specified day of testing.

10.1.3 Chest HRCT

Chest HRCT will be performed to obtain visually the approximate ratios (HRCT extent) of interstitial opacities (ground-glass opacities, reticular shadows, honeycomb pattern and cystic shadows) with five slides of a) upper aortic arch, b) carina, c) pulmonary vein confluence point, d) midway between c) and e), and e) immediately above the right diaphragm, and their mean will be calculated.

The investigator or subinvestigator will assess in which of the following ranges the ratios are included; 20% or less (≤ 20%), more than 20% to 70% or less (> 20% to ≤ 70%), or more than 70% (>70%). In addition, in combination with FVC, each severity classification of lung disease will be determined according to 10.1.4 Severity Classification of Lung Lesion.

10.1.4 Severity Classification of Lung Lesion

The investigator or subinvestigator will assess the severity of lung lesions using the severity classification of lung lesions specified in the Guidelines for Diagnostic Criteria, Severity Classification and Clinical Practice of Systemic Sclerosis 2016[7] (see Figure 10-2). Respiratory function test results obtained according to Section 10.1.2 and chest CT images obtained according to Section10.1.3 will be used for this assessment.

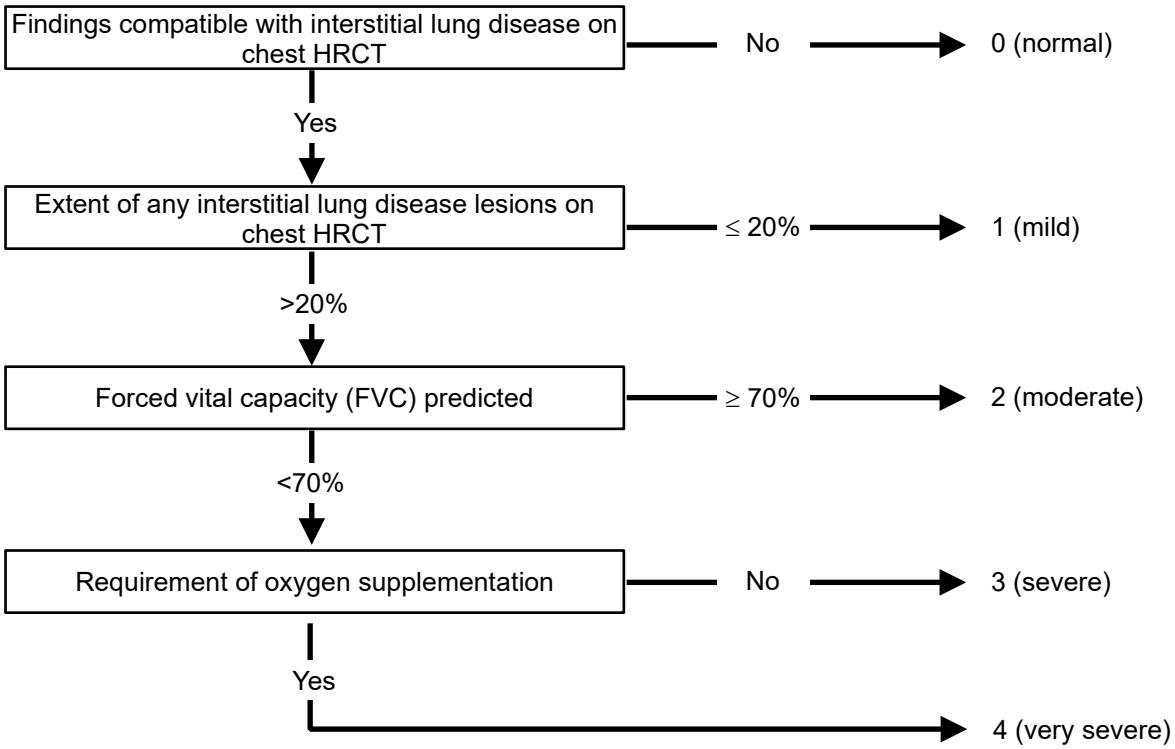


Figure 10-1　Severity classification of lung lesion

10.1.5 ACR-CRISS

ACR-CRISS is a composite outcome measure that is calculated as an index taking a value ranging from 0 to 1 for the probability of improving for participants based on the presence or absence of renal, pulmonary, and cardiac impairments and changes in the 5 core set items (mRSS, %FVC, PGA, PtGA, and HAQ-DI). Participants are considered improved and not improved when their ACR-CRISS is ≥ 0.6 and < 0.6, respectively. If participants meet any of the following criteria, the probability of improving is 0.0. The investigator or subinvestigator will assess whether participants met or not met the following criteria at specified visits. If patients do not meet any of the following criteria, an ACR-CRISS score will be calculated using the formula shown in 17.3.2 2).

- Onset of scleroderma renal crisis
- Decline in FVC% ≥15% (requiring reevaluation within 1 month), and %FVC of 80% or less
- Onset of left ventricular failure requiring treatment (defined as left ventricular ejection fraction ≤45%) *
- Onset of pulmonary arterial hypertension requiring right heart catheterization *

* Caused by SSc

10.1.6 The Number of Digital Ulcers

The investigator or subinvestigator will count the number of digital ulcers.

10.1.7 Patient-reported outcome

1）HAQ-DI

Participants will assess the degree of their difficulty in performing actions of eight functional categories (dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities) using HAQ-DI (Health assessment questionnaire disability index, Japanese version)[9] on a 4-point scale of 0 (Without any difficulty), 1 (Without some difficulty), 2 (Without much difficulty), and 3 (Unable to do).

2） FACIT-Fatigue

Participants will assess their fatigue over the past 7 days using FACIT-Fatigue Scale, Japanese version [10] on a 5-point scale from 0 (not at all) to 4 (very much).

3） FSSG.

Participants will assess their gastroesophageal reflux disease using Frequency Scale for the Symptoms of GERD (FSSG) [11] on a 5-point scale from 0 (never) to 4 (always).

10.1.8 Global improvement rating

1） PtGA

Participants will assess their general health status associated with SSc at visit using a 10-cm visual analog scale (VAS) from 0 (the best status) to 10 (the worst status) [12]. The investigator or subinvestigator or the clinical trial collaborator will measure the length (cm) from the left end to the first decimal place and record it.

2） PGA

The investigator or subinvestigator will assess participants' general health status associated with SSc in terms of Severity, Damage, and Overall disease using a 10-cm VAS from 0 (the best status) to 10 (the worst status) [12]. The investigator (or subinvestigator) or the clinical trial collaborator will measure and record the length (cm) from the left end to the first decimal place.

10.2 Efficacy Endpoints

10.2.1 Primary Endpoint

Change from baseline in mRSS at Week 24

10.2.2 Other Endpoints

1） Change from baseline in mRSS at Week 52
2） Change from baseline in HAQ-DI at Week 52
3） Change from baseline in HAQ-DI at Week 24
4） Change from baseline in %FVC at Week 52
5） Change from baseline in %FVC at Week 24
6） Change from baseline in DLco at Week 52
7） Change from baseline in DLco at Week 24
8） Change from baseline in PGA at Week 52
9） Change from baseline in PGA at Week 24
10） Change from baseline in PtGA at Week 52
11） Change from baseline in PtGA at Week 24
12） ACR-CRISS at Week 52
13） ACR-CRISS at Week 24
14） Change from baseline in the number of digital ulcers at Week 52

15） Change from baseline in the number of digital ulcers at Week 24
16） Time-course changes in the following parameters:
  a） HAQ-DI
  b） FACIT-Fatigue
  c） FSSG
  d） FVC
  e） %FVC
  f） DLco
  g） %DLco
  h） TLC
  i） FEV_1
  j） Severity assessment of lung lesion
  k） PGA
  l） PtGA
  m） ACR-CRISS
  n） The number of digital ulcers

10.3 Rationale for Efficacy Endpoints

1） mRSS

mRSS is used internationally to assess severity of SSc[13), 14)]. Moreover, mRSS is generally considered to be correlated with visceral involvement, etc. and change over a relatively short period of time by receiving treatment, etc. Therefore, change from baseline in mRSS at Week 24 has been selected as primary endpoint to evaluate the efficacy of this drug on SSc. Since SSc has a chronic course, change from baseline in mRSS at Week 52 has been also selected as an efficacy endpoint to discuss the clinical significance of this drug.

2） Respiratory Function Test

FVC in respiratory function tests has been shown to be a useful indicator for predicting vital prognosis in interstitial lung disease associated with SSc[15)] . %FVC and %DLco are useful parameters for screening pulmonary hypertension associated with SSc[16)]. Therefore, this test has been selected to evaluate the efficacy of this drug on lung lesion in an exploratory manner and to ensure the safety of participants.

3） Chest HRCT

Interstitial lung disease in SSc patients has been reported to be detected 50% to 60% by HRCT[17)]. Interstitial lung disease is the most common cause of death in SSc patients[18)]. Interstitial lung disease often occurs from the early stage of SSc, and therefore, it is useful to predict prognosis and determine whether the treatment is feasible for the patient. Moreover, the guidelines recommend to predict the risk of progression to end-stage pulmonary disease and determine whether the treatment is feasible for the patient by the fibrotic finding in HRCT and the extent of the lesion or of the entire lesion in conjunction with FVC-predicted values in respiratory function tests[7)]. Based on the above, this test has been selected to evaluate the efficacy of this drug on lung lesion in an exploratory manner and to ensure the safety of participants.

4） Severity Classification of Lung Lesion

The Guidelines for Diagnostic Criteria, Severity Classification and Clinical Practice of Systemic Sclerosis recommend to predict the risk of progression to end-stage pulmonary disease and determine whether the treatment is feasible for the patient by the fibrotic finding in HRCT, the extent of the lesion or of the entire lesion and FVC predictive value in respiratory function tests[7]. This parameter has been selected to evaluate the efficacy of this drug on lung lesion in an exploratory manner and to ensure the safety of participants.

5) ACR-CRISS

ACR-CRISS is a composite response index for clinical trials in early diffuse cutaneous SSc [19], which is generally used in clinical trials in SSc patients. This index has been selected to evaluate the efficacy of this drug on SSc in an exploratory manner.

6) The number of digital ulcers

Ulcers of the fingers and toes are complications of vascular disorder, one of the conditions of SSc, which occur frequently (35-60%) and arise from the early stage of the disease; therefore, they are considered to reflect the condition of SSc. Moreover, the ulcers are often refractory and recurrent, which is directly related to participants' activities of daily living (ADL) and decreased QOL. Accordingly, this parameter has been selected to evaluate the efficacy of this drug on SSc in an exploratory manner.

7) HAQ-DI

HAQ is a convenient self-administered questionnaire assessing physical function for activities of daily living. It was originally developed to evaluate the effect of rheumatoid arthritis on activities of daily living; however, it has been reported that HAQ-DI correlates with the degree of skin thickening, cardiac involvement, renal involvement, etc., also in SSc[20]. Moreover, along with mRSS, it is a widely used standard method to evaluate SSc. Based on the above, HAQ-DI has been selected to evaluate the efficacy of this drug on SSc in an exploratory manner.

8) FACIT-Fatigue

FACIT-Fatigue is a health-related quality of life that assesses fatigue and its impact on daily activities and functions in chronic diseases. Shortness of breath and fatigue occur in interstitial lung disease and pulmonary hypertension associated with SSc. FACIT-Fatigue has been proven to be reliable and useful in various diseases including SSc[10]. Thus, FACIT-Fatigue has been selected to evaluate the effects of this drug on fatigue and on daily living and functions in SSc, a chronic disease, in an exploratory manner.

9) FSSG

FSSG is a useful questionnaire to objectively assess the symptoms of Japanese participants with gastroesophageal reflux disease[11]. In SSc, esophageal involvement is complicated at a high rate from the early stage of the disease, and 80% to 90% of SSc patients have reflux esophagitis [1]. Esophageal involvements are also associated with the extent and duration of thickening[1]. Based on the above, FSSG has been selected to evaluate the efficacy of this drug on reflux esophagitis in SSc patients in an exploratory manner.

10) Global improvement rating (PtGA, PGA)

Global improvement rating is a widely used method to assess disease activity in clinical trials such as

in rheumatoid arthritis. This rating has been selected to evaluate the efficacy of this drug on SSc in an exploratory manner.

11. Safety Evaluation

11.1 Assessments for Safety Evaluations

1) Adverse events
   a) Symptoms and signs
   b) Abnormal laboratory test values
   c) Abnormal vital signs
   d) Abnormal electrocardiograms
2) Laboratory test values
3) Vital signs
4) Electrocardiograms
5) Echocardiography

11.2 Definition of Adverse Events

1) Adverse events (AEs)

An AE in the study will be defined as any undesirable or unexpected sign, symptom, disease, or aggravation of an existing condition occurring in a participant who is given an IP on or after the time of informed consent regardless of whether there is a causal relationship to the IP. The aggravation of diseases or symptoms that have occurred before the time of informed consent are also considered an AE.

The following events are not considered AE:

- Events for which medical treatment had been scheduled before the time of informed consent
- Aggravation of primary disease

2) Serious adverse events (SAEs)
   a) Results in death
   b) Is life-threatening
   c) Requires or prolongs inpatient hospitalization*

      *Excluding the following events;
      - Any hospitalization that had been scheduled before the time of informed consent (e.g., hospitalization for surgeries and detailed examinations)
      - Any hospitalization for examinations without any treatment (including bed rest treatment).
   d) Results in persistent or significant disability/incapacity
   e) Is a congenital anomaly/birth defect
   f) Is another medically important condition*

      *An important medical event that may not be immediately life-threatening or does not result in death or hospitalization but may jeopardize the safety of the patient or may require treatments to prevent one of the other outcomes listed in a) to e) above.

      e.g., bronchospasm requiring intensive care at an emergency room, blood dyscrasias or convulsions not leading to hospitalization, drug dependence, or drug abuse

3) Adverse events of special interest (AESIs)

AESIs in this study are defined as the following treatment-emergent events:

   a) AEs requiring discontinuation of study treatment

b） Injection-related reactions (including local and systemic injection site reactions)
Injection-related reactions are defined as AEs which develop within 24 hours after administration of IP.

c） Asthma

d） Atopic dermatitis

e） Skin symptoms with edematous erythema or scales

f） Skin infections

g） Non-skin infections

h） Suspected infection of infectious pathogen from the IP

・ Rationale for selection

b), c), d), f), and g)	These events should be monitored carefully because of being included in “important potential risks” in nemolizumab.
e)	These are events of interest closely monitored by the sponsor based on the results of clinical studies of nemolizumab in patients with atopic dermatitis
h)	The event should be carefully investigated in biological products in general.

11.3 Definitions of Safety Endpoints

1） Adverse events

a） Symptoms and signs
The investigator or subinvestigator will assess symptoms and signs in participants after the time of informed consent through the time of physical examination on the day of follow-up visit based on interview results and complaints from participants.

b） Abnormal laboratory test values
The investigator or subinvestigator will treat laboratory test results collected after the time of informed consent through the day of follow-up visit as AEs if the results meet any of the following criteria:

i. Accompanied with clinical symptoms
ii. Resulted in any change of study treatment (e.g., interruption or discontinuation of the IP).
iii. Resulted in medical treatment (including change of concomitant medications/therapies).
iv. Considered clinically significant by the investigator or subinvestigator.
v. Total bilirubin is >2-fold the upper limit of the reference value, and ALT or AST is >3-fold the upper limit of the reference value
vi. ALT or AST is >3-fold the upper limit of the reference value with clinical jaundice

Individual abnormal changes in laboratory test findings will be reported as individual AEs in principle. However, a single abnormal laboratory test finding or two or more abnormal laboratory test findings that are related to each other may be reported collectively as a single event under a single diagnosis if it is considered appropriate by the investigator or sub-investigator. If individual abnormal changes in laboratory test findings are regarded by the investigator or subinvestigator as manifestations of a symptom or a sign reported as an AE, the changes may be reported collectively with the AE of the symptom or sign.

Laboratory values may change depending on interindividual factors, such as sex, age, and lifestyle, and intraindividual factors, such as diurnal fluctuation, diet, exercise, body positioning, and sexual cycle. Therefore, the investigator or subinvestigator will determine whether the change in each laboratory test findings is a physiological change or an abnormal change after sufficiently taking into

consideration the demographics of each participant, such as the underlying disease and complication, baseline values, and the changes specific to each participant who have any periodic laboratory test before study participation.

c) Abnormal vital signs

The investigator or subinvestigator will treat measurement results collected after the time of informed consent through the day of follow-up visit as AEs if the results meet any of the following criteria:

i. Accompanied with clinical symptoms
ii. Resulted in any change of study treatment (e.g., interruption or discontinuation of the IP).
iii. Resulted in medical treatment (including change of concomitant medications/therapies).
iv. Considered clinically significant by the investigator or subinvestigator.

d) Abnormal electrocardiograms

The investigator or subinvestigator will assess AEs based on the results collected after the time of informed consent through the day of follow-up visit

e) Echocardiography

Echocardiographic images will be assessed for cardiac morphology, cardiac motion and blood flow during cardiac contraction and relaxation, and other parameters. The investigator or subinvestigator will record the presence or absence of abnormalities in the source documents.

11.4 Review and reporting of adverse events

The investigator or subinvestigator will assess the items shown in Table 11-1 regarding AEs occurring from after obtaining informed consent to the day of follow-up visit and fill the necessary information in the case report forms (CRFs).

The investigator or subinvestigator will report the SAEs according to Section 11.5 and the AESIs according to Section 11.6 to the sponsor. The investigator or subinvestigator will promptly report the other AEs to the sponsor.

Table 11-1 Assessments for adverse events

Assessments	Details of assessment	
Name of adverse event	Disease name/symptom, classification of the site of occurrence of adverse events	
Onset date	Classification of onset date, Onset date	
Action on investigational product	Treatment discontinuation, Treatment interruption, Dose reduction, No dose change, Not applicable, Unknown	
Treatment for the event	Presence or absence of treatment	
Outcomes and Date of outcome/Date of outcome obtained	Recovered/Resolved, Recovering/Resolving, Not Recovered/Not Resolved, Recovered/Resolved with sequelae, Death, and Unknown End date of AE, whether the AE is ongoing or not	
Severity	Mild	Transient, requiring minimal treatment and not interfering with daily life
	Moderate	Specified treatments relieve symptoms and do not result in permanent or significant disability but interfere with daily life
	Severe	Significant effect on advanced clinical condition or requiring intensive care or no longer allowing daily life.
Seriousness	Serious/Non-serious	
Definition of serious adverse events in Section 13.2	1. Results in death	
	2. Life-threatening	
	3. Requires or prolongs inpatient hospitalization	
	4. Results in persistent or significant disability/incapacity	
	5. Is a congenital anomaly/birth defect	
	6. Is another medically important condition	
Causal relationship with investigational product	Causality classification (according to the following causality classification), and rationale	
Causality classification*	Not related	Causal relationship is unlikely because the adverse event has no plausible temporal relationship to administration of IP, or the event can be explained by another factor. The rationale for no causal relationship is required to be described.
	Related	Causal relationship is presumed because there is a plausible temporal relationship between the onset of the adverse event and administration of investigational drug, and the event cannot be readily explained by another factor. The rationale for the causal relationship should be described if it is necessary to be explained.

*The following guidance can be taken into consideration on causality assessment: resolution of the event after discontinuation of IP; recurrence after restarting of IP; established causal relationship with IP or similar drugs; no confounding risk factors; consistency with the amount and duration of exposure to IP; almost clearly explainable involvement of the IP based on the correct past medical history; no reasonable possibility of causal relationship with concomitant therapy, etc.

11.5 Review and reporting of serious adverse events

1) The investigator will report any serious adverse events to the sponsor within 24 hours of getting to know the occurrence of the event. The investigator will report detailed information to the sponsor by using the “Report of Serious Adverse Events” form within 2 days of getting to know the occurrence of the event (the date the event was known is regarded as day 0). The study site’s own form may be used instead of the "Report of Serious Adverse Events". For additional reporting, new serious information (e.g., change in the name of the adverse event, causal relationship, outcome information, the severity category, etc.) should be reported to the sponsor according to the above rules when it becomes known.
2) The investigator will report the event to the study site according to the study site’s operating procedures.
3) The investigator will provide any additional information (e.g., autopsy reports, late-stage medical records, and other necessary information) on reported serious adverse events, as requested by the sponsor.

11.6 Reporting of adverse events of special interests (AESIs)

The investigator should report to the sponsor promptly when an AESI is noted. For atopic dermatitis and skin symptoms with edematous erythema or scaling, the necessary information (details of the symptoms/signs and the basis for determining the causal relationship with the IP) should be stated in the CRF. Any additional information should be provided, as requested by the sponsor.

At the time of physical examination on the day of follow-up visit, the final outcome of any AESI “not recovered/not resolved” falling under 1) below should be obtained according to 2). Concomitant medications and therapies will also be collected according to Sections 9.3.2.1 and 9.3.2.2 .

1) AESIs to be obtained
   a) AEs requiring discontinuation of study treatment
   b) Asthma
   c) Atopic dermatitis
   d) Skin symptoms with edematous erythema or scales
2) Period to obtain AESIs

   AESIs should be collected until the earlier of the following dates to obtain the final outcome information (the outcome and the date of outcome/outcome obtained).

   • Date of recovering or recovered
   • Date 6 months after the last dose of IP

11.7 Photography

Among AESIs, "atopic dermatitis" and "skin symptoms with edematous erythema or scales" will be photographed to examine the detailed skin findings of the events. Other adverse events of which the principal investigator or subinvestigator considers it necessary to take photographs will also be photographed.

The photographs taken will be used as a record of the occurrence of adverse event and a reference for safety evaluation.

11.8 Reporting of the Pregnancy of the Participant

1) If obtaining the information on the pregnancy of the participant who received the IP, the investigator or subinvestigator must immediately discontinue study treatment and take appropriate action for the participant, and follow up the participant until the completion of the pregnancy (e.g., delivery).
2) The investigator or subinvestigator will also report detailed information to the sponsor by using the “Report for Pregnancies during the Study” form.
3) Participant pregnancies are not regarded as adverse events.

11.9 Rationale for Safety Endpoints

1) In terms of safety protection of participants, it is considered decided that the echocardiography should be carried out periodically. Echocardiography is a useful examination for screening of pulmonary arterial hypertension caused by SSc, and the Guidelines for Diagnostic Criteria, Severity Classification and Clinical Practice of Systemic Sclerosisits recommends performing echocardiography. Pulmonary arterial hypertension caused by SSc has a poor prognosis and requires early detection

11.10 Follow-up of Adverse Events

For all adverse events developing during the study period (from the time of informed consent to the day of follow-up visit), the investigator or subinvestigator will provide appropriate treatments, and follow up until the event recovers to normal condition (within the reference ranges for laboratory test values), to the level before the consent was obtained, or until the investigator or subinvestigator considers that medical follow-up is no longer required. However, AESIs defined in Section 11.6 1) should be obtained according to Section11.6 even if the investigator or subinvestigator considers that their follow-up is not medically necessary.

11.11 Malfunctions of DCS

11.11.1 Reporting of Malfunctions of DCS

In the event of a malfunction of DCS, the principal investigator or subinvestigator will promptly report it to the sponsor according to the "Procedures for the Management of Investigational Products."

11.11.2 Collection and Reporting of Malfunction Information on DCS occurring at the Stage of Use on Participants

The principal investigator or subinvestigator will obtain the information shown in Table 11-2 on DCS malfunctions occurring after prescription to participants and record them in the CRFs

Table 11-2 Information to be obtained for DCS Malfunction Occurring after Prescription to Participants

Information	Details
Details of malfunction	Structural, material, functional defects, etc.
Presence or absence of SAEs (including possibility)	Presence or absence of SAEs or possibility of occurring SAEs due to malfunction
Date of incident	Date of incident
Presence or absence of AEs associated with the malfunction of DCS	Presence or absence of adverse events occurring associated with the malfunction of DCS

If a SAE occurs or may occur associated with a DCS malfunction, the SAE information together with the detailed information of the SAE will be sent to the sponsor in a "Serious Adverse Event and Malfunction Report" form to according to the procedures described in "11.5 Collection and Reporting of Serious Adverse Events." The "Serious Adverse Event and Malfunction Report" may be used in the form of the medical institution.

11.11.3 Storage of Malfunctioning DCS

The IP manager shall store malfunctioning DCSs appropriately at the study site, not discarding them.

11.12 Anticipated Adverse Drug Reactions

See the investigator's brochure of nemolizumab for anticipated adverse drug reactions of nemolizumab.

12. Biomarkers

12.1 Measurements of Biomarkers

1) Variable to be measured
   a) IL-31
   b) KL-6, SP-D, NT-proBNP
   c) Exploratory biomarkers

2) Collection of blood samples
   a) Blood samples will be collected on the day of study treatment initiation, at Week 4, 8, 12, 16, 20, 24, and 36, and Week 52 or on the day of visit for discontinuation. On the days of study treatment, blood samples will be collected before administration of IP.
   b) Blood samples will be collected on the day of study treatment initiation, at Week 4, 12, 24, and 36, and Week 52 or the day of visit for discontinuation. On the days of study treatment, blood samples will be collected before administration of IP.
   c) Blood samples will be collected on the day of study treatment initiation, at Week 12, 24, and Week 52 or the day of visit for discontinuation. On the days of study treatment, blood samples will be collected before administration of IP.

   The collected blood samples will be centrifuged to separate the serum, and the serum samples will be stored frozen until measured. The amount of blood collected, centrifugal conditions, and storage conditions are specified in a separate operating procedure.

12.2 Blood Biomarker Outcome Measures

1) Serum IL-31 level
   - Rationale for selection
     Since IL-31 is one of the cytokines considered to be involved in the disease state of SSc[8],this has been selected to evaluate the changes after administration of nemolizumab.

2) KL-6 and SP-D
   - Rationale for selection
     KL-6 and SP-D have been used as sensitive markers for interstitial pneumonitis in examination and measuring of disease progression or as a prognostic predictor in clinical practice. Moreover, increased levels of these have been reported to be associated with inflammatory pathological conditions such as ground-glass opacities on HRCT and elevated proportions of inflammatory cells in bronchoalveolar lavage fluid [21]. Based on the above, these have been selected in terms of safety protection of participants.

3) NT-proBN
   - Rationale for selection
     NT-proBNP is critical as a serological marker of pulmonary hypertension because it elevates in correlation with its severity in patients with SSc-PAH[22]. It is also important as a serological marker for overall some sort of because it elevates in the presence of any myocardial damage even without pulmonary hypertension[23]. Therefore, it has been set in terms of ensuring safety of participants.

4) Exploratory biomarkers

As exploratory biomarkers, IL-1α, IL-4, IL-6, IL-8, IL-13, IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, IL-17F, and IL-23 levels will be measured; however, cytokines for which adequate performance of the assay methods could not be validated will not be measured.

・ Rationale for selection

The major cytokines considered to be involved in pathological conditions of SSc have been selected to evaluate the changes after nemolizumab administration.

12.3 Measurement Method and Reporting of Results

1) Measurement methods

a) IL-31 and exploratory biomarkers will be measured using the Enzyme-Linked Immuno Sorbent Assay (ELISA) method. The measurements will be performed by [redacted] Corporation according to its assay protocol.

b) KL-6, SP-D and NT-proBNP will be measured by [redacted] Corporation according to its assay protocol.

c) Exploratory biomarkers will be measured using the Electro Chemi-Luminescence (ECL) method. The measurements will be performed by [redacted] Corporation according to its assay protocol.

2) Report of measurement results

a) IL-31, KL-6, SP-D, NT-proBNP and exploratory biomakers

[redacted] Corporation will prepare and submit a report of analysis results to the sponsor.

13. Pharmacokinetics

13.1 Pharmacokinetic Measurements

1) Variable to be measured

Serum concentration of nemolizumab

2) Collection of blood samples

Blood samples will be collected on the day of study treatment initiation, at Week 1, 2, 4, 8, 12, 16, 20, 24, and 36, Week 52 or on the day of visit for discontinuation, and on the day of follow up. On the days of study treatment, blood samples will be collected before administration of IP.

The collected blood samples will be centrifuged to separate the serum, and the serum samples will be stored frozen until measured. The amount of blood collected, centrifugal conditions, and storage conditions are specified in a separate operating procedure.

13.2 Pharmacokinetic Outcome Measures

1) Serum concentration of nemolizumab

2) Pharmacokinetic parameters: C_{max}、t_{max}、$AUC_{0\text{-}28day}$、AUC_{last}

・ Rationale for selection

Parameters necessary and evaluable to examine pharmacokinetics of nemolizumab have been selected in reference to “Clinical pharmacokinetic studies on drugs (PFSB/ELD No.796 of June 1, 2001).”

13.3 Measurement Method and Reporting of Results

1) Measurement method

Serum concentration of nemolizumab will be measured using the ELISA method. The measurements will be performed by [redacted] Laboratories, Ltd. according to its assay protocol.

2） Report of measurement results

[redacted] Laboratories, Ltd. will prepare and submit a report of analysis results to the sponsor.

14. Immunogenicity

14.1 Immunogenicity Measurements

1） Variable be measured

Serum anti-nemolizumab antibody

2） Collection of blood samples

Blood samples will be collected on the day of study treatment initiation, at Week 24 and 36, Week 52 or on the day of visit for discontinuation, and on the day of follow up. On the days of study treatment, blood samples will be collected before administration of IP.

The collected blood samples will be centrifuged to separate the serum, and the serum samples will be stored frozen until measured. The amount of blood collected, centrifugal conditions, and storage conditions are specified in a separate operating procedure.

14.2 Immunogenicity Outcome Measures

1） Serum anti-nemolizumab antibody

2） Neutralizing antibody concentrations

・ Rationale for selection

The variables have been selected to evaluate the effects of the development of anti-nemolizumab antibodies to efficacy and safety in participants.

14.3 Measurement Method and Reporting of Results

1） Measurement method

The serum anti-nemolizumab antibody will be measured using the ECL method. When anti-nemolizumab antibodies are detected, their characteristics will be determined using the cell-based assay (CBA) method. The measurement will be performed by [redacted] Corporation according to its assay protocol.

2） Report of measurement results

[redacted] Corporation will prepare and submit a report of analysis results to the sponsor.

15. Comprehensive Measurement of Autoantibodies

Comprehensive measurement of autoantibodies will be performed to determine the disease state of SSc and explore the patient-group for whom nemolizumab is effective.

15.1 Measurement Method and Reporting of Results

1） Collection of blood samples

Blood samples will be collected on the day of study treatment initiation, at Week 24, and Week 52 or on the day of visit for discontinuation. On the days of study treatment, blood samples will be collected before administration of IP.

The collected blood samples will be centrifuged to separate the serum, and the serum samples will be stored frozen until measured. The amount of blood collected, centrifugal conditions, and storage

conditions are specified in a separate operating procedure.

2) Measurement method
Autoantibodies will be measured comprehensively using HuPEX™ protein array. The measurement will be performed by [redacted] Corporation according to its assay protocol.

3) Report of measurement results
[redacted] Corporation will prepare and submit a report of analysis results to the sponsor. Measurement results will not be included in the clinical study report and will be summarized in a separate report.

16. CyTOF measurement

CyTOF measurement will be performed to explore the mechanism of action of nemolizumab in SSc.

16.1 Measurement Method and Reporting of Results

1) Collection of blood samples
Blood samples will be collected on the day of study treatment initiation, at Week 24, and Week 52 or on the day of visit for discontinuation. On the days of study treatment, blood samples will be collected before administration of IP.
PBMC preparation of collected blood samples will be performed by the day following sample collection. The amount of blood to be collected and storage conditions are specified in a separate operating procedure.

2) Measurement method
Measurement will be performed by [redacted], Inc. according to its assay protocol.

3) Report of measurement results
[redacted], Inc. will prepare and submit a report of analysis results to the sponsor. Measurement results will not be included in the clinical study report and will be summarized in a separate report.

17. Statistical Analysis

The major plans for statistical analyses are presented below. The details are provided in the Statistical Analysis Plan. This plan will be fixed prior to database lock on through discussions on data review etc.

17.1 Analysis Sets

17.1.1 Efficacy Analysis Set (Full Analysis Set: FAS)

The efficacy analysis set includes all participants assigned to treatment except for those who meet any of the following criteria:

1) Participants who are found not to have SSc
2) Participants who have received no dose of nemolizumab at all after assigned to treatment
3) Participants with no efficacy data at all after assigned to treatment

17.1.2 Safety Analysis Set

The safety analysis set includes all participants assigned to treatment except for those who meet any of the following criteria:

a） Participants who have received no dose of nemolizumab at all after assigned to treatment

2） Participants with no safety data at all after assigned to treatment

17.1.3 Pharmacokinetics Analysis Set

The pharmacokinetics analysis set includes all participants assigned to treatment except for those who meet any of the following criteria:

1) Participants who have received no dose of nemolizumab at all after assigned to treatment

2) Participants with no pharmacokinetic data at all after assigned to treatment

17.1.4 Biomarker Analysis Set

The biomarker analysis set includes all participants assigned to treatment except for those who meet any of the following criteria:

1) Participants who have received no dose of nemolizumab at all after assigned to treatment

2) Participants with no biomarker data at all after assigned to treatment

17.2 Data Handling

17.2.1 Common Rules

a） Handling of missing values

The missing values will not be imputed.

2） Handling of data on the day of visit for discontinuation

The data measured or evaluated on the day of visit for discontinuation will be handled as the data of the relevant evaluation period if the visit is within the allowance of any visit for evaluation period. However, such data will not be included in the analysis if another data has been obtained in the relevant evaluation period.

17.2.2 Data Handling on Pharmacokinetics

1) Handling of values below the lower limit of quantification (BLQ) and missing values for serum drug concentration data

Values BLQ will be handled as follows and missing values will not be imputed.

a) Tabulation: They will be reported as BLQ.

b) Changes over time and profiles and summary statistics: They will be replaced by 0. However, if the number of participants with BLQ values exceeds half number of participants in pharmacokinetic analysis set, the summary statistics of serum drug concentrations at that time point will not be calculated and reported as N.C. (not calculated).

2) Handling of pharmacokinetic parameters not calculable

Parameters not calculable should be handled as follows:

a) Tabulation: They will be reported as N.C.

b) Summary statistic: They will be left missing. However, if the number of unevaluable participants for a pharmacokinetic parameter exceeds half of participants to be evaluated, the summary statistic of the parameter will not be calculated and reported as N.C.

17.3 Statistical Analysis Plan

The statistical analysis plan is described below. Unless otherwise stated, continuous variables are summarized by number of participants, mean and its standard deviation, minimum value, 25% percentile, median value, 75% percentile, and maximum value, while categorical variables are summarized by the number and percentage of participants in each category.

17.3.1 Demographic and Other Baseline Characteristics, and Severity of Primary Disease

Demographic and other baseline characteristics and severity of primary disease will be summarized, or the summary statistics will be calculated on the FAS.

17.3.2 Efficacy Analysis

This study will be conducted to evaluate the efficacy of nemolizumab in SSc patients with moderate to severe skin thickening in an exploratory manner.

1) Analysis of the primary endpoint: Change from baseline in mRSS at Week 24
   Summary statistics will be calculated for mRSS at Week 24 and the change from baseline.

2) Summary of continuous data
   The following analyses will be performed on the FAS:
   - Summary statistics will be calculated for the following variables and indicators at each time point.
   - The scores or measurements of the following variables will be used to create a spaghetti plot for each participant

Variable	Indicator
mRSS Physician's Global Assessment Patient 's Global Assessment	Score Changes from baseline Percent change from baseline
HAQ-DI FACIT-Fatigue FSSG FVC % FVC DLco %DLco TLC FEV_1 The number of digital ulcers	Score or measurement Change from baseline
ACR-CRISS (Only Week 12, 24 and 52) Severity Classification of Lung Lesion (Figure 10-1)	Score

ACR CRISS is calculated using the following formula.:

$$\frac{\exp\left(-5.54 - 0.81 \times \Delta_{\mathrm{mRSS}} + 0.21 \times \Delta_{\mathrm{FVC\%}} - 0.40 \times \Delta_{\mathrm{pt-glob}} - 0.44 \times \Delta_{\mathrm{MD-glob}} - 3.41 \times \Delta_{\mathrm{HAQ-DI}}\right)}{1 + \exp\left(-5.54 - 0.81 \times \Delta_{\mathrm{mRSS}} + 0.21 \times \Delta_{\mathrm{FVC\%}} - 0.40 \times \Delta_{\mathrm{pt-glob}} - 0.44 \times \Delta_{\mathrm{MD-glob}} - 3.41 \times \Delta_{\mathrm{HAQ-DI}}\right)}$$

Δ_{mRSS}: mRSS change
$\Delta_{\mathrm{FVC\%}}$: Percent FVC change
$\Delta_{\mathrm{pt-glob}}$, $\Delta_{\mathrm{MD-glob}}$: Patient's / Physician's Global assessment change (cm)
$\Delta_{\mathrm{HAQ-DI}}$: HAQ-DI Score change

The score of participants occurring any of the following events is 0:
・Onset of scleroderma renal crisis
・Decline in FVC% ≥15% (requiring reevaluation within 1 month), and %FVC of 80% or less
・Onset of left ventricular failure requiring treatment (defined as left ventricular ejection fraction ≤45%) *
・Onset of pulmonary arterial hypertension requiring right heart catheterization *
*Caused by SSc

17.3.3 Safety Analysis

The following variables will be summarized on the safety analysis set:

1) Adverse events

The following data will be collected and tabulated for AEs and separately for the treatment-related AEs.

a) The number of participants included in the safety analysis set, and the number of participants with, and the number of occurrences of AEs, AEs by severity (mild, moderate, and severe), SAEs (total, fatal, and non-fatal), and AESIs will be calculated.
b) The number of participants with AEs will be calculated by SOC and PT using MedDRA/J.
c) For AESIs, the number of participants with AESIs, the number of participants with AESIs by PT will be calculated by the category.

2) Laboratory test values

a) Laboratory test values throughout the treatment period

For the continuous variables, summary statistics will be calculated by laboratory parameter and time point. For the categorical variables, the number of participants will be calculated by category. The percentage of participants will be calculated using the number of observed participants at each time point.

b) Changes in individual participants during the treatment period

A spaghetti plot will be created for each participant using individual test values by laboratory parameter of continuous variables.

3) Vital signs, physical findings, and other assessments related to safety

a) Vital signs, electrocardiogram and echocardiography throughout the study period

For the continuous variables, summary statistics will be calculated by vital sign, electrocardiogram parameter, and echocardiography parameter. For the categorical variables, the number and percentage of participants will be calculated by category. The percentage of participants will be calculated using the number of observed participants at each time point.

17.3.4 Analyses of Drug Concentrations and Pharmacokinetic Parameters

The following variables will be summarized on the pharmacokinetic analysis set.

1) Serum concentrations of nemolizumab

a) Summary statistics including coefficient of variation and geometric mean of serum nemolizumab concentrations will be calculated by time point.
b) The serum nemolizumab concentration-time profile will be created using mean serum drug concentrations and their standard deviations.
c) The serum nemolizumab concentration-time profile will be created by participant.
d) The serum nemolizumab concentration-time profile will be created by participant where participants who tested positive for the first time after study treatment (in blue), those who had tested positive since before treatment (in red), and those who tested negative at all time points (in black) for anti-nemolizumab antibodies in serum in the confirmatory test will be identified by color.

2) Pharmacokinetic parameters (C_{max}, t_{max}, $AUC_{0\text{-}28Day}$, and AUC_{last})

Summary statistics including coefficient of variation and geometric mean of parameters will be calculated.

17.3.5 Analysis of Immunogenicity

The following variables will be tabulated from the pharmacokinetics analysis set.

1) Serum anti-nemolizumab antibody
   a) The percentage of participants with positive serum anti-nemolizumab antibodies will be calculated by test (Screening, Confirmatory, and Neutralizing) and time point. The positive rate in the Confirmatory test and the Neutralizing test is based on the number of participants having undergone the screening test.
   b) The number of and the percentage of participants who tested positive for anti-nemolizumab antibodies will be determined in this study. According to Shankar's definition,[24] among participants who tested positive for anti-nemolizumab antibodies for the first time after study treatment or both before and after study treatment, a positive participant is defined as a participant with a ≥ 4-fold increase in difference in antibody titer.

17.3.6 Analysis of Biomarker

Details will be described in the Statistical Analysis Plan.

17.4 Determination of Sample Size

17.4.1 Target Sample Size

The target sample size for this study is 8 participants.

17.4.2 Rationale for Sample Size

The number of participants required to determine the efficacy of this drug for SSc was set at 8. Since no statistical evaluation is planned, the number is not based on the level of significance and power.

17.5 Data Review

Data review will be performed before data fixation. In the data review, the appropriateness of data handling and analysis methods, etc., will be examined, and analysis sets, data handling, and an analysis plan will be determined. If a change in the statistical analysis plan is required after data review, the statistical analysis plan will be revised and documented.

18. Agreement on the Protocol and Protocol Deviation/Amendment

18.1 Agreement of and Compliance with the Protocol

The investigator will, before the sponsor requests to conduct the study at the study site, agree in writing with the sponsor on the contents of the protocol and conducting the study in compliance with the protocol. The investigator will do the same when the protocol is revised through discussion with the sponsor or according to the instructions of the head of the study site on the basis of the opinion of the institutional review board (IRB).

18.2 Protocol Deviation/Amendment

1) The investigator or subinvestigator should not deviate from or amend the protocol without prior written agreement with the sponsor and without written approval based on a prior review by the IRB. However, the investigator or subinvestigator may deviate from or amend the protocol without prior agreement with the sponsor or without prior approval from the IRB in the following cases where:
    a) it is medically unavoidable to avoid immediate danger to a participant
    b) it is on administrative matters of the study (e.g., change of the name of study site, change of the address or phone number of study site, and change of job title of the investigator)

2) The investigator or subinvestigator will record all deviations from the protocol. The investigator will prepare a document only for deviations from the protocol to avoid immediate danger to the participant with the reason for deviation or for other medically unavoidable reasons and immediately submit it to the sponsor and the head of the study site. The investigator will also submit the document to the IRB via the head of the study site, obtain approval from the IRB, and obtain in writing approval of the head of the study site and agreement of the sponsor.

3) If the protocol amendment is appropriate when the investigator is unable to comply with the protocol to avoid any immediate hazard to participants or due to other unavoidable medical reasons, the investigator will submit a draft amendment to the protocol to the sponsor as soon as possible to obtain written approval of the sponsor. Furthermore, the investigator will submit a draft amendment to the protocol to the head of the study site, obtain approval from the IRB and the head of the study site.

19. Case Report Form

The EDC system (Table 19-1) will be used in this study. The original CRFs will be those generated in the EDC system. The validated EDC system will be used in this study.

The data and audit trails entered in EDC system by the investigator, subinvestigator involved in CRF preparation, and CRCs are stored in the EDC server.

Table 19-1 EDC system

Name of EDC system	[redacted]
Name of EDC system development Company	[redacted]
Input method	Data entry via the web
Input terminal	Personal computer available at study sites

19.1 Data to be collected in CRF

The data to be collected in the CRFs is shown below.

19.1.1 Participants assigned to treatment

1) Date of written informed consent
2) Visit dates
3) Participant demographics
4) Major therapies received for SSc in the past
5) Inclusion and exclusion criteria
6) Complications
7) Concomitant Medications/Concomitant Therapies
8) Patient-reported Outcomes
9) Global improvement rating
10) mRSS
11) The number of digital ulcers
12) Respiratory function test
13) Electrocardiogram
14) Echocardiography
15) HRCT
16) Severity of pulmonary lesions
17) ACR-CRISS
18) Vital signs
19) Body weight
20) Laboratory tests
21) Biomarkers
22) Serum nemolizumab levels
23) Immunogenicity measurement
24) Comprehensive measurements of autoantibodies
25) CyTOF measurement
26) Dosing status of IP
27) Adverse events

    Information on outcome of an adverse event is to be collected until the follow-up visit.
28) The details of adverse events of atopic dermatitis and skin symptoms with edematous erythema or

scaling as well as the basis for determining the causal relationship with the IP

29) Malfunction of DCS

30) Status of study entry after screening, enrollment, completion/discontinuation of the study
completion status of study entry after screening, completion status of enrollment, study completion status, date of completion, date and reason for discontinuation if discontinued, and impact of COVID-19

31) Follow-up visit
Whether there was a follow-up visit or not, date of follow-up visit, date of determination and reason if no follow-up visit, and impact of COVID-19

32) Others
   a) Comment on each assessment
   b) Unscheduled visits

19.1.2 Participants Who Discontinue the Study before study entry after screening and those Who Discontinue the Study before enrollment

The following data will be collected and documented in the CRF for respective participants:

1) to 6) for participants having discontinued the study before study entry after screening

1) to 6) and 7) to 16) for participants having discontinued the study before enrollment

1) Date of written informed consent
2) Visit dates
3) Participant demographics
4) Inclusion and exclusion criteria
5) Adverse events
6) Date of and reason for discontinuation
7) mRSS
8) The number of digital ulcers
9) Respiratory function test
10) Vital signs
11) Body weight
12) Severity of pulmonary lesions
13) HRCT
14) Echocardiography
15) Electrocardiograms
16) Laboratory tests

19.2 Source Data for Information Entered in Case Report Form

Source data for information entered in the case report forms are as follows:

1) Medical records
2) Laboratory test slips
3) Serious Adverse Event Report (copy)
4) Serious Adverse Event and Device Malfunction Report (copy)
5) Informed consent forms
6) Participant screening logs
7) IP accountability records
8) ECG measurement results

9） Respiratory function test
10） Patient QOL questionnaire (paper)

19.3 Information in the Case Report Forms Treated as Source Data

Any information of the following items described only in the CRF will be treated as the original data.

1） Presence or absence of data for each item
2） Indication of drug/therapy
3） Seriousness and severity of adverse event, causality of adverse event to IP, and presence or absence of abnormal laboratory changes
4） Date of and reason for study discontinuation
5） All comments

19.4 Guidelines for Preparation of Case Report Form

The investigator, subinvestigator involved in CRF preparation, and CRCs will have to receive training before preparing CRFs. The sponsor will create an account management table to specify the authority given to each person in the place of a list of signatures/seals.

1） The investigator or subinvestigator will accurately prepare CRFs based on the source documents of enrolled participants according to the “Guidance for CRF Preparation.”
2） The investigator or subinvestigator will promptly prepare the CRF once the evaluation of the participant at each visit is completed.
3） CRCs may fill out or transcript and correct CRFs on the basis of the source documents. The investigator will review the entries, transcriptions, and corrections made by CRCs and electronically sign the CRFs.
4） The investigator will review the CRFs prepared at the study site and electronically sign the CRFs.
5） The investigator will submit the CRFs to the sponsor. In addition, the investigator will obtain a copy of the CRFs from the sponsor at the end of the study and retain them electronically.
6） If data in the CRF shows a discrepancy with the source document, the investigator will prepare a document explaining the discrepancy and submit it to the sponsor. The investigator will also retain a copy of the record.

19.5 Modification and Amendment to Case Report Forms

1） The investigator, subinvestigator, or CRCs will amend the CRFs according to the “Guidance for CRF Preparation” provided by the sponsor.
2） The investigator will review the modifications or amendments made by the subinvestigator or, CRCs and electronically sign the CRF.

20. Follow-up report of adverse events of special interest

For adverse events of interest falling under those specified in Section 11.6 1) which are “not recovered/not resolved” at the time of physical examination on the day of follow-up visit, the investigator will report their following information from after the physical examination of the follow-up visit to the time of obtaining the final outcome in the format separately specified by the sponsor.

1） Outcome and date of outcome/date of outcome obtained
2） Drugs used for the adverse event
3） Therapies performed for the adverse event

21. Direct Access to Source Documents

The investigator, subinvestigator, and the head of the study site will allow study monitoring, the sponsor's audit, and inspections by the IRB and regulatory authorities, and their direct access to all study-related documents, including the source documents.
When regulations on direct access are stipulated at the study site, they will be followed.

22. Quality Control and Quality Assurance

Risk management of this study will be performed based on the risk management plan prepared according to the standard operating procedures of [redacted]

1) Monitoring
The CRA will request the investigator and subinvestigator, etc. to comply with the GCP, related regulatory notifications, and study protocol throughout the study period, and will then assess their compliance. If any deviation from the GCP, related regulatory notifications, and the study protocol is found by monitoring, the CRA will inform the investigator immediately and the head of the study site as necessary and take appropriate measures to prevent the recurrence of the deviation. Furthermore, on the basis of direct access to the source documents, the CRA will verify whether the CRFs are completed accurately and are consistent with the source documents.

2) Quality control
a) Standardization of assessments
Prior to the start of the study, the sponsor will explain the standards of the assessment and the protocol to the investigator and subinvestigator, etc.

3) Quality control of CRF data
The quality control of CRF data will be performed according to the SOPs of Maruho Co., Ltd. When necessary, a case review meeting may be held by the medical expert and the sponsor to determine the handling of individual cases.

4) Audit
The auditor will assess whether the study is being conducted in accordance with GCP, the protocol, and relevant operating procedures separately and independently from the monitoring and quality control activities performed by the clinical study department. The auditor will also assess whether the study is being conducted properly and that the reliability of the study data is being maintained by direct access to study-related documents and records or other methods.

23. Completion, Discontinuation, or Interruption of the Study

23.1 Completion of the Study

Upon the completion of the study, the investigator will report the completion and a summary of study results in writing to the head of the study site. Once receiving the report of study completion from the investigator, the head of the study site will notify the IRB and the sponsor of the fact the summary of study results.

23.2 Discontinuation or Interruption of the Study

The investigator will, when interrupting or discontinuing the study at his/her own discretion, promptly report it and the reason in writing to the head of the study site. Once receiving the report of study discontinuation

or interruption from the investigator, the head of the study site will promptly notify the IRB and the sponsor of the fact and the reason in writing.
The sponsor will, when deciding the discontinuation or interruption of the study or the termination of development of the IP, promptly notify the head of the study site of the fact and the reason in writing. Once receiving a notification of interruption or discontinuation of the study or the termination of development from the sponsor, the head of the study site will promptly notify the investigator and the IRB of the fact and the reason in writing.

24. Archiving of Records

1) Study site
The head of the study site should retain the documents and records related to this study to be archived at the study site (hereinafter, the study-related records) until the elapse of 15 years after either the date of the marketing approval of the investigational drug or the date of decision of discontinuation of the development of the investigational drug.
For archiving the study-related records, the head of the study site will assign a storage manager. The head of the study site and the storage manager must take necessary measures so that these records are not lost or disposed of during the retention period and that they can be presented at the request of the sponsor, regulatory authorities, etc.
When the retention period of records to be archived at the study site expires, the sponsor will promptly notify the head of the study site of the fact.

2) Sponsor
The sponsor should retain the study-related records to be archived at the sponsor site until the elapse of 15 years after either the date of the marketing approval of the investigational drug or the date of the decision of discontinuation of the development of the investigational drug.

25. Publication Policy

1) The study site may not disclose or divulge data on the study provided by the sponsor or information such as study results to any third party without prior permission of the sponsor. If intending to publish the information obtained from the study to external parties such as academic conferences, the study site must obtain prior permission from the sponsor.
2) The founder of the IRB shall accept the sponsor's request (if any) for prior checking of a summary of the meeting minutes specified in Article 28, Paragraph 2-6 of the GCP to ensure the summary does not include the description infringing on the sponsor's intellectual property rights. When necessary, the founder may publish the summary after taking appropriate measures such as data masking.
3) The sponsor may freely use information obtained from this study for application for marketing approval for the test drug, product summary, promotional materials, publications, presentations at academic societies, and other materials to be submitted to the Ministry of Health, Labour, and Welfare.
4) When publishing information, sufficient attention must be paid to participant privacy.

26. Use of study-related data

1) The sponsor may use information obtained from this study (the study-related data) for application for marketing approval for the test drug, product summary, promotional materials, publications, presentations at academic societies, and other materials to be submitted to the Ministry of Health, Labor, and Welfare.
2) The sponsor may use the study-related data for the research and development of other than the test

drug and otherwise academic research when considered necessary.

27. Ethics

27.1 Institutional Review Board

Prior to the execution of the clinical study agreement, the IRB will review the contents of the protocol, informed consent form, and other explanatory documents, as well as the appropriateness of conducting the study. After the execution of the clinical study agreement, the IRB will continuously review the appropriateness of continuing the study.

27.2 Ethical Conduct of the Study

This study shall be conducted in compliance with the Ministerial Ordinance on Good Clinical Practice for Drugs and related notifications, the ethical principles based on the Declaration of Helsinki, and the protocol.

27.3 Protection of Participants' Confidentiality

To protect the participants' confidentiality, the investigator or subinvestigator will use participant identification codes instead of names to identify participants when completing CRFs and reporting adverse events and other study-related data to the sponsor. The sponsor's CRA and auditors will similarly protect any confidential participant information obtained during the course of the study in accordance with the provisions of Article 80-2, Paragraph 10 of the Act on Securing Quality, Efficacy, and Safety of Products Including Pharmaceuticals".

27.4 Participant Selection and Informed Consent

27.4.1 Participant Selection

During the selection of participants, the investigator or subinvestigator should carefully consider the advisability of asking for a patient to participate in the study taking into consideration the health condition, symptoms, age, sex, ability to consent, dependency on the investigator or subinvestigator, and status of participation in other clinical studies from the viewpoints of human rights protection and based on the protocol-specified inclusion and exclusion criteria. If a patient who is visiting another hospital is enrolled in the study, the investigator or subinvestigator will consider eligibility for study participation after examining the details of the medical treatment.

27.4.2 Informed Consent

1) Prior to the assessment for study participation, the investigator or subinvestigator will fully explain the study to each participant by using the informed consent form and other explanatory documents that describe the items provided in "27.4.3 Explanations to Participants." After this explanation, written voluntary consent to participate in the study will be obtained from the participant personally.
2) In cooperation with the sponsor, the investigator will prepare the informed consent and other explanatory documents that will be used to obtain the participants' consent to participate in the study and revise them as needed. The prepared or revised informed consent form and other explanatory documents should be approved by the IRB before use.
3) The investigator will comply with the ethical principles when preparing or revising the informed consent form and other explanatory documents.
4) The investigator or subinvestigator who provided the explanation, and the participant will each sign and date on the informed consent form. If a CRC makes a supplemental explanation, the CRC will also sign and date on the form.
5) The investigator or subinvestigator will provide the participant with the signed and dated informed

consent form (copy), and other explanatory documents before the participant participates in the study.

6) The investigator, subinvestigator, and CRC should not put pressure or unjustified influence on the participants to participate or continue participating in the study.
7) The informed consent form and other explanatory documents for the participants or information provided orally when explaining the study must not contain any words or suggestions that cause the participants to relinquish their rights. Furthermore, the consent materials and explanation must not contain any words or suggestions that absolve the investigator, subinvestigator, CRC, study site, or sponsor of their legal responsibilities.
8) Nontechnical vocabulary that the participants can understand should be used as much as possible during the verbal explanation and in written explanation and the informed consent form.
9) The investigator or subinvestigator will provide the participant with the opportunity to ask questions and sufficient time to decide whether to participate in the study before obtaining the participant's consent. The investigator, subinvestigator, or CRC (as someone providing additional explanation) must answer all questions to the satisfaction of the participant.
10) If information is obtained that could potentially affect the participants' willingness to continue participating the study, the investigator or subinvestigator must promptly give the information to the participants and ask whether the participants are willing to continue participating the study. In such cases, the fact that this information has been given to the participants will be recorded in the source documents.
11) If significant new information that may be related to the participants' consent is obtained, the investigator should promptly revise the informed consent form and other explanatory documents for the participants on the basis of this information.
12) When the informed consent form and other explanatory documents for participants are revised, the investigator or subinvestigator will promptly give the information which the amendment is based on to participants and ask whether the participants are willing to continue participation in the study. Furthermore, the investigator or subinvestigator will again explain the study using the revised informed consent form and other explanatory documents for participants and obtain voluntary written informed consent to continue participation in the study from each participant. The investigator or subinvestigator will provide the participants with the newly signed and dated revised informed consent form (copy) and the other explanatory documents.

27.4.3 Explanations to Participants

1) This study is being conducted for the purpose of investigation (i.e., this study involves research).
2) Study objective
3) Name, job title, and contact information of the investigator.
4) The study method (including the investigative aspect of the study, the participant inclusion criteria, and the probability of being assigned to each treatment)
5) The expected benefits to the participant's physical and mental health and the expected disadvantages to the participant of the IP
6) The presence or absence of other treatments available to the participant and the expected important benefits and risks of the treatments
7) The participant's scheduled duration of participation in the study
8) Participation in the study is voluntary, and the participant can refuse or withdraw consent to participate in the study at any time.
9) The participant will not undergo any disadvantages as a result of refusing or withdrawing consent to

participate in the study, and the participant will not lose any benefits that the participant should receive if he or she does not participate in the study.

10) The CRAs, auditors, and the IRB which deliberated the protocol, and regulatory authorities will have direct access to medical records and similar documents on the condition that the participant's confidentiality will be protected. At such times, the participant's confidentiality will be protected. The participant allows direct access to such materials by signing the informed consent form.
11) The participant's confidentiality will be protected if the study results are published.
12) The consultation service to the study site where the participant should make inquiries or should contact if the participant desires further information regarding the study or participant's rights or if study-related injury occurs.
13) The compensation and treatment available to the participant in the event of study-related injury.
14) The types of IRBs that review the appropriateness of the study, the matters reviewed by each IRB, and other matters related to the IRBs involved in this study.
15) Matters to be communicated to participants on this study
    - The planned number of participants in the study
    - If information is obtained that could potentially affect the participant's willingness to continue participating the study, that information will be promptly reported to the participant.
    - The conditions or reasons to withdraw participants from the study
    - Information for the financial responsibility of the participant in the study
    - Information related to payments to the participant
    - Instructions to be followed by the participant
    - Study staff will obtain medical information from other physicians with the consent of the participant.

28. Payments

Measures taken to reduce the participant's financial burden resulting from participation in the study (if any) should be stipulated in writing after a discussion with the study site. Provisions for other necessary expenses will also be stipulated in writing after another discussion with each study site.

29. Compensation for Injuries

If a participant suffers from an injury attributable to the study and seeks compensation from the study site, the sponsor shall be fully responsible for the compensation unless the injury is due to an intentional error or a medical error by the study site. Prior to conducting the study, the sponsor will purchase product liability insurance for the IP as a measure to compensate for injuries.

30. Responses to COVID-19

30.1 If participants are found to have confirmed COVID-19 (including asymptomatic pathogen carriers) or suspected COVID-19, or found to have been in close contact with a confirmed or suspected COVID-19 patient

1) Administration of investigational product
    a) The investigator or subinvestigator should not administer the IP unless it is confirmed that the participant meets the following criteria on the day of administration:
        i. For participants who have confirmed (including asymptomatic pathogen carriers) or suspected COVID-19
        - At least 20 days after the onset of symptoms and 72 hours after the symptoms have

resolved: or

- The symptoms have resolved, and the participant has been confirmed not to carry the pathogen.

ii. For participants having been in close contact with a confirmed or suspected COVID-19 patient

- At least 15 days after close contact

30.2 Discontinuation of the study due to the influence of COVID-19

If the study has been discontinued due to the influence of COVID-19, the investigator or subinvestigator will record in the source document and the CRF that the study was discontinued due to COVID-19.

30.3 Deviations from the protocol due to the influence of COVID-19

If a protocol deviation has occurred due to the influence of COVID-19, the investigator or subinvestigator will keep a record in the source document so as to make it clear that the deviation occurred due to the influence of COVID-19.

31. Study Period

December 2021 to November 2024

32. Administrative Structure

32.1 Sponsor

[redacted], Representative Director, President & CEO, Maruho Co., Ltd.
[redacted] Osaka [redacted]

32.2 Sponsor Organization

1) Head of Clinical Trial

[redacted], General Manager, Clinical Development Department, Maruho Co., Ltd

Major roles:

a) [redacted]

b) [redacted]

c) [redacted]

2) Clinical Trial Supervisor

[redacted], Clinical Development Department, Maruho Co., Ltd.

Major roles:

[redacted]

3) Medical Safety Officer

[redacted], MD, PhD, Senior Medical Director, Maruho Co., Ltd.

Major roles:

a) [redacted]

b) [redacted]

[redacted]

4） Clinical Research Associate Leader

[redacted], Clinical Development Department, Maruho Co., Ltd.

Major roles:

[redacted]

32.3 Study Sites and Investigators

Study Center：The University of [redacted], [redacted] Tokyo [redacted]

Investigator：[redacted]

32.4 Medical Expert

[redacted]

Professor, Department of Dermatology, [redacted], The University of [redacted]

32.5 Contract Research Organization

1） Clinical Testing Laboratory

[redacted] Corporation, [redacted] Tokyo [redacted]

2） Biomarker Measurement Institution

[redacted] Corporation, [redacted] Tokyo [redacted]

3） Anti-Drug Antibody Measurement Institution

[redacted] Corporation, [redacted] Tokyo [redacted]

4） Drug Concentration Measurement Institution

[redacted] Laboratories, Ltd., [redacted] Tokyo [redacted]

5） Autoantibody Measurement Institution

[redacted] Corporation, [redacted] Tokyo 135-0064

6） CyTOF Measurement Institution

[redacted] Research Center, Inc., [redacted], Tokyo [redacted]

33. Contact Information

33.1 Contact Information

[redacted], Clinical Development Department, Maruho Co., Ltd.

[redacted] Kyoto [redacted]
TEL [redacted] (dial in)
FAX [redacted]

33.2 Emergency Contact (Saturdays and Sundays, National Holidays, Nights)

[redacted] Clinical Development Department, Maruho Co., Ltd. TEL [redacted]
[redacted], Clinical Development Department, Maruho Co., Ltd. TEL [redacted]

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Project
M5250C

Protocol
M525101-21

A Phase II Study of Nemolizumab in Patients with Systemic Sclerosis

Single-arm multiple-dose study

Protocol

Version 2.0

Maruho Co., Ltd.

Date of Preparation: June 22, 2022

List of Definitions of Abbreviations and Technical Terms

Acronym/Abbreviation/ Technical term	Full text/Definition
ACR-CRISS	American College of Rheumatology Combined Response Index in diffuse cutaneous Systemic Sclerosis
ADL	Activities of daily living
AE	Adverse events
AIDS	Acquired immunodeficiency syndrome
ALB	Albumin
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma/serum concentration-time curve
$AUC_{0\text{-}28day}$	Area under the serum concentration-time curve 0-28day
AUC_{last}	Area under the serum concentration-time curve from zero to last observed concentration time point
A/G ratio	Albumin-Globulin ratio
BLQ	Below the lower limit of quantification
CBA	Cell-based assay
CK	Creatine kinase
C_{max}	Maximum concentration in plasma/serum
COVID-19	Coronavirus disease 2019
CREA	Creatinine
CRP	C reactive protein
CTCAE	Common terminology criteria for adverse events
CyTOF	Cytometry by time of flight
D-Bil	Direct bilirubin
DCS	Dual chamber syringe
dcSSc	Diffuse cutaneous SSc
DLco	Diffusing capacity of lung for carbon monoxide
ECG	Electrocardiogram
ECL	Electro Chemi Luminescence
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
EULAR	European League Against Rheumatism
FAS	Full analysis set
FACIT-Fatigue	Functional assessment of chronic illness therapy-Fatigue
FEV_1	Forced expiratory volume in one second
FSSG	Frequency Scale for the Symptoms of GERD
FU	Follow up
FVC	Forced vital capacity
GCP	Good clinical practice

Acronym/Abbreviation/ Technical term	Full text/Definition
γ-GT	γ-Glutamyl transpeptidase
HAQ-DI	Health assessment questionnaire disability index
Hb	Hemoglobin
HBc antibody	Hepatitis B core antibody
HBs antigen	Hepatitis B surface antigen
HBV	Hepatitis B virus
hCG	human chorionic gonadotrophin
HCV	Hepatitis C virus
HDL-C	High-density lipoprotein cholesterol
HIV	Human immunodeficiency virus
HRCT	High-resolution computed tomography
Ht	Hematocrit
IL	Interleukin
IL-31RA	Interleukin-31 receptor A
IP	Investigational product
IRB	Institutional review board
JCOG	Japan clinical oncology group
KL-6	Krebs von den lungen-6
lcSSc	Limited cutaneous SSc
LDH	Lactic acid dehydrogenase
LDL-C	Low density lipoprotein cholesterol
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA/J	Medical dictionary for regulatory activities / Japanese edition
mRSS	Modified rodman total skin thickness score
nemolizumab	Humanized anti-human interleukin-receptor A (IL-31RA) monoclonal antibody
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
PAH	Pulmonary arterial hypertension
PGA	Physician’s global assessment
Plt	Platelet
PT	Preferred term
PtGA	Patient’s global assessment
QFT-3G	QuantiFERON-TB Gold
RBC	Red blood cell
SAE	Serious adverse event
SP-D	Surfactant protein D
SOC	System organ class
SSc	Systemic sclerosis
TARC	Thymus and activation-regulated chemokine

Acronym/Abbreviation/ Technical term	Full text/Definition
T-Bil	Total-bilirubin
TC	Total cholesterol
TG	Triglyceride
TLC	Total lung capacity
t_{max}	Time to reach the maximum concentration in plasma/serum
TP	Total protein
T-SPOT	T-SPOT®.TB
UA	Uric acid
UN	Urea nitrogen
VAS	Visual analogue scale
WBC	White blood cell

Protocol Synopsis

1. Study objectives

1.1 Primary Objective

To exploratorily evaluate the efficacy of nemolizumab in systemic sclerosis (SSc) patients with moderate to severe skin thickening

1.2 Secondary Objective

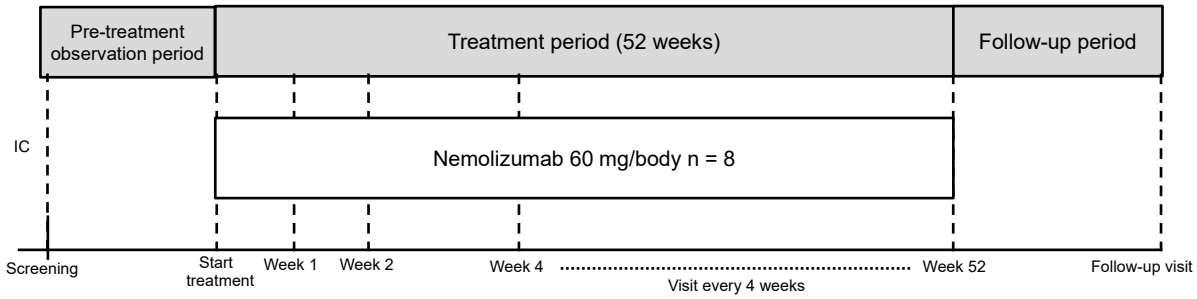
To evaluate the safety and pharmacokinetics of nemolizumab in SSc patients with moderate to severe skin thickening

2. Study Design

This is a phase II, single-arm, multiple-dose study consisting of a pre-treatment observation period (1-4 weeks) and a treatment period (52 weeks). The pre-treatment observation period is from the day of screening to the day of study treatment initiation, and participants will visit the site a total of twice, for screening and for study treatment initiation. Treatment period is from the day of study treatment initiation and every 4 weeks thereafter. Participants having received study treatment will be followed up 84 days after the day of the last dose of study treatment. Follow-up period is from Visit17 (Week 52) or the day of discontinuation visit to the day of follow-up visit.

Study phase: Phase II
Study type: Open-label, single-arm, multiple-dose study
Participants: SSc patients with moderate to severe skin thickening
Target Sample Size: 8 participants

Figure 2-1: Study Schema



1) Pre-treatment observation period

The investigator or subinvestigator will make observations and assessments at the screening visit specified in Table 4-1 after obtaining informed consent from the participant.

2) Treatment period

The investigator or subinvestigator will administer the investigational product (IP) (nemolizumab, 60 mg/body) every 4 weeks (Q4W) at visits until Week 48 after making observations and assessments on the day of study treatment initiation specified in Table 4-1. In addition, the investigator or subinvestigator will make perform observations and assessments at each visit specified in Table 4-1.

3） Follow-up period

All participants having received the IP will be scheduled to visit for follow-up 12 weeks after the day of the last dose of study treatment (the day of follow-up visit). On the day of the follow-up visit, the investigator or subinvestigator will evaluate the safety and efficacy after completion of study treatment for all participants.

3. Target Indication and Inclusion and Exclusion Criteria for Patients

3.1 Target Indication

SSc

3.2 Inclusion Criteria

Participants must meet all of the following criteria for study entry:

Inclusion Criteria	Assessment timing		
	Day of Informed Consent	Day of Screening	Day of treatment start
1） Patients aged 20 to 70 years at the time of informed consent	X	–	–
2） Patients meeting the classification criteria for SSc in ACR and EULAR 2013	X	–	–
3） Patients with systemic sclerosis who have moderate to severe skin thickening, with mRSS of 10 to 22 on both the screening and treatment initiation dates	–	X	X
4） Patients considered by the investigator or subinvestigator to be competent to perform the protocol-specified self-assessment	X	X	X

3.3 Exclusion Criteria

Participants who meet any of the following criteria will be excluded from study entry:

Exclusion Criteria	Confirmation timing		
	Day of informed consent	Day of Screening	Day of treatment start
1） Patients complicated with diseases considered inappropriate for participation in clinical trials, such as serious* cardiac/hepatic/renal/pulmonary/hematologic disease *Refer to the Criteria for Seriousness Classification of Adverse Drug Reactions. (PAB/SD Notification No.80 by the Director of Safety Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare dated June 29, 1992) and the Common Terminology Criteria for Adverse Events v 5.0 Japanese JCOG version (CTCAE v 5.0-JCOG).	X	X	X
2） Patients complicated with congestive heart failure [New York Heart Association (NYHA) Functional Class III or IV]	X	X	X
3） Patients having any of the following complications or concomitant/concurrent diseases: a） Severe chronic pulmonary disease (including %FVC < 60%, or %DLco < 40% on the day of screening, calculated from the New Reference Values for Spirometry in Japanese adults calculated with the LMS	X	X	X

Exclusion Criteria	Confirmation timing		
	Day of informed consent	Day of Screening	Day of treatment start
Method (the Japanese Respiratory Society)" b) Serious complications associated with SSc other than interstitial lung disease* (e.g., renal crisis) * Interstitial lung disease is excluded if it falls under Item a) of 3) c) Poorly controlled asthma that requires steroids (systemic), intravenous infusion of aminophylline, subcutaneous injection of adrenaline 0.1%, oxygen inhalation, or antibody drugs d) Diseases to affect the assessment of SSc			
4) Patients with a history of malignant tumor, who are receiving no treatment and have had no recurrence /relapse for ≥5 years at the time of informed consent, or patients with a history of radical treatment for cervical intraepithelial neoplasia at the time of informed consent may be included in the study	X	X	X
5) Patients with Immune deficiency (e.g., congenital immunodeficiency, AIDS, or HIV).	X	X	X
6) Patients with a history or current hypersensitivity (including anaphylaxis) to immunoglobulin products (plasma-derived preparations or genetic recombinant monoclonal antibodies)	X	X	X
7) Patients weighing < 30.0 kg or > 120 kg on the day of study treatment initiation	–	–	X
8) Patients whose laboratory test values on the day of screening meet any of the following criteria: a) AST or ALT > 2 times the upper limit of normal b) Serum creatinine ≥2.0 mg/dL c) WBC <3000 cells/μL	–	–	X
9) Patients infected with hepatitis B virus (HBV) or hepatitis C virus (HCV) (Positive for HBs antigen or HBc antibody on the day of screening, positive for anti-HCV antibody on the day of screening) The allowed exceptions are as follows: ・ Patients confirmed not to be infected with HBV at the time of the HBV-DNA test performed before study treatment initiation in the case of negative for HBs antigen and positive for HBc antibody in the hepatitis B test performed on the day of screening. ・ Patients confirmed not to be infected with HCV at the time of the HCV-RNA test performed before study treatment initiation in the case of positive for anti-HCV antibody in the hepatitis C test performed on the day of screening	–	–	X
10) Patients with latent or active tuberculosis based on the result of the screening TB test. The allowed exception is patients deemed not to be infected with tuberculosis according to the "Guidelines for the use of interferon-γ release assay (Prevention Committee of the Japanese Society for Tuberculosis).	–	–	X
11) Patients with either of the following infectious diseases: ・ Recurrent/chronic infections or other active infections	X	X	X

Exclusion Criteria		Confirmation timing		
		Day of informed consent	Day of Screening	Day of treatment start
deemed by the investigator to possibly aggravated by participating in the study. ・ Infections (including skin infections) requiring systemic antibiotics, antivirals, or antifungals within 7 days prior to the day of study treatment initiation.				
12) Patients who have received oral steroids (> 10 mg/day of prednisolone or equivalent), dosage of receiving oral steroids have been changed (from ≤ 10 mg/day of prednisolone or equivalent), or newly treated with oral steroids, within 14 days before the day of study treatment initiation		–	–	X
13) Patients who have received any of the following therapies within the indicated period prior to the day of study treatment initiation		–	(X)*	X
a) Within 365 days	Cyclophosphamide			
b) Within 120 days or 5 times the elimination half-life of the drug, whichever is longer	Antibody drugs			
c) Within 28 days	・ Live vaccines ・ The following systemic medications: – Antifibrotic drugs (e.g., pirfenidone, nintedanib) – Immunosuppressants (e.g., cyclosporine, tacrolimus, azathioprine, mycophenolate mofetil, mizoribine, sulfasalazine, leflunomide, methotrexate, hydroxychloroquine, D-penicillamine, sirolimus) – Tyrosine kinase inhibitors (e.g., imatinib) – JAK inhibitors (e.g., tofacitinib, upadacitinib) – Endothelin receptor agonists (e.g., bosentan, ambrisentan, macitentan) – Phosphodiesterase-5 inhibitors (e.g., sildenafil, tadalafil) – Prostaglandin analogue (e.g., alprostadil, epoprostenol) – Riociguat ・ Injections of corticosteroids (excluding joint injections) ・ Phototherapy			

Exclusion Criteria	Confirmation timing		
	Day of informed consent	Day of Screening	Day of treatment start
・ High-dose intravenous immunoglobulin therapy			
14） Patients who are within 120 days from the end of participation in other clinical trials or post-marketing clinical studies (i.e., the last day of administration of another IP or post-marketing clinical study drug) until the day of study treatment initiation, or participating in other clinical trials or post-marketing clinical studies	–	(X)*	X
15） Women who are pregnant, breastfeeding, possibly pregnant, or unwilling to use appropriate contraception measures as instructed by the investigator during the study period	X	X	X
16） Patients who meet any of the following criteria: a） Having not met eligibility for participation when participating in this study in the past d） Having previously received nemolizumab (including placebo)	X	X	X
17） Patients with confirmed or suspected COVID-19	–	X	X
18） Patients with a history of confirmed or suspected COVID-19 excluding those meeting any of the following criteria: • At least 20 days after the onset of symptoms and at least 72 hours after the resolution of symptoms. • Confirmed not to carry SARS-Cov-2.	–	X	X
19） Patients found to have close contacts with COVID-19 patients within 14 days before the day of study treatment initiation	–	–	X
20） Other patients who are considered ineligible for the study by the investigator	X	X	X

*The exclusion criteria will be assessed with the expected date of study treatment initiation as the starting point.

4. Schedule of Study Procedures and Assessments

Table 4-1 Schedule of Study Procedures and Assessments

Visit	1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17/ discont	FU
Visit name	IC day	Screening	Treatment initiation	W 1	W 2	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 52 or discont	FU[J]
Reference day	-	-14	1	8	15	29	57	85	113	141	169	197	225	253	281	309	337	365/ discont	Day of last dose +84
Visit window	-	-16/+9	-	±2	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7/ day of discon+14	±7
Screening/management																			
Informed consent	X[a]																		
Physician examinations	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient Background	X	X	X																
Body weight		X	X			X	X	X	X	X	X	X	X	X	X	X	X		
Registration		X 1st	X 2nd															X Time of discont	
Efficacy evaluation																			
mRSS[b]		X	X			X		X			X			X				X	X
Respiratory function test[C]		X						X			X							X	
Chest HRCT[d]		X									X							X	
Severity classification of the lung		X									X							X	

Visit	1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17/ discont	FU
Visit name	IC day	Screening	Treatment initiation	W 1	W 2	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 52 or discont	FU[j]
ACR-CRISS								X			X							X	
Number of digital ulcers		X	X					X			X			X				X	
Physician's Global Assessment			X					X			X			X				X	
HAQ-DI			X					X			X			X				X	
FACIT-Fatigue			X					X			X			X				X	
FSSG			X					X			X			X				X	
Patient's Global Assessment			X					X			X			X				X	
Safety evaluation																			
Vital signs		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Echocardiography		X									X							X	
Electrocardiogram		X									X							X	
Photography[e]			X																
Laboratory tests																			
Hematology Blood chemistry TARC Urinalysis		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy[f] and TB[g] tests		X																	
Hepatitis B and C tests[h]		X						(X)			(X)			(X)			(X)		(X)
Antinuclear antibodies test			X																
PK analysis and immunogenicity																			

Visit	1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17/ discont	FU
Visit name	IC day	Screening	Treatment initiation	W 1	W 2	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 52 or discont	FU[j]
Serum nemolizumab concentrations			X	X	X	X	X	X	X	X	X			X				X	X
Anti-nemolizumab antibody assay			X								X			X				X	X
Biomarkers																			
IL-31			X			X	X	X	X	X	X			X				X	
KL-6, SP-D, NT-proBNP			X			X		X			X			X				X	
Exploratory biomarkers			X					X			X							X	
Investigational product administration																			
Administration[i]			X			X	X	X	X	X	X	X	X	X	X	X	X		
Others																			
Comprehensive measurement of autoantibodies			X								X							X	
CyTOF measurement			X								X							X	
Adverse Events		→																	
Concomitant medications and therapies		→																	

[a] To be obtained before the observation/tests for the study, and may be obtained on the same day as the day of screening
[b] In principle, the same investigator or subinvestigator will evaluate each participant throughout the study.
[c] If the %FVC decreases by ≥ 15% from baseline, %FVC will be measured again within 1 month.
[d] If having been performed within 1 month of the specified timepoint, not necessary to be performed at the specified timepoint, and the results within 1 month will be substituted.

[e] Not to be performed if refused by the participant.
If any of the following treatment-emergent adverse events occurs, photographs of the affected skin areas of the adverse event should be taken while the event (at least once) is occurring and at the final outcome evaluation, in addition to the scheduled visit (i.e., the day of study treatment initiation).
• Atopic dermatitis
• Adverse events with skin symptoms of edematous erythema or scaling
• Any other adverse event for which the investigator or subinvestigator considers that photography is necessary.

[f] To be performed on female participants excluding those who never become pregnant.

[g] May be conducted on another day after the day of screening before the day of study treatment initiation

[h] • Hepatitis B
The participants who test negative for HBs antigen and positive for HBc antibody will undergo HBV-DNA measurement before the day of study treatment initiation. The participants enrolled through HBV-DNA measurement will undergo HBV-DNA measurement once every three months.
•
Hepatitis C
The participants who test positive for the anti-HCV antibody will undergo HCV-RNA measurement before the day of study treatment initiation. The participants enrolled through HCV-RNA measurement will undergo HCV-RNA measurement once every three months.

i To be administered after all observation/tests are performed. If the IP cannot be administered within the window indicated, the next dose should be administered 14 days or later after the day of the previous dose.

[j] Participants who discontinued the study will visit the site 84 days (±7 days) after the day of the last dose of study treatment for observation/tests at FU shown in Table 4-1. Participants discontinued the study before study treatment initiation need not to undergo observation/tests scheduled on the day of visit for discontinuation.

5. Treatment Method

5.1 Method of Administration

The investigator or subinvestigator will slowly administer the IP, nemolizumab (one DCS [0.6 ml]) subcutaneously to the upper arm, abdomen, or thigh of the participants. The IP may be administered by a person qualified to administer it under the instruction of the investigator or subinvestigator.

5.2 Treatment Period

52 weeks

All participants who have received at least one dose of the IP will visit the site 12 weeks after the day of the last dose of study treatment for follow-up.

5.3 Concomitant Medications and Therapies

5.3.1 Restricted Concomitant Medications

The following medications may be continued at a stable dose if used for at least 14 days before the day of study treatment initiation. However, the dose may be reduced at the discretion of the investigator or subinvestigator, and after dose reduction, the dose may be increased up to that used at the day of study treatment initiation.

・Oral steroids (≤ 10 mg/day of prednisolone or equivalent)

5.3.2 Prohibited Concomitant Medications and Therapies

Concomitant use of medications and therapies listed below is prohibited in this study.

- From the day of study treatment initiation to Week 52 or to the physical examination on the day of visit for discontinuation

1） The following systemic medications:
   a） Antifibrotic drugs (e.g., pirfenidone, nintedanib)
   b） Immunosuppressants (e.g., cyclophosphamide, cyclosporine, tacrolimus, azathioprine, mycophenolate mofetil, mizoribine, sulfasalazine, leflunomide, methotrexate, hydroxychloroquine, D-penicillamine, sirolimus)
   c） Tyrosine kinase inhibitors (e.g., imatinib)
   d） JAK inhibitors (e.g., tofacitinib, upadacitinib)
   e） Endothelin receptor agonists (e.g., bosentan, ambrisentan, macitentan)
   f） Phosphodiesterase-5 inhibitors (e.g., sildenafil, tadalafil)
   g） Prostaglandin analogues (e.g., alprostadil, epoprostenol)
   h） Riociguat
2） Injections of corticosteroids (excluding joint injections)
3） Phototherapy
4） High-dose intravenous immunoglobulin therapy
5） Antibody drugs
6） Live vaccines

- From the day of study treatment initiation to the day of follow-up visit

1） Other drugs and medical devices under development

6. Study Discontinuation of Individual Participants

6.1 Discontinuation Criteria

1) Use of other antibody drugs by Week 52 visit
2) Use of live vaccines by Week 52 visit
3) The investigator or subinvestigator determined that an adverse event which would prevent the continuation of the study has occurred.
4) The participant is found to fail to meet any of the inclusion criteria or to meet any of the exclusion criteria.
5) The participant is found to be pregnant.
6) The investigator or subinvestigator has determined that the participant should be withdrawn from the study due to inadequate response to the IP.
7) The participant requests to withdraw from the study.
8) The participant no longer visits the medical institution, and the study cannot be continued.
9) The participant has died.
10) The sponsor has determined the participant discontinuation from the study due to significant protocol deviations.
11) The sponsor has prematurely terminated the study.
12) The investigator or subinvestigator has determined to withdraw the participant from the study for any other reasons.

7. Efficacy Evaluation

7.1 Primary Endpoint

Change from baseline in mRSS at Week 24

7.2 Other Endpoints

1) Change from baseline in mRSS at Week 52
2) Change from baseline in HAQ-DI at Week 52
3) Change from baseline in HAQ-DI at Week 24
4) Change from baseline in %FVC at Week 52
5) Change from baseline in %FVC at Week 24
6) Change from baseline in DLco at Week 52
7) Change from baseline in DLco at Week 24
8) Change from baseline in PGA at Week 52
9) Change from baseline in PGA at Week 24
10) Change from baseline in PtGA at Week 52
11) Change from baseline in PtGA at Week 24
12) ACR-CRISS at Week 52
13) ACR-CRISS at Week 24
14) Change from baseline in the number of digital ulcers at Week 52
15) Change from baseline in the number of digital ulcers at Week 24
16) Time-course change in the following items:
    a) HAQ-DI
    b) FACIT-Fatigue
    c) FSSG
    d) FVC

e） %FVC
f） DLco
g） %DLco
h） TLC
i） FEV_1
j） Severity evaluation of lung lesion
k） PGA
l） PtGA
m） ACR-CRISS
n） The number of digital ulcers

8. Safety Evaluation

8.1 Assessments for Safety Evaluations

1） Adverse events
   a） Symptoms and signs
   b） Abnormal laboratory test values
   c） Abnormal vital signs
   d） Abnormal electrocardiograms
2） Laboratory test values
3） Vital signs
4） Electrocardiogram
5） Echocardiography

9. Target Sample Size

8 participants

10. Study Period

December 2021 to October 2023

Table of Contents

1. Introduction

1.1 Background of Development

1.1.1 Pathophysiology and epidemiology of systemic sclerosis

Systemic scleroderma (SSc) is a systemic autoimmune disease characterized by fibrosis and vasculopathy of skin and various internal organs such as lung and classified as a connective tissue disease. Skin fibrosis, a common symptom in patients with SSc, is considered to be excessive deposition of the extracellular matrix mainly composed of collagen. [1)] In Japan, SSc is designated as an intractable disease; according to the information of the Japan Intractable Diseases Information Center, the number of SSc patients is about 20,000. [2)] The male-to-female ratio of patients is 1:12 and is more prevalent in women between the ages of 30 and 50 years.

SSc is classified as either diffuse cutaneous systemic scleroderma (dcSSc) in which skin thickening extends to the proximal extremities (i.e. the upper arms and the thighs) or the trunk or limited cutaneous systemic scleroderma (lcSSc) in which skin thickening is limited to the distal extremities (i.e. the forearms and the lower legs) and the face.[3)] In dcSSc patients, as skin thickening progresses, visceral involvement such as in the lungs, gastrointestinal tract, kidneys, and heart, and joint flexion contracture progress. In dcSSc in particular, it is widely recognized that the degree of skin thickening correlates with that of fibrotic lesions in internal organs, and higher severity of skin thickening has been reported to be associated with higher rates of visceral involvement including in the lungs and lower survivals. [4), 5), 6)] In addition, fibrosis of internal organs, as well as skin thickening, develops at an early stage, in which slight tissue damage accumulates and progresses to irreversible organ damage. Therefore, treatment should be initiated as early as possible, especially in patients in whom the condition is predicted to become severe. In lcSSc patients, on the other hand, skin thickening progresses slowly and are not eligible for aggressive treatment. However, lcSSc with the possibility of rapid and widespread progression of skin thickening may be eligible for treatment.[7)]

1.1.2 Therapeutic treatment of systemic sclerosis and its issues

The etiology of SSc has not been clarified, and the main treatment methods are symptomatic treatments and disease-modifying drugs that inhibit disease progression. The progression and sites of involvement of SSc are different for each patient, and accordingly, the treatment method is selected based on the symptom of each patient.

Diagnostic Criteria, Severity Classification and Guidelines of Systemic Sclerosis[7)] state that oral corticosteroids are thought to be empirically valid for patients with progressing skin thickening at an early stage but that they have risk factors for inducing renal crisis. Cyclophosphamide is the most recommended treatment option for both skin thickening and interstitial lung disease in patients with SSc; however, it has a problem of difficulty in long-term administration because of its carcinogenicity, immunosuppression, and side effects of drug such as hemorrhagic cystitis. Other drugs for SSc symptoms are prostacyclin, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors for the treatment of pulmonary hypertension, calcium channel blockers for the treatment of cardiac involvement, intravenous prostaglandin E1 or prostacyclin for the treatment of disturbed blood flow in the fingers, and proton pump inhibitors for the treatment of reflux esophagitis. However, due to limited efficacy or safety issues of these therapeutic agents, the disease burden remains high and there is a great unmet medical need.

1.1.3 Summary description and significance of the development of nemolizumab

Nemolizumab is a monoclonal antibody that recognizes interleukin-31 receptor A (IL-31RA) in humans, which competitively inhibits the binding of interleukin-31 (IL-31) to its receptor, thereby blocking subsequent signal transduction into the cells. Nemolizumab was initially developed by [redacted] Co., Ltd.; the worldwide development and marketing rights, except in Japan and Taiwan,

were granted to [redacted] in 2016, while the development and marketing rights in the field of skin diseases in Japan were granted to [redacted].

IL-31 is a cytokine produced mainly from activated T cells. IL-31 is present at higher levels in serum in SSc than in healthy individuals; IL-31 positive cells were identified in inflammatory infiltrates in fibrotic lesions in the skin and lungs[8)]. Moreover, an *in vitro* study with dermal fibroblasts from healthy individuals showed IL-31 increased collagen production in these cells, and IL-31 administration to mice induced skin and lung fibrosis in an *in vivo* study, suggesting that IL-31 induces skin and lung fibrosis via inducing collagen production in fibroblasts[8)].These results indicate that IL-31 is a key cytokine involved in the development of SSc, and therefore, nemolizumab is expected to inhibit the progression of or ameliorate of skin and pulmonary fibrosis in SSc.

From the above, nemolizumab is considered to be a possible new treatment option for SSc. Thus, this study has been developed to explore the efficacy and safety of nemolizumab in SSc patients.

1.2 Guidelines, Consultation with Pharmaceuticals and Medical Devices Agency (PMDA), etc., Referenced for Study Planning

This study has been planned in reference to the “Diagnostic criteria, severity classification and guidelines of systemic sclerosis.”

2. Study objectives

2.1 Primary Objective

To exploratorily evaluate the efficacy of nemolizumab in systemic sclerosis (SSc) patients with moderate to severe skin thickening

2.2 Secondary Objective

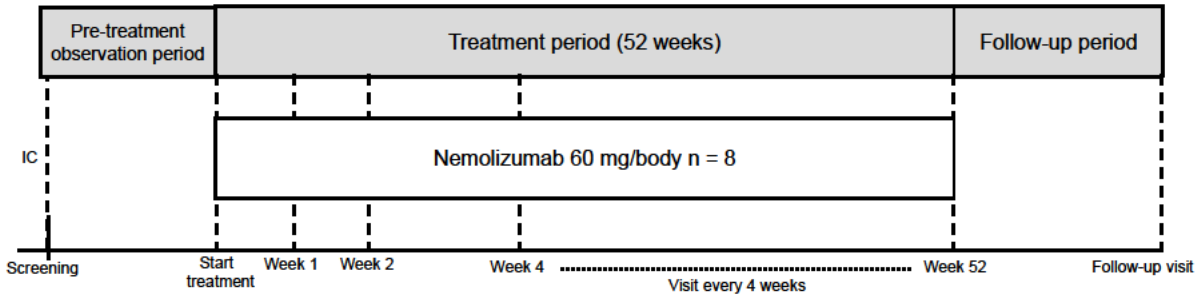
To evaluate the safety and pharmacokinetics of nemolizumab in SSc patients with moderate to severe skin thickening

3. Study Design

This is a phase II, single-arm, multiple-dose study consisting of a pre-treatment observation period (1-4 weeks) and a treatment period (52 weeks). The pre-treatment observation period is from the day of screening to the day of study treatment initiation, and participants will visit the site a total of twice, for screening and for study treatment initiation. The treatment period is from the day of study treatment initiation to Visit 17 (Week 52), during which participants will visit a total of 15 times: Week1,2 and 4, and every four weeks thereafter. Participants having received study treatment will be followed up 84 days after the day of the last dose of study treatment. Follow-up period is from Visit17 (Week 52) or the day of discontinuation visit to the day of follow-up visit.

Study phase: Phase II
Study type: Open-label, single-arm, multiple-dose study
Participants: SSc patients with moderate to severe skin thickening
Target Sample Size: 8 participants

Figure 3-1: Study Schema



1) Pre-treatment observation period
The investigator or subinvestigator will make observations and assessments at the screening visit specified in Table 9-1 after obtaining informed consent from the participant.

2) Treatment period
The investigator or subinvestigator will administer the investigational product (IP) (nemolizumab, 60 mg/body) every 4 weeks (Q4W) at visits until Week 48 after making observations and assessments on the day of study treatment initiation specified in Table 9-1. In addition, the investigator or subinvestigator will make perform observations and assessments at each visit specified in Table 9-1.

3) Follow-up period

All participants having received the IP will be scheduled to visit for follow-up 12 weeks after the day of the last dose of study treatment (the day of follow-up visit). On the day of the follow-up visit, the investigator or subinvestigator will evaluate the safety and efficacy after completion of study treatment for all participants.

4. Target Indication and Inclusion and Exclusion Criteria for Participants

The investigator or subinvestigator will ensure before enrollment that all inclusion criteria are met and none of the exclusion criteria are met.

4.1 Target Indication

SSc

4.2 Inclusion Criteria

Participants must meet all of the following criteria for study entry:

Inclusion Criteria	Assessment timing		
	Day of Informed Consent	Day of Screening	Day of treatment start
1) Patients aged 20 to 70 years at the time of informed consent	X	–	–
2) Patients meeting the classification criteria for SSc in ACR and EULAR 2013	X	–	–
3) Patients with systemic sclerosis who have moderate to severe skin thickening, with mRSS of 10 to 22 on both the screening and treatment initiation dates	–	X	X
4) Patients considered by the investigator or subinvestigator to be competent to perform the protocol-specified self-assessment	X	X	X

・ Rationale for inclusion criteria

1)	Established for safety consideration and to select patients with a sufficient capacity for judgment
2)	Established to standardize the diagnostic criteria for SSc for participants
3)	Established to include only patients with moderate to severe symptoms who are considered to be target patients for this drug.
4)	Established to select patients who can comply with the protocol-specified activities.

4.3 Exclusion criteria

Participants who meet any of the following criteria will be excluded from study entry:

Exclusion Criteria	Confirmation timing		
	Day of informed consent	Day of Screening	Day of treatment start
1) Patients complicated with diseases considered inappropriate for participation in clinical trials, such as serious* cardiac/hepatic/renal/pulmonary/hematologic disease *Refer to the Criteria for Seriousness Classification of Adverse Drug Reactions. (PAB/SD Notification No.80 by the Director	X	X	X

Exclusion Criteria	Confirmation timing		
	Day of informed consent	Day of Screening	Day of treatment start
of Safety Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare dated June 29, 1992) and the Common Terminology Criteria for Adverse Events v 5.0 Japanese JCOG version (CTCAE v 5.0-JCOG).			
2) Patients complicated with congestive heart failure [New York Heart Association (NYHA) Functional Class III or IV]	X	X	X
3) Patients having any of the following complications or concomitant/concurrent diseases: a) Severe chronic pulmonary disease (including %FVC < 60%, or %DLco < 40% on the day of screening, calculated from the New Reference Values for Spirometry in Japanese adults calculated with the LMS Method (the Japanese Respiratory Society)" b) Serious complications associated with SSc other than interstitial lung disease* (e.g., renal crisis) * Interstitial lung disease is excluded if it falls under Item a) of3) c) Poorly controlled asthma that requires steroids (systemic), intravenous infusion of aminophylline, subcutaneous injection of adrenaline 0.1%, oxygen inhalation, or antibody drugs d) Diseases to affect the assessment of SSc	X	X	X
4) Patients with a history of malignant tumor, who are receiving no treatment and have had no recurrence /relapse for ≥5 years at the time of informed consent, or patients with a history of radical treatment for cervical intraepithelial neoplasia at the time of informed consent may be included in the study	X	X	X
5) Patients with Immune deficiency (e.g., congenital immunodeficiency, AIDS, or HIV).	X	X	X
6) Patients with a history or current hypersensitivity (including anaphylaxis) to immunoglobulin products (plasma-derived preparations or genetic recombinant monoclonal antibodies)	X	X	X
7) Patients weighing < 30.0 kg or > 120 kg on the day of study treatment initiation	–	–	X
8) Patients whose laboratory test values on the day of screening meet any of the following criteria: a) AST or ALT > 2 times the upper limit of normal b) Serum creatinine ≥2.0 mg/dL c) WBC <3000 cells/μL	–	–	X
9) Patients infected with hepatitis B virus (HBV) or hepatitis C virus (HCV) (Positive for HBs antigen or HBc antibody on the day of screening, positive for anti-HCV antibody on the day of screening) The allowed exceptions are as follows: ・ Patients confirmed not to be infected with HBs at the time of the HBV-DNA test performed before study treatment initiation in the case of negative for HBs antigen and positive for HBc antibody in the hepatitis B test	–	–	X

Exclusion Criteria		Confirmation timing		
		Day of informed consent	Day of Screening	Day of treatment start
performed on the day of screening. ・ Patients confirmed not to be infected with HCV at the time of the HCV-RNA test performed before study treatment initiation in the case of positive for anti-HCV antibody in the hepatitis C test performed on the day of screening				
10) Patients with latent or active tuberculosis based on the result of the screening TB test. The allowed exception is patients deemed not to be infected with tuberculosis according to the "Guidelines for the use of interferon-γ release assay (Prevention Committee of the Japanese Society for Tuberculosis).		–	–	X
11) Patients with either of the following infectious diseases: ・ Recurrent/chronic infections or other active infections deemed by the investigator to possibly aggravated by participating in the study ・ Infections (including skin infections) requiring systemic antibiotics, antivirals, or antifungals within 7 days prior to the day of study treatment initiation.		X	X	X
12) Patients who have received oral steroids (> 10 mg/day of prednisolone or equivalent), dosage of receiving oral steroids have been changed (from ≤ 10 mg/day of prednisolone or equivalent), or newly treated with oral steroids, within 14 days before the day of study treatment initiation		–	–	X
13) Patients who have received any of the following therapies within the indicated period prior to the day of study treatment initiation		–	(X)*	X
a) Within 365 days	Cyclophosphamide			
b) Within 120 days or 5 times the elimination half-life of the drug, whichever is longer	Antibody drugs			
c) Within 28 days	i. Live vaccines ii. The following systemic medications: – Antifibrotic drugs (e.g., pirfenidone, nintedanib) – Immunosuppressants (e.g., cyclosporine, tacrolimus, azathioprine, mycophenolate mofetil, mizoribine, sulfasalazine, leflunomide, methotrexate, hydroxychloroquine, D-penicillamine, sirolimus) – Tyrosine kinase inhibitors (e.g., imatinib)			

Exclusion Criteria		Confirmation timing		
		Day of informed consent	Day of Screening	Day of treatment start
	– JAK inhibitors (e.g., tofacitinib, upadacitinib) – Endothelin receptor agonists (e.g., bosentan, ambrisentan, macitentan) – Phosphodiesterase-5 inhibitors (e.g., sildenafil, tadalafil) – Prostaglandin analogue (e.g., alprostadil, epoprostenol) – Riociguat iii. Injections of corticosteroids (excluding joint injections) iv. Phototherapy v. High-dose intravenous immunoglobulin therapy			
14) Patients who are within 120 days from the end of participation in other clinical trials or post-marketing clinical studies (i.e., the last day of administration of another IP or post-marketing clinical study drug) until the day of study treatment initiation, or participating in other clinical trials or post-marketing clinical studies		–	(X)*	X
15) Women who are pregnant, breastfeeding, possibly pregnant, or unwilling to use appropriate contraception measures as instructed by the investigator during the study period		X	X	X
16) Patients who meet any of the following criteria: a) Having not met eligibility for participation when participating in this study in the past b) Having previously received nemolizumab (including placebo)		X	X	X
17) Patients with confirmed or suspected COVID-19		–	X	X
18) Patients with a history of confirmed or suspected COVID-19 excluding those meeting any of the following criteria: • At least 20 days after the onset of symptoms and at least 72 hours after the resolution of symptoms. • Confirmed not to carry SARS-Cov-2.		–	X	X
19) Patients found to have close contacts with COVID-19 patients within 14 days before the day of study treatment initiation		–	–	X
20) Other patients who are considered ineligible for the study by the investigator		X	X	X

*The exclusion criteria will be assessed with the expected date of study treatment initiation as the starting point.

・ Rationale for exclusion criteria

1) to 6), 8) to 11), 15), and 17) to 19)	Established considering the safety of participants
7)	Since the dose in this study is 60 mg/body, the upper body weight limit was set not to be lower than the dose (0.5 mg/kg) proven effective in the studies conducted to date in patients with atopic dermatitis, in view of efficacy. The lower

	limit of body weight was set to ensure the safety of participants so that the exposure does not exceed that at the maximum dose (2.0 mg/kg) confirmed to be tolerated after repeated administration of IP.
12)	Established considering the impact on the efficacy of the IP and to ensure the safety of the participants.
13) a), b), c) ii), iii), v),14)	Established considering the impact on the efficacy and safety evaluation of the IP. The period was considered necessary for washout based on the duration of treatment effect and half-live of each drug and therapy.
13) c), i)	Established considering the impact on the safety evaluation of the IP. The period was considered necessary for washout based on the duration of treatment effect and half-live of each drug
13) c), iv)	Established considering the impact on the efficacy evaluation of the IP. The period was considered necessary for washout based on the duration of treatment effect and half-live of each therapy.
16)	1) Established to exclude patients ineligible for this study 2) Established to exclude the impact on the evaluation of efficacy and safety
20)	Established as a general criterion to exclude patients considered ineligible for this study by the investigator or subinvestigator.

5. Study Discontinuation of Individual Participants

The investigator or subinvestigator will withdraw the participant signing informed consent from the study and take appropriate measures if participant meets any of the following discontinuation criteria before observation/tests at Visit 17 (Week 52). Even if the participant requests withdrawal from the study, the participant's data will be used.

5.1 Discontinuation criteria

1) Use of other antibody drugs by Week 52 visit
2) Use of live vaccines by Week 52 visit
3) The investigator or subinvestigator determined that an adverse event which would prevent the continuation of the study has occurred.
4) The participant is found to fail to meet any of the inclusion criteria or to meet any of the exclusion criteria.
5) The participant is found to be pregnant.
6) The investigator or subinvestigator has determined that the participant should be withdrawn from the study due to inadequate response to the IP.
7) The participant requests to withdraw from the study.
8) The participant no longer visits the medical institution, and the study cannot be continued
9) The participant has died.
10) The sponsor has determined the participant discontinuation from the study due to significant protocol deviations.

The sponsor has prematurely terminated the study.
The investigator or subinvestigator has determined to withdraw the participant from the study for any other reasons.

・ Rationale for discontinuation criteria

1) to 3), 5)	Established considering the safety of the participants
4)	Established because the participants are considered ineligible for the study
6)	Established to reduce disadvantages for the participants

7)	Established because it is considered the rights of participants
8) to 11)	Established for contingencies
12)	Established to allow participant discontinuation from the study at the discretion of the investigator or subinvestigator.

5.2 Procedure for Discontinuation

5.2.1 Discontinuation before Enrollment

1) For the participant not led to enrollment because of not satisfying the inclusion criteria, meeting any of the exclusion criteria or other reasons, the investigator or subinvestigator will explain the reason to withdraw the participant from the study, take appropriate action for the participant. The investigator or subinvestigator will ascertain and record the date of discontinuation and the reason for discontinuation in the source documents. A visit for discontinuation and observation/tests scheduled on the day of visit for discontinuation will not be performed.
2) The investigator, subinvestigator, or CRC will record the data for the items described in Section 19.1.2 in the CRF.

5.2.2 Discontinuation after Enrollment

1) The investigator or subinvestigator will explain the reason to withdraw the participant from the study and take appropriate action, ascertain and record the reason for discontinuation in the source documents.
2) The investigator or subinvestigator will perform the observation/tests scheduled on the day of visit for discontinuation. When determining to discontinue the study on a day other than the day of the visit, the investigator or subinvestigator will instruct the participant to come to the study site as early as possible. However, if the day of visit for discontinuation is on or after 77 days from the last dose of study treatment.
3) The investigator, subinvestigator, or CRC will record the data of the items described in Section 19.1.1 in the CRF.

5.3 Handling of Participants Who Fail to Visit the Study Site

5.3.1 Participants Discontinuing Study Site Visit Between the Day of Informed Consent and the Day of Enrollment

When a participant discontinues visiting the study site after the day of informed consent but before enrollment, the investigator or subinvestigator will perform follow-up of the participant through contact with him/her by telephone, letter or other means to record the method and the result of follow-up, reason(s) for not visiting with the date of such information obtained, presence or absence of adverse events, and other information obtained in the source document.

5.3.2 Participants Discontinuing Study Site Visit in the Period after the Enrollment up to Visit 17 (Week 52)

If a participant discontinues visiting the study site after assigned to treatment, the investigator or subinvestigator will identify the whereabouts of the participant as far as possible and encourage him/her to visit the study site. If the participant dose not visit the study site, the investigator or subinvestigator will perform follow-up of the participant through contact with him/her by telephone, letter, or other means to document the method of follow-up, reason(s) for not visiting with the date of such information obtained, presence or absence of adverse events, and other information obtained.

5.3.3 Participants Discontinuing Study Site Visit during the Follow-up Period

The participant who cannot visit the study site within the window of the follow-up visit will be encouraged to visit the study site on the nearest day to the window. If the participant does not visit the study site, the investigator or subinvestigator will perform follow up of the participant through contact with him/her by telephone, letter, and other means to document the method of follow-up, reason(s) for not visiting with the

date of such information obtained, the presence or absence of adverse events, and other information obtained.

6. Participant Enrollment

6.1 Informed Consent

The investigator or subinvestigator will fully explain the study to participants who are considered eligible for the study and obtain written consent before the procedures for the study (see Section 27.4 for the method and points to note for obtaining informed consent).
The investigator or subinvestigator will record the participant information on the participant screening log and provide the participant identification code. The participant identification will be AF001-XXX and will be coded in order of informed consent acquisition. Each participant will use the same participant identification code from informed consent to completion of the study.

6.2 Notification when the Participant is Treated by Another Doctor

The investigator or subinvestigator will ask participants whether or not they are being treated by another doctor. When a participant is being treated by another doctor, the investigator or subinvestigator will notify the doctor of his/her participation in the study after obtaining his/her consent. In addition, the investigator or subinvestigator will record this notification to the doctor in the medical record, etc.

6.3 Enrollment Procedure of Participants

1) For first and second registration.
   For participants considered eligible for the study on the day of screening and on the day of study treatment initiation, the investigator or subinvestigator will enter the necessary information in the source documents, and then fill out a registration form and fax it to the sponsor. The registration form should be filled out and faxed after the source documents have been prepared, which can be performed by the CRC.

2) For discontinuation before assigned to treatment
   For participants discontinued from the study after informed consent but before second registration, the investigator or subinvestigator will enter the necessary information in the source documents, and then fill out a registration form and fax it to the sponsor. The registration form should be filled out and faxed after the source documents have been prepared, which can be performed by the CRC.

3) Correction of entries in the source documents
   When an error is found in the information registered, the investigator or subinvestigator will correct the data in the source document and enter the necessary information in a registration form as needed, and then fax it to the sponsor to correct such data. The registration form should be filled out and faxed after the source documents have been corrected, which can be performed by the CRC.

7. Investigational Product

7.1 Name, Dosage Form, and Strength of the IP

Name, dosage form, and strength of the IPs are indicated in Table 7-1.

Table 7-1 Name, dosage form and strength of investigational product

Name of investigational product	Formulation	Active ingredient and strength (Per DCS)	Storage condition (Before preparation)
Nemolizumab	Injection (DCS)	nemolizumab 75 mg (lyophilized) Nemolizumab is overfilled to ensure injectable nemolizumab 60 mg from one DCS in consideration of the loss of the prepared drug solution during administration. The active ingredient level after preparation is 100 mg/mL.	2°C to 8°C Protection from light

7.2 Packaging and Labeling

7.2.1 Packaging

One DCS of the IP is contained in a small box.

7.2.2 Labeling

The small box is labeled with a statement for clinical study use only, the name and address of the sponsor, identification number, lot number, and storage method.

7.3 Storage and Management of Investigational Products

The investigational product manager at each study site will store and manage the IPs according to the "Operating Procedure for Investigational Product Management" prepared by the sponsor and other procedures specified at each site.

8. Treatment Method

8.1 Dispensing of Investigational Products

The investigator or subinvestigator will dispense one DCS of the IP at the following visits:
<Dispensing visits>
Day of study treatment initiation, Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48

8.2 Preparation of Investigational Products

The investigator or subinvestigator, the investigational product manager or the person in charge of preparation of the IP will prepare injection solutions of IPs according to the "Standard Operating Procedure for Investigational Product Management."

8.3 Method of Administration

On the days of administration (see Table 9-1: Schedule), the investigator or subinvestigator will subcutaneously inject one DCS (0.6-mL) of nemolizumab slowly to the participant either in the upper arm, abdomen, or thigh. The IP may be administered by a person qualified to administer it under the instruction of the investigator or subinvestigator.

・ Precautions
  - The IP will be administered after all observation/tests scheduled at the visit have been completed.
  - The IP will be administered within the window of the specified visit. However, if the IP cannot be administered within the window, the next dose should be administered 14 days or later after the

previous dose.

- If the participant's body weight is lower than 30.0 kg on the day of administration, the IP must not be administered.

・ Rationale for selection>

1） Dosage: 60 mg/body Q4W

A phase III study in Japanese patients with atopic dermatitis has demonstrated the long-term safety of nemolizumab 60 mg/body Q4W. This study has been designed to exploratorily evaluate the efficacy of nemolizumab in SSc patients at 60 mg/body Q4W which has shown the long-term efficacy in SSc patients.

2） Treatment Period

The treatment period has been set at 52 weeks because long-term observation is required to evaluate the efficacy of nemolizumab on skin thickening in SSc patients in an exploratory manner.

3） Day of Follow-up Visit

Considering the serum elimination half-life after a single dose of nemolizumab ranges from 12.6 to 14.6 days in patients with atopic dermatitis, the day of follow-up visit has been set to collect information such as the occurrence of adverse events on the day of 5 times the elimination half-life (84 days ± 7 days) from the day of the last dose.

8.4 Concomitant Medications and Therapies

8.4.1 Restricted Concomitant Medications

The following medications may be continued at a stable dose if used for at least 14 days before the day of study treatment initiation. However, the dose may be reduced at the discretion of the investigator or subinvestigator, and after dose reduction, the dose may be increased up to that used at the day of study treatment initiation.

・Oral steroids (≤ 10 mg/day of prednisolone or equivalent)

8.4.2 Duration and Method of Inspection

The investigator or subinvestigator will collect the information of concomitant medications/therapies by interviewing participants according to Section.9.3.2

8.4.3 Prohibited Concomitant Medications and Therapies

Concomitant use of medications and therapies listed below is prohibited in this study.

- From the day of study treatment initiation to Week 52 or to the physical examination on the day of visit for discontinuation

1） The following systemic medications:

a） Antifibrotic drugs (e.g., pirfenidone, nintedanib)

b） Immunosuppressants (e.g., cyclophosphamide, cyclosporine, tacrolimus, azathioprine, mycophenolate mofetil, mizoribine, sulfasalazine, leflunomide, methotrexate, hydroxychloroquine, D-penicillamine, sirolimus)

c） Tyrosine kinase inhibitors (e.g., imatinib)

d） JAK inhibitors (e.g., tofacitinib, upadacitinib)

e） Endothelin receptor agonists (e.g., bosentan, ambrisentan, macitentan)

f） Phosphodiesterase-5 inhibitors (e.g., sildenafil, tadalafil)

g） Prostaglandin analogues (e.g., alprostadil, epoprostenol)
h） Riociguat

2） Injections of corticosteroids (excluding joint injections)
3） Phototherapy
4） High-dose intravenous immunoglobulin therapy
5） Antibody drugs
6） Live vaccines

・ Rationale for selection

1) 2) 4) 5)	Established considering the impact on the efficacy of the IP and the safety of participants
3)	Established considering the impact on the efficacy evaluation of the IP
6)	Established considering the safety of participants

- From the day of study treatment initiation to the day of follow-up visit

1） Other drugs and medical devices under development

・ Rationale for selection

1)	Established considering the safety of participants and the impact on the efficacy of the IP.

8.4.4 Instructions to participants

The investigator or subinvestigator will examine the implementation status of the treatment of SSc at each visit and give instructions to the participants on treatment of SSc according to the therapeutic guidance specified in Sections 8.4.1 and 8.4.3.

9. Study Procedures and Assessments and the Schedule

9.1 Schedule of Study Procedures and Assessments

Observation, tests and sample collection will be performed according to the schedule shown in Table 9-1.

Table 9-1: Schedule

Visit	1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17/ discont	FU
Visit name	IC day	Screening	Treatment initiation	W 1	W 2	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 52 or discont	FU[j]
Reference day	-	-14	1	8	15	29	57	85	113	141	169	197	225	253	281	309	337	365/ discont	Day of last dose +84
Visit window	-	-16/+9	-	±2	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7/ day of discon+14	±7
Screening/management																			
Informed consent	X[a]																		
Physical examinations	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Demographics	X	X	X																
Body weight		X	X			X	X	X	X	X	X	X	X	X	X	X	X		
Registration		X 1st	X 2nd															X Time of discont	
Efficacy evaluation																			
mRSS[b]		X	X			X		X			X			X				X	X
Respiratory function test[C]		X						X			X							X	
Chest HRCT[d]		X									X							X	

Visit	1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17/ discont	FU
Visit name	IC day	Screening	Treatment initiation	W 1	W 2	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 52 or discont	FU[j]
Severity classification of the lung		X									X							X	
ACR-CRISS								X			X							X	
Number of digital ulcers		X	X					X			X			X				X	
Physician's Global Assessment			X					X			X			X				X	
HAQ-DI			X					X			X			X				X	
FACIT-Fatigue			X					X			X			X				X	
FSSG			X					X			X			X				X	
Patient's Global Assessment			X					X			X			X				X	
Safety evaluation																			
Vital signs		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Echocardiography		X									X							X	
Electrocardiogram		X									X							X	
Photography[e]			X																
Laboratory tests																			
Hematology Blood chemistry TARC Urinalysis		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy[f] and TB[g] tests		X																	
Hepatitis B and C tests[h]		X						(X)			(X)			(X)			(X)		(X)
Antinuclear antibodies test			X																

Visit	1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17/ discont	FU
Visit name	IC day	Screening	Treatment initiation	W 1	W 2	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 52 or discont	FU[j]
PK analysis and immunogenicity																			
Serum nemolizumab concentrations			X	X	X	X	X	X	X	X	X			X				X	X
Anti-nemolizumab antibody assay			X								X			X				X	X
Biomarkers																			
IL-31			X			X	X	X	X	X	X			X				X	
KL-6, SP-D, NT-proBNP			X			X		X			X			X				X	
Exploratory biomarkers			X					X			X							X	
Investigational product administration																			
Administration[i]			X			X	X	X	X	X	X	X	X	X	X	X	X		
Others																			
Comprehensive measurement of autoantibodies			X								X							X	
CyTOF measurement			X								X							X	
Adverse Events		→																	
Concomitant medications and therapies		→																	

[a] To be obtained before the observation/tests for the study, and may be obtained on the same day as the day of screening
[b] In principle, the same investigator or subinvestigator will evaluate each participant throughout the study.
[c] If the %FVC decreases by ≥ 15% from baseline, %FVC will be measured again within 1 month.
[d] If having been performed within 1 month of the specified timepoint, not necessary to be performed at the specified timepoint, and the results within 1 month will be substituted.

[e] Not to be performed if refused by the participant.
If any of the following treatment-emergent adverse events occurs, photographs of the affected skin areas of the adverse event should be taken while the event (at least once) is occurring and at the final outcome evaluation, in addition to the scheduled visit (i.e., the day of study treatment initiation). The photography on the scheduled visit (day of study treatment initiation) will be performed according to Section 9.3.5.4
• Atopic dermatitis
• Adverse events with skin symptoms of edematous erythema or scaling
• Any other adverse event for which the investigator or subinvestigator considers that photography is necessary.

[f] To be performed on female participants excluding those who never become pregnant.

[g] May be conducted on another day after the day of screening before the day of study treatment initiation

[h] • Hepatitis B
The participants who test negative for HBs antigen and positive for HBc antibody will undergo HBV-DNA measurement before the day of study treatment initiation. The participants enrolled through HBV-DNA measurement will undergo HBV-DNA measurement once every three months.
• Hepatitis C
The participants who test positive for anti-HCV antibody will undergo HCV-RNA measurement before the day of study treatment initiation. The participants enrolled through HCV-RNA measurement will undergo HCV-RNA measurement once every three months.

i To be administered after all observation/tests are performed. If the IP cannot be administered within the window indicated, the next dose should be administered 14 days or later after the day of the previous dose.

[j] Participants who discontinued the study will visit the site 84 days (±7 days) after the day of the last dose of study treatment for observation/tests at FU shown in Table 4-1. Participants discontinued the study before study treatment initiation need not to undergo observation/tests scheduled on the day of visit for discontinuation.

9.2 Definition of the Days of Observation, Tests, and Sample Collection

The days of observation, tests, and sample collection will be defined as follows. Table 9-1 shows the visit window of the assessment day.

9.2.1 Day of Informed Consent

The day when informed consent is obtained from the participant is defined as the day of informed consent.

9.2.2 Day of screening

The day of screening is defined as the day of first registration after completion of protocol-specified assessments. The day of informed consent may be the same day as the day of screening.
All observation/tests scheduled for the day of screening must be performed on the same day. The tuberculosis test may be performed after the day of screening; however, the test result should be reviewed before the day of study treatment initiation.

9.2.3 Day of Study Treatment Initiation

The day of study treatment initiation is defined as the day when the participant is enrolled after completion of protocol-specified assessments. All assessments scheduled for the day of study treatment initiation must be performed on the same day.
The day of study treatment initiation is Day 1, and the day before the day of study treatment initiation is Day -1.

9.2.4 Day of Assessment (Weeks 1, 2, 4, 8, 12, through 52)

Week 1 through Week 52 are days when participants visit the study site for protocol-specified observation/tests.

9.2.5 Day of Study Treatment

The day of study treatment is defined as the day when the IP is administered to the participant according to the schedule of Table 9-1 after the protocol-specified assessments are implemented.

9.2.6 Day of Discontinuation

The day of discontinuation is defined as the day when the investigator or subinvestigator determines to withdraw the participant from the study.

9.2.7 Day of Discontinuation Visit

The day of visit for discontinuation is defined as the day when the protocol-specified observation/tests scheduled for discontinuation are performed for the participant who is determined to be withdrawn from the study after study treatment initiation and visit the study site for the procedure.

9.2.8 Day of Follow-up Visit

The day of follow-up visit is defined as the day when the protocol-specified observation/tests are performed for the participant who visits the study site 84 days (±7 days) after the day of the last dose of study treatment.

9.3 Observation, Tests and Sample Collection

9.3.1 Participant Demographics

The investigator or subinvestigator will perform following assessments on the day of informed consent, the day of screening and the day of study treatment initiation.

1） Assessments on the day of informed consent
- Primary disease (diagnosis)
- Time of onset of primary disease
- Classification of primary disease (diffuse cutaneous SSc [dcSSc] or limited cutaneous SSc [lcSSc])
- Main therapy given for SSc in the past
- Date of birth
- Sex
- Complication (any disease which is ongoing at the time of informed consent)
- Race
- Inclusion and exclusion criteria (see “4. Target Indication and Inclusion and Exclusion Criteria for Participants”)

2） Assessments on the day of screening
- Inclusion and exclusion criteria (see “4. Target Indication and Inclusion and Exclusion Criteria for Participants”)
- Height

3） Assessments on the day of study treatment initiation
- Inclusion and exclusion criteria (see “4. Target Indication and Inclusion and Exclusion Criteria for Participants”)

9.3.2 Prior and Concomitant Medications and Therapies
9.3.2.1 Prior and concomitant medications
The investigator or subinvestigator will review the following medications for each participant:

1） Medications intended to treat SSc
- Used from 28 days before the day of study treatment initiation to the physical examination at the follow-up visit

2） Medications intended to treat adverse events

a） Medications intended to treat adverse events of special interest defined in Section 11.6 :
Used from the day of study treatment initiation (after initiating study treatment) to the final outcome evaluation.

b） Medications intended to treat adverse events except for 1):
Used from the day of study treatment initiation (after initiating study treatment) to the physical examination at the follow-up visit.

3） All concomitant medications other than 1), and 2)
- Used from the day of study treatment initiation (after initiating study treatment) to Week 52 or the day of discontinuation visit.

Information to be obtained	Presence or absence of concomitant medications, and the drug name, dosage, drug use classification, start and end dates of use, and indication for use of each concomitant medication
Notes	The following information is not required to be collected: ・Diagnostic agents, infusions, fluid replacement, nutritional agents, disinfectants, anesthetics for surgery, laxatives and suppository for barium examination (unless these drugs were used for treatment or are included in the prohibited concomitant medications) ・Dosage of 3) ・Among medications of 1), those newly used in participants who discontinued

	from the study on or after the physical examination at the discontinuation visit.

9.3.2.2 Prior and concomitant therapies

The investigator or subinvestigator will collect the data of the following therapies:

1) Therapies to treat SSc
   - Performed from 28 days before the day of study treatment initiation to the physical examination at the follow-up visit.
2) Concomitant therapies intended to treat adverse events
   a) Concomitant therapies intended to treat adverse events of special interest defined in Section 11.6
      - Performed from the day of study treatment initiation (after initiating study treatment) to the final outcome evaluation.
   b) Concomitant therapies intended to treat adverse events except for 1)
      - Performed from the day of study treatment initiation (after initiating study treatment) to the physical examination at the follow-up visit.
   c) Prohibited concomitant therapies
      - Performed from the day of study treatment initiation (after initiating study treatment) to Week 52 or the day of discontinuation visit.

Information to be obtained	Presence or absence of therapy, and the name of therapy, site to which concomitant therapy is applied, start and end dates of application and purpose of use of concomitant therapy
Notes	Among therapies of 1), those newly performed to participants who discontinued from the study on or after the physical examination at the discontinuation visit are not required.

9.3.3 Body Weight

The investigator or subinvestigator will measure the body weight of participants at the following timepoints:

Data to be obtained	Body weight
Time points	Day of screening, Day of study treatment initiation, Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48
Notes	・On the days of study treatment, measurement will be performed, and the results will be reviewed before administration of IP. ・Participants weighing less than 30.0 kg on the day of study treatment are not allowed to receive study treatment.

9.3.4 Efficacy Evaluation

9.3.4.1 Evaluation of Skin Findings

The investigator or subinvestigator will perform the following assessments:

Assessment	mRSS
Time points	Day of screening, Day of study treatment initiation, Week 4, 12, 24, and 36, Week 52 or Day of discontinuation visit, Day of follow-up visit
Notes	・On the day of study treatment, assessment will be performed before the treatment. ・mRSS assessment will be performed by a skilled physician experienced in scoring skin sclerosis. ・In principle, the same investigator or subinvestigator will perform assessment throughout the study period for each participant in order to minimize inter-assessor variability.

9.3.4.2 Respiratory function test

Spirometry will be performed according to the separately specified procedure.

Assessment	• Forced vital capacity (FVC) and %FVC • Diffusing capacity of lung for carbon monoxide (DLco) and % DLco • Total lung capacity (TLC) and forced expiratory volume in one second (FEV_1)
Time points	Day of screening, Week 12, and 24, Week 52 or Day of discontinuation visit
Notes	• If the %FVC decreases by ≥ 15% from baseline, %FVC will be measured again within 1 month to examine whether the %FVC decreases by ≥ 15% from baseline or not.

9.3.4.3 Chest HRCT

HRCT will be performed according to the regulations or procedures or the test manual of the study site.

Time points	• Day of screening, Week 24, Week 52 or Day of discontinuation visit
Notes	If having been performed within 1 month of the specified timepoint, it is not necessary to be performed at the specified timepoints, and the results within 1 month will be substituted.

9.3.4.4 Severity of pulmonary lesions

The investigator or subinvestigator will evaluate the severity of pulmonary lesions based on the results of respiratory function test and chest HRCT according to 10.1.4 .

Time points	Day of screening, Week 24, Week 52 or Day of discontinuation visit

9.3.4.5 ACR-CRISS

The investigator or subinvestigator will assess whether the participant fall under the following criteria:

Evaluations	• Onset of scleroderma renal crisis • Interstitial lung disease with a decline in %FVC ≥15% (requiring reconfirmation within 1 month), and %FVC of 80% or less • Onset of left ventricular failure requiring treatment (defined as left ventricular ejection fraction ≤45%) * • Onset of pulmonary arterial hypertension requiring right heart catheterization * *Caused by SSc
Time points	Week 12 and 24, Week 52 or Day of discontinuation visit

9.3.4.6 The Number of Digital Ulcers

The investigator or subinvestigator will count the number of digital ulcers.

Time points	• Day of screening, Day of study treatment initiation, Week 12, 24 and 36, Week 52 or Day of discontinuation visit
Notes	• In principle, the same investigator or subinvestigator will perform assessment throughout the study period for each participant in order to minimize inter-assessor variability.

9.3.4.7 Patient-reported outcome

The participants will perform the following assessments:

Evaluations	HAQ-DI, FACIT-Fatigue and FSSG
Time points	Day of study treatment initiation, Week 12, 24, and 36, Week 52 or Day of discontinuation visit
Notes	・ The participants will perform each assessment before receiving the examination and evaluation by the physician at the above visits. ・ The investigator or subinvestigator must not attend the assessments by the participants.

9.3.4.8 Global improvement rating

9.3.4.8.1 Patient's Global Assessment (PtGA)

The participants will assess the overall condition of SSc using a visual analog scale (VAS).

Time points	Day of study treatment initiation, Week 12, 24, and 36, Week 52 or Day of discontinuation visit
Notes	・ The participants will perform each assessment before receiving the examination and evaluation by the physician at the above visits. ・ The investigator or subinvestigator must not attend the assessments by the participants.

9.3.4.8.2 Physician's Global Assessment (PGA)

The investigator or subinvestigator will assess the overall condition of SSc of each participant using a VAS.

Time points	Day of study treatment initiation, Week 12, 24, and 36, Week 52 or Day of discontinuation visit
Notes	・ In principle, the same investigator or subinvestigator will perform assessment throughout the study period for each participant in order to minimize inter-assessor variability.

9.3.5 Safety Evaluation

9.3.5.1 Vital signs

The investigator or subinvestigator will perform the following measurements:

Measurements	Body temperature, pulse rate, and blood pressure (systolic/diastolic)
Time points	Day of screening, Day of study treatment initiation, Week 1, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48, Week 52 or Day of discontinuation visit, Day of follow-up visit
Notes	・ On the day of study treatment, measurements will be performed, and the results will be reviewed before the treatment. ・ The vital signs will be measured at rest in the sitting position.

9.3.5.2 ECG

The investigator or subinvestigator will perform the following measurements:

Measurements	PR interval, QRS interval, QT interval, heart rate and presence or absence of abnormalities
Time points	Day of screening, Week 24, Week 52 or Day of discontinuation visit

Notes	・ On the day of study treatment, measurements will be performed, and the results will be reviewed before the treatment. ・ The same electrocardiograph will be used for each participant at each measurement whenever possible. ・ ECG will be performed at rest in the supine position.

9.3.5.3 Echocardiography

Echocardiography will be performed according to the regulations, procedures, or the test manual of the study site.

Time points	Day of screening, Week 24, Week 52 or Day of discontinuation visit
Notes	・ On the day of study treatment, measurements will be performed, and the results will be reviewed before the treatment.

9.3.5.4 Photography

The investigator or subinvestigator will perform photography according to the separately specified procedure.

Sites to be Photographed	1） Anterior and dorsal views of the upper body (excluding the face) 2） Skin appearance of adverse events
Time points	1） Day of study treatment initiation 2） Duration of the following adverse events (at least once occurrence) after study treatment initiation and at the final outcome evaluation: ・ Atopic dermatitis ・ Adverse events with skin symptoms accompanied by edematous erythema or scaling ・ Any other adverse event for which the investigator or subinvestigator considers that photography is necessary.
Notes	1) and 2): ・ The photos will be retained by the study site and collected by the sponsor. When personal information can be identified from the photos, the photos must be collected with the personal information being masked. ・ Photography will not be performed if refused by the participant.

9.3.6 Laboratory tests

Laboratory tests will be performed at the central laboratory. The investigator or subinvestigator will collect blood and urine samples from participants before study treatment initiation and submit them to the central laboratory. Tuberculosis test may be performed in an in-hospital laboratory.

1） Hematology and serum chemistry tests
2） Immunological tests (thymus and activation-regulated chemokines [TARC])
3） Urinalysis

Time points	Day of screening, Day of study treatment initiation, Week 1, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48, Week 52 or Day of discontinuation visit, Day of follow-up visit
Notes	1) 2) and 3): ・ On the day of study treatment, blood and urine will be collected before the treatment. ・ The test result should be reviewed before the next study treatment. 1) and 2): ・ When aggregation or coagulation is observed in “Plt” because of a reason other than manual technique, blood will be collected into a blood collecting tube containing 3.2% sodium citrate in addition to a conventional blood collection tube from the next visit.

4） Pregnancy test

Time points	Day of screening
Notes	・ The test will be performed on female participants. However, those who are considered unable to become pregnant (e.g., menopausal women* and women who have had total hysterectomy) will be excluded. *: Defined as those who are amenorrhea for at least 12 months without any medical reason.

5） Tuberculosis test

Time points	Day of screening
Notes	・ If the test cannot be performed on the day of screening, it may be performed on another day after the day of screening but before study treatment initiation. In such cases, the rest results should be reviewed before administration of IP on the day of study treatment initiation.

6） Hepatitis B and C tests

Time points	a） Day of screening b） Week 12, 24, 36 and 48, Day of follow-up visit
Notes	a） The participants who test negative for HBs antigen and positive for HBc antibody on the day of screening will undergo HBV-DNA measurement before the day of study treatment initiation. The participants who test positive for anti-HCV antibody on the day of screening will undergo HCV-RNA measurement before the day of study treatment initiation. b） The participants enrolled through HBV-DNA measurement before the day of study treatment initiation will undergo HBV-DNA measurement once every three months. The participants enrolled through HCV-RNA measurement before the day of study treatment initiation will undergo HCV-RNA measurement once every three months.

7） Antinuclear antibodies test

Time points	Day of study treatment initiation
Notes	・ Blood will be collected before administration of IP on the day of study treatment initiation

Table 9-2: Clinical Laboratory Assessments

Laboratory tests	Parameters
Hematology	Hb, Ht, Plt, RBC, WBC, differential leukocyte count, MCV, MCH, and MCHC
Serum chemistry	Na, K, Cl, UN, CREA, Ca, T-Bil, D-Bil, TP, ALB, ALT (GPT), AST (GOT), ALP, P, LDH, CK, UA, TC, LDL-C, HDL-C, TG, A/G ratios, γ-GTs, and CRP
Immunology	TARC
Urinalysis	Protein, occult blood, urinary sugar, and urobilinogen
Pregnancy	Urine hCG
Tuberculosis	Interferon gamma release assay (Central measurement: T-SPOT, in-house examination: T-SPOT or QFT-3G)
Hepatitis B and C	HBs antigen, HBc antibody, HBV-DNA, Anti-HCV antibody, and HCV-RNA
Antinuclear antibodies	Anti-Scl-70 antibodies, anti-centromere antibodies, and anti-RNA polymerase-III antibodies

9.3.7 Pharmacokinetics

The investigator or subinvestigator will collect blood samples for central measurement of serum drug concentrations.

To be measured	Serum concentration of nemolizumab
Time points	Day of study treatment initiation, Week 1, 2, 4, 8, 12, 16, 20, 24, and 36, Week 52 or Day of discontinuation visit, Day of follow-up visit
Notes	• On the day of study treatment, blood will be collected before the treatment.

9.3.8 Immunogenicity

The investigator or subinvestigator will collect blood samples for central measurement of serum anti-nemolizumab antibodies and neutralizing antibodies.

To be measured	Serum anti-nemolizumab antibodies and neutralizing antibodies
Time points	Day of study treatment initiation, Week 24 and 36, Week 52 or Day of discontinuation visit, Day of follow-up visit
Notes	• On the day of study treatment, blood will be collected before the treatment.

9.3.9 Biomarker measurement

The investigator or subinvestigator will collect blood samples for central measurement of serum biomarkers.

To be measured	1) IL-31 2) KL-6, SP-D, NT-proBNP 3) Exploratory biomarkers
Time points	1) Day of study treatment initiation, Week 4, 8, 12, 16, 20, 24, and 36, Week 52 or Day of discontinuation visit 2) Day of study treatment initiation, Week 4, 12, 24, and 36, Week 52 or Day of discontinuation visit 3) Day of study treatment initiation, Week 12 and 24, Week 52 or Day of discontinuation visit
Notes	1) 2) 3) :

	On the day of study treatment, blood will be collected before the treatment

9.3.10 Comprehensive measurement of autoantibodies

The investigator or subinvestigator will collect blood samples for comprehensive measurement of autoantibodies. The measurement will be performed centrally.

Time points	Day of study treatment initiation, Week 24, Week 52 or Day of discontinuation visit
Notes	• On the day of study treatment, blood will be collected before the treatment.

9.3.11 CyTOF measurement

The investigator or subinvestigator will collect blood samples for central measurement of CyTOF.

Time points	Day of study treatment initiation, Week 24, Week 52 or Day of discontinuation visit
Notes	• On the day of study treatment, blood will be collected before the treatment.

9.3.12 Assessment of Adverse Events

The investigator or sub-investigator will assess the adverse events according to the procedure described in "11.4 Review and reporting of adverse events."

9.3.13 Investigation of Malfunction of DCS

The investigator or subinvestigator will investigate malfunction of DCS according to "11.11 Malfunctions of DCS."

9.3.14 Amount of Blood and Urine Samples to be Collected

In principle, the amounts of blood and urine samples to be collected on each assessment day will follow Table 9-3 unless additional tests are required.

Table 9-3: Amount of blood and urine samples to be collected

1)		Day of screening*	Day of treatment initiation	Week 1	Week 2	Week 4	Week 8, 16 and 20	Week 12**	Week 24**, and Week 52 or Day of discontinuation visit	Week 28, 32, 40, 44 and 48**	Week 36	FU**
Amount of blood collected	Laboratory tests	17 mL	6 mL	6 mL	-	6 mL	6 mL	6 mL	6 mL	6 mL	6 mL	6 mL
	Serum nemolizumab concentration	-	3 mL	3 mL	3 mL	3 mL	3 mL	3 mL	3 mL	-	3 mL	3 mL
	Anti-nemolizumab antibody	-		-	-	-	-	-		-	-	
	Antinuclear antibodies test	-	6 mL	-	-	-	-	-	-	-	-	-
	Biomarker measurement	-	12 mL	-	-	9 mL	3 mL	12 mL	12 mL	-	9 mL	-
	Comprehensive measurement of autoantibodies	-	5 mL	-	-	-	-	-	5 mL	-	-	-
	CyToF measurement	-	5 mL	-	-	-	-	-	5 mL	-	-	-
Total amount of blood collected		17 mL	37 mL	9 mL	3 mL	18 mL	12 mL	21 mL	31 mL	6 mL	18 mL	9 mL
Amount of urine collected		10 mL	10 mL	10 mL	-	10 mL	10 mL	10 mL	10 mL	10 mL	10 mL	10 mL

* : The participants found to require measurement of HBV-DNA or HCV-RNA as a result of the hepatitis B and hepatitis C tests performed on the day of screening will need an additional 5 mL of blood to be drawn before the day of study treatment initiation.

** : The participants enrolled through HBV-DNA or HCV-RNA will need an additional 5 mL of blood to be drawn on Week 12, 24, 36 and 48, and on the day of follow up visit.

10. Efficacy Evaluation

10.1 Efficacy Assessments

10.1.1 Assessment of Skin Findings

1) Modified Rodnan Total Skin Thickness Score (mRSS)

The investigator or subinvestigator will assess the degree of skin thickening for each of 17 sites (fingers of both hands, dorsum of both hands, both forearms, both upper arms, face, anterior chest, abdomen, both thighs, both lower legs, and dorsum of both feet) with a 4-point scale from 0 to 3 according to Table 10-1 on each specified day of assessment. Total score will be 0 to 51.

Table 10-1 Scoring the degree of skin thickening by two-step pinching method

Score	Skin thickening	Broad pinching	Slight pinching	Skin thickness when pinched broadly
0	Normal	Possible	Possible	Not thick
1	Mild	Possible	Possible	Thick
2	Moderate	Possible	Impossible	Thicker
3	Severe	Impossible	Impossible	–

10.1.2 Respiratory Function Test

Spirographic examinations, including the flow-volume curve, lung volume measurements, and diffusing lung capacity for carbon monoxide (DL_{CO}) will be performed on each specified day of testing.

10.1.3 Chest HRCT

Chest HRCT will be performed to obtain visually the approximate ratios (HRCT extent) of interstitial opacities (ground-glass opacities, reticular shadows, honeycomb pattern and cystic shadows) with five slides of a) upper aortic arch, b) carina, c) pulmonary vein confluence point, d) midway between c) and e), and e) immediately above the right diaphragm, and their mean will be calculated.

The investigator or subinvestigator will assess in which of the following ranges the ratios are included; 20% or less (≤ 20%), more than 20% to 70% or less (> 20% to ≤ 70%), or more than 70% (>70%). In addition, in combination with FVC, each severity classification of lung disease will be determined according to 10.1.4 Severity Classification of Lung Lesion.

10.1.4 Severity Classification of Lung Lesion

The investigator or subinvestigator will assess the severity of lung lesions using the severity classification of lung lesions specified in the Guidelines for Diagnostic Criteria, Severity Classification and Clinical Practice of Systemic Sclerosis 2016[7] (see Figure 10-2). Respiratory function test results obtained according to Section 10.1.2 and chest CT images obtained according to Section10.1.3 will be used for this assessment.

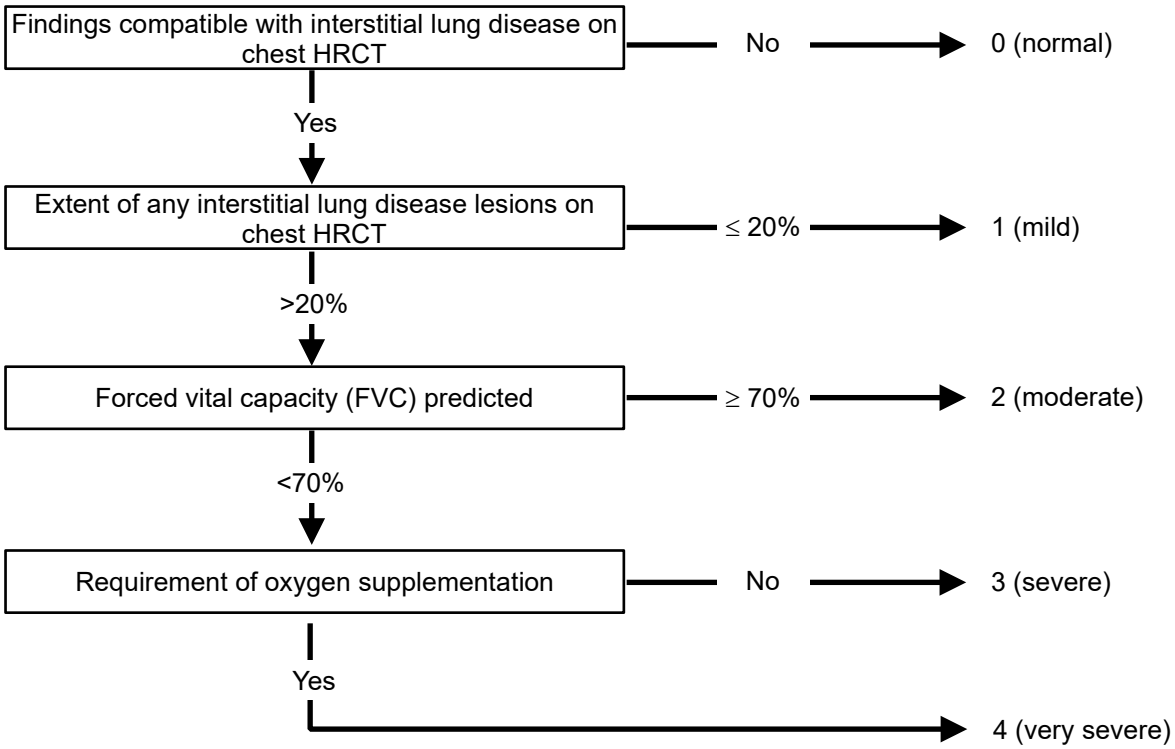


Figure 10-1　Severity classification of lung lesion

10.1.5 ACR-CRISS

ACR-CRISS is a composite outcome measure that is calculated as an index taking a value ranging from 0 to 1 for the probability of improving for participants based on the presence or absence of renal, pulmonary, and cardiac impairments and changes in the 5 core set items (mRSS, %FVC, PGA, PtGA, and HAQ-DI). Participants are considered improved and not improved when their ACR-CRISS is ≥ 0.6 and < 0.6, respectively. If participants meet any of the following criteria, the probability of improving is 0.0. The investigator or subinvestigator will assess whether participants met or not met the following criteria at specified visits. If patients do not meet any of the following criteria, an ACR-CRISS score will be calculated using the formula shown in 17.3.2 2).

- Onset of scleroderma renal crisis
- Decline in FVC% ≥15% (requiring reevaluation within 1 month), and %FVC of 80% or less
- Onset of left ventricular failure requiring treatment (defined as left ventricular ejection fraction ≤45%) *
- Onset of pulmonary arterial hypertension requiring right heart catheterization *

* Caused by SSc

10.1.6 The Number of Digital Ulcers

The investigator or subinvestigator will count the number of digital ulcers.

10.1.7 Patient-reported outcome

1）HAQ-DI

Participants will assess the degree of their difficulty in performing actions of eight functional categories (dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities) using HAQ-DI (Health assessment questionnaire disability index, Japanese version)[9] on a 4-point scale of 0 (Without any difficulty), 1 (Without some difficulty), 2 (Without much difficulty), and 3 (Unable to do).

2） FACIT-Fatigue

Participants will assess their fatigue over the past 7 days using FACIT-Fatigue Scale, Japanese version [10] on a 5-point scale from 0 (not at all) to 4 (very much).

3） FSSG.

Participants will assess their gastroesophageal reflux disease using Frequency Scale for the Symptoms of GERD (FSSG) [11] on a 5-point scale from 0 (never) to 4 (always).

10.1.8 Global improvement rating

1） PtGA

Participants will assess their general health status associated with SSc at visit using a 10-cm visual analog scale (VAS) from 0 (the best status) to 10 (the worst status) [12]. The investigator or subinvestigator or the clinical trial collaborator will measure the length (cm) from the left end to the first decimal place and record it.

2） PGA

The investigator or subinvestigator will assess participants' general health status associated with SSc in terms of Severity, Damage, and Overall disease using a 10-cm VAS from 0 (the best status) to 10 (the worst status) [12]. The investigator (or subinvestigator) or the clinical trial collaborator will measure and record the length (cm) from the left end to the first decimal place.

10.2 Efficacy Endpoints

10.2.1 Primary Endpoint

Change from baseline in mRSS at Week 24

10.2.2 Other Endpoints

1） Change from baseline in mRSS at Week 52
2） Change from baseline in HAQ-DI at Week 52
3） Change from baseline in HAQ-DI at Week 24
4） Change from baseline in %FVC at Week 52
5） Change from baseline in %FVC at Week 24
6） Change from baseline in DLco at Week 52
7） Change from baseline in DLco at Week 24
8） Change from baseline in PGA at Week 52
9） Change from baseline in PGA at Week 24
10） Change from baseline in PtGA at Week 52
11） Change from baseline in PtGA at Week 24
12） ACR-CRISS at Week 52
13） ACR-CRISS at Week 24
14） Change from baseline in the number of digital ulcers at Week 52

15） Change from baseline in the number of digital ulcers at Week 24
16） Time-course changes in the following parameters:
  a） HAQ-DI
  b） FACIT-Fatigue
  c） FSSG
  d） FVC
  e） %FVC
  f） DLco
  g） %DLco
  h） TLC
  i） FEV_1
  j） Severity assessment of lung lesion
  k） PGA
  l） PtGA
  m） ACR-CRISS
  n） The number of digital ulcers

10.3 Rationale for Efficacy Endpoints

1） mRSS

mRSS is used internationally to assess severity of SSc[13), 14)]. Moreover, mRSS is generally considered to be correlated with visceral involvement, etc. and change over a relatively short period of time by receiving treatment, etc. Therefore, change from baseline in mRSS at Week 24 has been selected as primary endpoint to evaluate the efficacy of this drug on SSc. Since SSc has a chronic course, change from baseline in mRSS at Week 52 has been also selected as an efficacy endpoint to discuss the clinical significance of this drug.

2） Respiratory Function Test

FVC in respiratory function tests has been shown to be a useful indicator for predicting vital prognosis in interstitial lung disease associated with SSc[15)] . %FVC and %DLco are useful parameters for screening pulmonary hypertension associated with SSc[16)]. Therefore, this test has been selected to evaluate the efficacy of this drug on lung lesion in an exploratory manner and to ensure the safety of participants.

3） Chest HRCT

Interstitial lung disease in SSc patients has been reported to be detected 50% to 60% by HRCT[17)]. Interstitial lung disease is the most common cause of death in SSc patients[18)]. Interstitial lung disease often occurs from the early stage of SSc, and therefore, it is useful to predict prognosis and determine whether the treatment is feasible for the patient. Moreover, the guidelines recommend to predict the risk of progression to end-stage pulmonary disease and determine whether the treatment is feasible for the patient by the fibrotic finding in HRCT and the extent of the lesion or of the entire lesion in conjunction with FVC-predicted values in respiratory function tests[7)]. Based on the above, this test has been selected to evaluate the efficacy of this drug on lung lesion in an exploratory manner and to ensure the safety of participants.

4） Severity Classification of Lung Lesion

The Guidelines for Diagnostic Criteria, Severity Classification and Clinical Practice of Systemic Sclerosis recommend to predict the risk of progression to end-stage pulmonary disease and determine whether the treatment is feasible for the patient by the fibrotic finding in HRCT, the extent of the lesion or of the entire lesion and FVC predictive value in respiratory function tests[7]. This parameter has been selected to evaluate the efficacy of this drug on lung lesion in an exploratory manner and to ensure the safety of participants.

5) ACR-CRISS

ACR-CRISS is a composite response index for clinical trials in early diffuse cutaneous SSc [19], which is generally used in clinical trials in SSc patients. This index has been selected to evaluate the efficacy of this drug on SSc in an exploratory manner.

6) The number of digital ulcers

Ulcers of the fingers and toes are complications of vascular disorder, one of the conditions of SSc, which occur frequently (35-60%) and arise from the early stage of the disease; therefore, they are considered to reflect the condition of SSc. Moreover, the ulcers are often refractory and recurrent, which is directly related to participants' activities of daily living (ADL) and decreased QOL. Accordingly, this parameter has been selected to evaluate the efficacy of this drug on SSc in an exploratory manner.

7) HAQ-DI

HAQ is a convenient self-administered questionnaire assessing physical function for activities of daily living. It was originally developed to evaluate the effect of rheumatoid arthritis on activities of daily living; however, it has been reported that HAQ-DI correlates with the degree of skin thickening, cardiac involvement, renal involvement, etc., also in SSc[20]. Moreover, along with mRSS, it is a widely used standard method to evaluate SSc. Based on the above, HAQ-DI has been selected to evaluate the efficacy of this drug on SSc in an exploratory manner.

8) FACIT-Fatigue

FACIT-Fatigue is a health-related quality of life that assesses fatigue and its impact on daily activities and functions in chronic diseases. Shortness of breath and fatigue occur in interstitial lung disease and pulmonary hypertension associated with SSc. FACIT-Fatigue has been proven to be reliable and useful in various diseases including SSc[10]. Thus, FACIT-Fatigue has been selected to evaluate the effects of this drug on fatigue and on daily living and functions in SSc, a chronic disease, in an exploratory manner.

9) FSSG

FSSG is a useful questionnaire to objectively assess the symptoms of Japanese participants with gastroesophageal reflux disease[11]. In SSc, esophageal involvement is complicated at a high rate from the early stage of the disease, and 80% to 90% of SSc patients have reflux esophagitis [1]. Esophageal involvements are also associated with the extent and duration of thickening[1]. Based on the above, FSSG has been selected to evaluate the efficacy of this drug on reflux esophagitis in SSc patients in an exploratory manner.

10) Global improvement rating (PtGA, PGA)

Global improvement rating is a widely used method to assess disease activity in clinical trials such as

in rheumatoid arthritis. This rating has been selected to evaluate the efficacy of this drug on SSc in an exploratory manner.

11. Safety Evaluation

11.1 Assessments for Safety Evaluations

1) Adverse events
   a) Symptoms and signs
   b) Abnormal laboratory test values
   c) Abnormal vital signs
   d) Abnormal electrocardiograms
2) Laboratory test values
3) Vital signs
4) Electrocardiograms
5) Echocardiography

11.2 Definition of Adverse Events

1) Adverse events (AEs)

An AE in the study will be defined as any undesirable or unexpected sign, symptom, disease, or aggravation of an existing condition occurring in a participant who is given an IP on or after the time of informed consent regardless of whether there is a causal relationship to the IP. The aggravation of diseases or symptoms that have occurred before the time of informed consent are also considered an AE.

The following events are not considered AE:

- Events for which medical treatment had been scheduled before the time of informed consent
- Aggravation of primary disease

2) Serious adverse events (SAEs)
   a) Results in death
   b) Is life-threatening
   c) Requires or prolongs inpatient hospitalization*

      *Excluding the following events;
      - Any hospitalization that had been scheduled before the time of informed consent (e.g., hospitalization for surgeries and detailed examinations)
      - Any hospitalization for examinations without any treatment (including bed rest treatment).
   d) Results in persistent or significant disability/incapacity
   e) Is a congenital anomaly/birth defect
   f) Is another medically important condition*

      *An important medical event that may not be immediately life-threatening or does not result in death or hospitalization but may jeopardize the safety of the patient or may require treatments to prevent one of the other outcomes listed in a) to e) above.

      e.g., bronchospasm requiring intensive care at an emergency room, blood dyscrasias or convulsions not leading to hospitalization, drug dependence, or drug abuse

3) Adverse events of special interest (AESIs)

AESIs in this study are defined as the following treatment-emergent events:

   a) AEs requiring discontinuation of study treatment

b） Injection-related reactions (including local and systemic injection site reactions)
Injection-related reactions are defined as AEs which develop within 24 hours after administration of IP.

c） Asthma

d） Atopic dermatitis

e） Skin symptoms with edematous erythema or scales

f） Skin infections

g） Non-skin infections

h） Suspected infection of infectious pathogen from the IP

・ Rationale for selection

b), c), d), f), and g)	These events should be monitored carefully because of being included in “important potential risks” in nemolizumab.
e)	These are events of interest closely monitored by the sponsor based on the results of clinical studies of nemolizumab in patients with atopic dermatitis
h)	The event should be carefully investigated in biological products in general.

11.3 Definitions of Safety Endpoints

1） Adverse events

a） Symptoms and signs
The investigator or subinvestigator will assess symptoms and signs in participants after the time of informed consent through the time of physical examination on the day of follow-up visit based on interview results and complaints from participants.

b） Abnormal laboratory test values
The investigator or subinvestigator will treat laboratory test results collected after the time of informed consent through the day of follow-up visit as AEs if the results meet any of the following criteria:

i. Accompanied with clinical symptoms
ii. Resulted in any change of study treatment (e.g., interruption or discontinuation of the IP).
iii. Resulted in medical treatment (including change of concomitant medications/therapies).
iv. Considered clinically significant by the investigator or subinvestigator.
v. Total bilirubin is >2-fold the upper limit of the reference value, and ALT or AST is >3-fold the upper limit of the reference value
vi. ALT or AST is >3-fold the upper limit of the reference value with clinical jaundice

Individual abnormal changes in laboratory test findings will be reported as individual AEs in principle. However, a single abnormal laboratory test finding or two or more abnormal laboratory test findings that are related to each other may be reported collectively as a single event under a single diagnosis if it is considered appropriate by the investigator or sub-investigator. If individual abnormal changes in laboratory test findings are regarded by the investigator or subinvestigator as manifestations of a symptom or a sign reported as an AE, the changes may be reported collectively with the AE of the symptom or sign.

Laboratory values may change depending on interindividual factors, such as sex, age, and lifestyle, and intraindividual factors, such as diurnal fluctuation, diet, exercise, body positioning, and sexual cycle. Therefore, the investigator or subinvestigator will determine whether the change in each laboratory test findings is a physiological change or an abnormal change after sufficiently taking into

consideration the demographics of each participant, such as the underlying disease and complication, baseline values, and the changes specific to each participant who have any periodic laboratory test before study participation.

c) Abnormal vital signs

The investigator or subinvestigator will treat measurement results collected after the time of informed consent through the day of follow-up visit as AEs if the results meet any of the following criteria:

i. Accompanied with clinical symptoms
ii. Resulted in any change of study treatment (e.g., interruption or discontinuation of the IP).
iii. Resulted in medical treatment (including change of concomitant medications/therapies).
iv. Considered clinically significant by the investigator or subinvestigator.

d) Abnormal electrocardiograms

The investigator or subinvestigator will assess AEs based on the results collected after the time of informed consent through the day of follow-up visit

e) Echocardiography

Echocardiographic images will be assessed for cardiac morphology, cardiac motion and blood flow during cardiac contraction and relaxation, and other parameters. The investigator or subinvestigator will record the presence or absence of abnormalities in the source documents.

11.4 Review and reporting of adverse events

The investigator or subinvestigator will assess the items shown in Table 11-1 regarding AEs occurring from after obtaining informed consent to the day of follow-up visit and fill the necessary information in the case report forms (CRFs).

The investigator or subinvestigator will report the SAEs according to Section 11.5 and the AESIs according to Section 11.6 to the sponsor. The investigator or subinvestigator will promptly report the other AEs to the sponsor.

Table 11-1 Assessments for adverse events

Assessments	Details of assessment	
Name of adverse event	Disease name/symptom, classification of the site of occurrence of adverse events	
Onset date	Classification of onset date, Onset date	
Action on investigational product	Treatment discontinuation, Treatment interruption, Dose reduction, No dose change, Not applicable, Unknown	
Treatment for the event	Presence or absence of treatment	
Outcomes and Date of outcome/Date of outcome obtained	Recovered/Resolved, Recovering/Resolving, Not Recovered/Not Resolved, Recovered/Resolved with sequelae, Death, and Unknown End date of AE, whether the AE is ongoing or not	
Severity	Mild	Transient, requiring minimal treatment and not interfering with daily life
	Moderate	Specified treatments relieve symptoms and do not result in permanent or significant disability but interfere with daily life
	Severe	Significant effect on advanced clinical condition or requiring intensive care or no longer allowing daily life.
Seriousness	Serious/Non-serious	
Definition of serious adverse events in Section 13.2	1. Results in death	
	2. Life-threatening	
	3. Requires or prolongs inpatient hospitalization	
	4. Results in persistent or significant disability/incapacity	
	5. Is a congenital anomaly/birth defect	
	6. Is another medically important condition	
Causal relationship with investigational product	Causality classification (according to the following causality classification), and rationale	
Causality classification*	Not related	Causal relationship is unlikely because the adverse event has no plausible temporal relationship to administration of IP, or the event can be explained by another factor. The rationale for no causal relationship is required to be described.
	Related	Causal relationship is presumed because there is a plausible temporal relationship between the onset of the adverse event and administration of investigational drug, and the event cannot be readily explained by another factor. The rationale for the causal relationship should be described if it is necessary to be explained.

*The following guidance can be taken into consideration on causality assessment: resolution of the event after discontinuation of IP; recurrence after restarting of IP; established causal relationship with IP or similar drugs; no confounding risk factors; consistency with the amount and duration of exposure to IP; almost clearly explainable involvement of the IP based on the correct past medical history; no reasonable possibility of causal relationship with concomitant therapy, etc.

11.5 Review and reporting of serious adverse events

1) The investigator will report any serious adverse events to the sponsor within 24 hours of getting to know the occurrence of the event. The investigator will report detailed information to the sponsor by using the “Report of Serious Adverse Events” form within 2 days of getting to know the occurrence of the event (the date the event was known is regarded as day 0). The study site’s own form may be used instead of the "Report of Serious Adverse Events". For additional reporting, new serious information (e.g., change in the name of the adverse event, causal relationship, outcome information, the severity category, etc.) should be reported to the sponsor according to the above rules when it becomes known.
2) The investigator will report the event to the study site according to the study site’s operating procedures.
3) The investigator will provide any additional information (e.g., autopsy reports, late-stage medical records, and other necessary information) on reported serious adverse events, as requested by the sponsor.

11.6 Reporting of adverse events of special interests (AESIs)

The investigator should report to the sponsor promptly when an AESI is noted. For atopic dermatitis and skin symptoms with edematous erythema or scaling, the necessary information (details of the symptoms/signs and the basis for determining the causal relationship with the IP) should be stated in the CRF. Any additional information should be provided, as requested by the sponsor.

At the time of physical examination on the day of follow-up visit, the final outcome of any AESI “not recovered/not resolved” falling under 1) below should be obtained according to 2). Concomitant medications and therapies will also be collected according to Sections 9.3.2.1 and 9.3.2.2 .

1) AESIs to be obtained
   a) AEs requiring discontinuation of study treatment
   b) Asthma
   c) Atopic dermatitis
   d) Skin symptoms with edematous erythema or scales
2) Period to obtain AESIs

   AESIs should be collected until the earlier of the following dates to obtain the final outcome information (the outcome and the date of outcome/outcome obtained).

   • Date of recovering or recovered
   • Date 6 months after the last dose of IP

11.7 Photography

Among AESIs, "atopic dermatitis" and "skin symptoms with edematous erythema or scales" will be photographed to examine the detailed skin findings of the events. Other adverse events of which the principal investigator or subinvestigator considers it necessary to take photographs will also be photographed.

The photographs taken will be used as a record of the occurrence of adverse event and a reference for safety evaluation.

11.8 Reporting of the Pregnancy of the Participant

1) If obtaining the information on the pregnancy of the participant who received the IP, the investigator or subinvestigator must immediately discontinue study treatment and take appropriate action for the participant, and follow up the participant until the completion of the pregnancy (e.g., delivery).
2) The investigator or subinvestigator will also report detailed information to the sponsor by using the “Report for Pregnancies during the Study” form.
3) Participant pregnancies are not regarded as adverse events.

11.9 Rationale for Safety Endpoints

1) In terms of safety protection of participants, it is considered decided that the echocardiography should be carried out periodically. Echocardiography is a useful examination for screening of pulmonary arterial hypertension caused by SSc, and the Guidelines for Diagnostic Criteria, Severity Classification and Clinical Practice of Systemic Sclerosisits recommends performing echocardiography. Pulmonary arterial hypertension caused by SSc has a poor prognosis and requires early detection

11.10 Follow-up of Adverse Events

For all adverse events developing during the study period (from the time of informed consent to the day of follow-up visit), the investigator or subinvestigator will provide appropriate treatments, and follow up until the event recovers to normal condition (within the reference ranges for laboratory test values), to the level before the consent was obtained, or until the investigator or subinvestigator considers that medical follow-up is no longer required. However, AESIs defined in Section 11.6 1) should be obtained according to Section11.6 even if the investigator or subinvestigator considers that their follow-up is not medically necessary.

11.11 Malfunctions of DCS

11.11.1 Reporting of Malfunctions of DCS

In the event of a malfunction of DCS, the principal investigator or subinvestigator will promptly report it to the sponsor according to the "Procedures for the Management of Investigational Products."

11.11.2 Collection and Reporting of Malfunction Information on DCS occurring at the Stage of Use on Participants

The principal investigator or subinvestigator will obtain the information shown in Table 11-2 on DCS malfunctions occurring after prescription to participants and record them in the CRFs

Table 11-2 Information to be obtained for DCS Malfunction Occurring after Prescription to Participants

Information	Details
Details of malfunction	Structural, material, functional defects, etc.
Presence or absence of SAEs (including possibility)	Presence or absence of SAEs or possibility of occurring SAEs due to malfunction
Date of incident	Date of incident
Presence or absence of AEs associated with the malfunction of DCS	Presence or absence of adverse events occurring associated with the malfunction of DCS

If a SAE occurs or may occur associated with a DCS malfunction, the SAE information together with the detailed information of the SAE will be sent to the sponsor in a "Serious Adverse Event and Malfunction Report" form to according to the procedures described in "11.5 Collection and Reporting of Serious Adverse Events." The "Serious Adverse Event and Malfunction Report" may be used in the form of the medical institution.

11.11.3 Storage of Malfunctioning DCS

The IP manager shall store malfunctioning DCSs appropriately at the study site, not discarding them.

11.12 Anticipated Adverse Drug Reactions

See the investigator's brochure of nemolizumab for anticipated adverse drug reactions of nemolizumab.

12. Biomarkers

12.1 Measurements of Biomarkers

1) Variable to be measured
   a) IL-31
   b) KL-6, SP-D, NT-proBNP
   c) Exploratory biomarkers

2) Collection of blood samples
   a) Blood samples will be collected on the day of study treatment initiation, at Week 4, 8, 12, 16, 20, 24, and 36, and Week 52 or on the day of visit for discontinuation. On the days of study treatment, blood samples will be collected before administration of IP.
   b) Blood samples will be collected on the day of study treatment initiation, at Week 4, 12, 24, and 36, and Week 52 or the day of visit for discontinuation. On the days of study treatment, blood samples will be collected before administration of IP.
   c) Blood samples will be collected on the day of study treatment initiation, at Week 12, 24, and Week 52 or the day of visit for discontinuation. On the days of study treatment, blood samples will be collected before administration of IP.

   The collected blood samples will be centrifuged to separate the serum, and the serum samples will be stored frozen until measured. The amount of blood collected, centrifugal conditions, and storage conditions are specified in a separate operating procedure.

12.2 Blood Biomarker Outcome Measures

1) Serum IL-31 level
   ・ Rationale for selection
   Since IL-31 is one of the cytokines considered to be involved in the disease state of SSc[8)],this has been selected to evaluate the changes after administration of nemolizumab.

2) KL-6 and SP-D
   ・ Rationale for selection
   KL-6 and SP-D have been used as sensitive markers for interstitial pneumonitis in examination and measuring of disease progression or as a prognostic predictor in clinical practice. Moreover, increased levels of these have been reported to be associated with inflammatory pathological conditions such as ground-glass opacities on HRCT and elevated proportions of inflammatory cells in bronchoalveolar lavage fluid [21)]. Based on the above, these have been selected in terms of safety protection of participants.

3) NT-proBN
   ・ Rationale for selection
   NT-proBNP is critical as a serological marker of pulmonary hypertension because it elevates in correlation with its severity in patients with SSc-PAH[22)]. It is also important as a serological marker for overall some sort of because it elevates in the presence of any myocardial damage even without pulmonary hypertension[23)]. Therefore, it has been set in terms of ensuring safety of participants.

4) Exploratory biomarkers

As exploratory biomarkers, IL-1α, IL-4, IL-6, IL-8, IL-13, IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, IL-17F, and IL-23 levels will be measured; however, cytokines for which adequate performance of the assay methods could not be validated will not be measured.

・ Rationale for selection

The major cytokines considered to be involved in pathological conditions of SSc have been selected to evaluate the changes after nemolizumab administration.

12.3 Measurement Method and Reporting of Results

1) Measurement methods

a) IL-31 and exploratory biomarkers will be measured using the Enzyme-Linked Immuno Sorbent Assay (ELISA) method. The measurements will be performed by [redacted] Corporation according to its assay protocol.

b) KL-6, SP-D and NT-proBNP will be measured by [redacted] Corporation according to its assay protocol.

c) Exploratory biomarkers will be measured using the Electro Chemi-Luminescence (ECL) method. The measurements will be performed by [redacted] Corporation according to its assay protocol.

2) Report of measurement results

a) IL-31, KL-6, SP-D, NT-proBNP and exploratory biomakers

[redacted] Corporation will prepare and submit a report of analysis results to the sponsor.

13. Pharmacokinetics

13.1 Pharmacokinetic Measurements

1) Variable to be measured

Serum concentration of nemolizumab

2) Collection of blood samples

Blood samples will be collected on the day of study treatment initiation, at Week 1, 2, 4, 8, 12, 16, 20, 24, and 36, Week 52 or on the day of visit for discontinuation, and on the day of follow up. On the days of study treatment, blood samples will be collected before administration of IP.

The collected blood samples will be centrifuged to separate the serum, and the serum samples will be stored frozen until measured. The amount of blood collected, centrifugal conditions, and storage conditions are specified in a separate operating procedure.

13.2 Pharmacokinetic Outcome Measures

1) Serum concentration of nemolizumab

2) Pharmacokinetic parameters: C_{max}、t_{max}、$AUC_{0\text{-}28day}$、AUC_{last}

・ Rationale for selection

Parameters necessary and evaluable to examine pharmacokinetics of nemolizumab have been selected in reference to “Clinical pharmacokinetic studies on drugs (PFSB/ELD No.796 of June 1, 2001).”

13.3 Measurement Method and Reporting of Results

1) Measurement method

Serum concentration of nemolizumab will be measured using the ELISA method. The measurements will be performed by [redacted] Laboratories, Ltd. according to its assay protocol.

2） Report of measurement results

[redacted] Laboratories, Ltd. will prepare and submit a report of analysis results to the sponsor.

14. Immunogenicity

14.1 Immunogenicity Measurements

1） Variable be measured

Serum anti-nemolizumab antibody

2） Collection of blood samples

Blood samples will be collected on the day of study treatment initiation, at Week 24 and 36, Week 52 or on the day of visit for discontinuation, and on the day of follow up. On the days of study treatment, blood samples will be collected before administration of IP.

The collected blood samples will be centrifuged to separate the serum, and the serum samples will be stored frozen until measured. The amount of blood collected, centrifugal conditions, and storage conditions are specified in a separate operating procedure.

14.2 Immunogenicity Outcome Measures

1） Serum anti-nemolizumab antibody

2） Neutralizing antibody concentrations

・ Rationale for selection

The variables have been selected to evaluate the effects of the development of anti-nemolizumab antibodies to efficacy and safety in participants.

14.3 Measurement Method and Reporting of Results

1） Measurement method

The serum anti-nemolizumab antibody will be measured using the ECL method. When anti-nemolizumab antibodies are detected, their characteristics will be determined using the cell-based assay (CBA) method. The measurement will be performed by [redacted] Corporation according to its assay protocol.

2） Report of measurement results

[redacted] Corporation will prepare and submit a report of analysis results to the sponsor.

15. Comprehensive Measurement of Autoantibodies

Comprehensive measurement of autoantibodies will be performed to determine the disease state of SSc and explore the patient-group for whom nemolizumab is effective.

15.1 Measurement Method and Reporting of Results

1） Collection of blood samples

Blood samples will be collected on the day of study treatment initiation, at Week 24, and Week 52 or on the day of visit for discontinuation. On the days of study treatment, blood samples will be collected before administration of IP.

The collected blood samples will be centrifuged to separate the serum, and the serum samples will be stored frozen until measured. The amount of blood collected, centrifugal conditions, and storage

conditions are specified in a separate operating procedure.

2) Measurement method
Autoantibodies will be measured comprehensively using HuPEX™ protein array. The measurement will be performed by P[redacted] Corporation according to its assay protocol.

3) Report of measurement results
[redacted] Corporation will prepare and submit a report of analysis results to the sponsor. Measurement results will not be included in the clinical study report and will be summarized in a separate report.

16. CyTOF measurement

CyTOF measurement will be performed to explore the mechanism of action of nemolizumab in SSc.

16.1 Measurement Method and Reporting of Results

1) Collection of blood samples
Blood samples will be collected on the day of study treatment initiation, at Week 24, and Week 52 or on the day of visit for discontinuation. On the days of study treatment, blood samples will be collected before administration of IP.
PBMC preparation of collected blood samples will be performed by the day following sample collection. The amount of blood to be collected and storage conditions are specified in a separate operating procedure.

2) Measurement method
Measurement will be performed by [redacted], Inc. according to its assay protocol.

3) Report of measurement results
[redacted]. will prepare and submit a report of analysis results to the sponsor. Measurement results will not be included in the clinical study report and will be summarized in a separate report.

17. Statistical Analysis

The major plans for statistical analyses are presented below. The details are provided in the Statistical Analysis Plan. This plan will be fixed prior to database lock on through discussions on data review etc.

17.1 Analysis Sets

17.1.1 Efficacy Analysis Set (Full Analysis Set: FAS)

The efficacy analysis set includes all participants assigned to treatment except for those who meet any of the following criteria:

1) Participants who are found not to have SSc
2) Participants who have received no dose of nemolizumab at all after assigned to treatment
3) Participants with no efficacy data at all after assigned to treatment

17.1.2 Safety Analysis Set

The safety analysis set includes all participants assigned to treatment except for those who meet any of the following criteria:

a） Participants who have received no dose of nemolizumab at all after assigned to treatment

2） Participants with no safety data at all after assigned to treatment

17.1.3 Pharmacokinetics Analysis Set

The pharmacokinetics analysis set includes all participants assigned to treatment except for those who meet any of the following criteria:

1) Participants who have received no dose of nemolizumab at all after assigned to treatment

2) Participants with no pharmacokinetic data at all after assigned to treatment

17.1.4 Biomarker Analysis Set

The biomarker analysis set includes all participants assigned to treatment except for those who meet any of the following criteria:

1) Participants who have received no dose of nemolizumab at all after assigned to treatment

2) Participants with no biomarker data at all after assigned to treatment

17.2 Data Handling

17.2.1 Common Rules

a） Handling of missing values

The missing values will not be imputed.

2） Handling of data on the day of visit for discontinuation

The data measured or evaluated on the day of visit for discontinuation will be handled as the data of the relevant evaluation period if the visit is within the allowance of any visit for evaluation period. However, such data will not be included in the analysis if another data has been obtained in the relevant evaluation period.

17.2.2 Data Handling on Pharmacokinetics

1) Handling of values below the lower limit of quantification (BLQ) and missing values for serum drug concentration data

Values BLQ will be handled as follows and missing values will not be imputed.

a) Tabulation: They will be reported as BLQ.

b) Changes over time and profiles and summary statistics: They will be replaced by 0. However, if the number of participants with BLQ values exceeds half number of participants in pharmacokinetic analysis set, the summary statistics of serum drug concentrations at that time point will not be calculated and reported as N.C. (not calculated).

2) Handling of pharmacokinetic parameters not calculable

Parameters not calculable should be handled as follows:

a) Tabulation: They will be reported as N.C.

b) Summary statistic: They will be left missing. However, if the number of unevaluable participants for a pharmacokinetic parameter exceeds half of participants to be evaluated, the summary statistic of the parameter will not be calculated and reported as N.C.

17.3 Statistical Analysis Plan

The statistical analysis plan is described below. Unless otherwise stated, continuous variables are summarized by number of participants, mean and its standard deviation, minimum value, 25% percentile, median value, 75% percentile, and maximum value, while categorical variables are summarized by the number and percentage of participants in each category.

17.3.1 Demographic and Other Baseline Characteristics, and Severity of Primary Disease

Demographic and other baseline characteristics and severity of primary disease will be summarized, or the summary statistics will be calculated on the FAS.

17.3.2 Efficacy Analysis

This study will be conducted to evaluate the efficacy of nemolizumab in SSc patients with moderate to severe skin thickening in an exploratory manner.

1) Analysis of the primary endpoint: Change from baseline in mRSS at Week 24
   Summary statistics will be calculated for mRSS at Week 24 and the change from baseline.

2) Summary of continuous data
   The following analyses will be performed on the FAS:
   - Summary statistics will be calculated for the following variables and indicators at each time point.
   - The scores or measurements of the following variables will be used to create a spaghetti plot for each participant

Variable	Indicator
mRSS Physician's Global Assessment Patient 's Global Assessment	Score Changes from baseline Percent change from baseline
HAQ-DI FACIT-Fatigue FSSG FVC % FVC DLco %DLco TLC FEV_1 The number of digital ulcers	Score or measurement Change from baseline
ACR-CRISS (Only Week 12, 24 and 52) Severity Classification of Lung Lesion (Figure 10-1)	Score

ACR CRISS is calculated using the following formula.:

$$\frac{\exp\left(-5.54 - 0.81 \times \Delta_{\mathrm{mRSS}} + 0.21 \times \Delta_{\mathrm{FVC\%}} - 0.40 \times \Delta_{\mathrm{pt-glob}} - 0.44 \times \Delta_{\mathrm{MD-glob}} - 3.41 \times \Delta_{\mathrm{HAQ-DI}}\right)}{1 + \exp\left(-5.54 - 0.81 \times \Delta_{\mathrm{mRSS}} + 0.21 \times \Delta_{\mathrm{FVC\%}} - 0.40 \times \Delta_{\mathrm{pt-glob}} - 0.44 \times \Delta_{\mathrm{MD-glob}} - 3.41 \times \Delta_{\mathrm{HAQ-DI}}\right)}$$

Δ_{mRSS}: mRSS change
$\Delta_{\mathrm{FVC\%}}$: Percent FVC change
$\Delta_{\mathrm{pt-glob}}$, $\Delta_{\mathrm{MD-glob}}$: Patient's / Physician's Global assessment change (cm)
$\Delta_{\mathrm{HAQ-DI}}$: HAQ-DI Score change

The score of participants occurring any of the following events is 0:
・Onset of scleroderma renal crisis
・Decline in FVC% ≥15% (requiring reevaluation within 1 month), and %FVC of 80% or less
・Onset of left ventricular failure requiring treatment (defined as left ventricular ejection fraction ≤45%) *
・Onset of pulmonary arterial hypertension requiring right heart catheterization *
*Caused by SSc

17.3.3 Safety Analysis

The following variables will be summarized on the safety analysis set:

1) Adverse events

The following data will be collected and tabulated for AEs and separately for the treatment-related AEs.

a) The number of participants included in the safety analysis set, and the number of participants with, and the number of occurrences of AEs, AEs by severity (mild, moderate, and severe), SAEs (total, fatal, and non-fatal), and AESIs will be calculated.
b) The number of participants with AEs will be calculated by SOC and PT using MedDRA/J.
c) For AESIs, the number of participants with AESIs, the number of participants with AESIs by PT will be calculated by the category.

2) Laboratory test values

a) Laboratory test values throughout the treatment period

For the continuous variables, summary statistics will be calculated by laboratory parameter and time point. For the categorical variables, the number of participants will be calculated by category. The percentage of participants will be calculated using the number of observed participants at each time point.

b) Changes in individual participants during the treatment period

A spaghetti plot will be created for each participant using individual test values by laboratory parameter of continuous variables.

3) Vital signs, physical findings, and other assessments related to safety

a) Vital signs, electrocardiogram and echocardiography throughout the study period

For the continuous variables, summary statistics will be calculated by vital sign, electrocardiogram parameter, and echocardiography parameter. For the categorical variables, the number and percentage of participants will be calculated by category. The percentage of participants will be calculated using the number of observed participants at each time point.

17.3.4 Analyses of Drug Concentrations and Pharmacokinetic Parameters

The following variables will be summarized on the pharmacokinetic analysis set.

1) Serum concentrations of nemolizumab

a) Summary statistics including coefficient of variation and geometric mean of serum nemolizumab concentrations will be calculated by time point.
b) The serum nemolizumab concentration-time profile will be created using mean serum drug concentrations and their standard deviations.
c) The serum nemolizumab concentration-time profile will be created by participant.
d) The serum nemolizumab concentration-time profile will be created by participant where participants who tested positive for the first time after study treatment (in blue), those who had tested positive since before treatment (in red), and those who tested negative at all time points (in black) for anti-nemolizumab antibodies in serum in the confirmatory test will be identified by color.

2) Pharmacokinetic parameters (C_{max}, t_{max}, $AUC_{0\text{-}28Day}$, and AUC_{last})

Summary statistics including coefficient of variation and geometric mean of parameters will be calculated.

17.3.5 Analysis of Immunogenicity

The following variables will be tabulated from the pharmacokinetics analysis set.

1) Serum anti-nemolizumab antibody
   a) The percentage of participants with positive serum anti-nemolizumab antibodies will be calculated by test (Screening, Confirmatory, and Neutralizing) and time point. The positive rate in the Confirmatory test and the Neutralizing test is based on the number of participants having undergone the screening test.
   b) The number of and the percentage of participants who tested positive for anti-nemolizumab antibodies will be determined in this study. According to Shankar's definition,[24] among participants who tested positive for anti-nemolizumab antibodies for the first time after study treatment or both before and after study treatment, a positive participant is defined as a participant with a ≥ 4-fold increase in difference in antibody titer.

17.3.6 Analysis of Biomarker

Details will be described in the Statistical Analysis Plan.

17.4 Determination of Sample Size

17.4.1 Target Sample Size

The target sample size for this study is 8 participants.

17.4.2 Rationale for Sample Size

The number of participants required to determine the efficacy of this drug for SSc was set at 8. Since no statistical evaluation is planned, the number is not based on the level of significance and power.

17.5 Data Review

Data review will be performed before data fixation. In the data review, the appropriateness of data handling and analysis methods, etc., will be examined, and analysis sets, data handling, and an analysis plan will be determined. If a change in the statistical analysis plan is required after data review, the statistical analysis plan will be revised and documented.

18. Agreement on the Protocol and Protocol Deviation/Amendment

18.1 Agreement of and Compliance with the Protocol

The investigator will, before the sponsor requests to conduct the study at the study site, agree in writing with the sponsor on the contents of the protocol and conducting the study in compliance with the protocol. The investigator will do the same when the protocol is revised through discussion with the sponsor or according to the instructions of the head of the study site on the basis of the opinion of the institutional review board (IRB).

18.2 Protocol Deviation/Amendment

1) The investigator or subinvestigator should not deviate from or amend the protocol without prior written agreement with the sponsor and without written approval based on a prior review by the IRB. However, the investigator or subinvestigator may deviate from or amend the protocol without prior agreement with the sponsor or without prior approval from the IRB in the following cases where:
    a) it is medically unavoidable to avoid immediate danger to a participant
    b) it is on administrative matters of the study (e.g., change of the name of study site, change of the address or phone number of study site, and change of job title of the investigator)

2) The investigator or subinvestigator will record all deviations from the protocol. The investigator will prepare a document only for deviations from the protocol to avoid immediate danger to the participant with the reason for deviation or for other medically unavoidable reasons and immediately submit it to the sponsor and the head of the study site. The investigator will also submit the document to the IRB via the head of the study site, obtain approval from the IRB, and obtain in writing approval of the head of the study site and agreement of the sponsor.

3) If the protocol amendment is appropriate when the investigator is unable to comply with the protocol to avoid any immediate hazard to participants or due to other unavoidable medical reasons, the investigator will submit a draft amendment to the protocol to the sponsor as soon as possible to obtain written approval of the sponsor. Furthermore, the investigator will submit a draft amendment to the protocol to the head of the study site, obtain approval from the IRB and the head of the study site.

19. Case Report Form

The EDC system (Table 19-1) will be used in this study. The original CRFs will be those generated in the EDC system. The validated EDC system will be used in this study.

The data and audit trails entered in EDC system by the investigator, subinvestigator involved in CRF preparation, and CRCs are stored in the EDC server.

Table 19-1 EDC system

Name of EDC system	[redacted]
Name of EDC system development Company	[redacted].
Input method	Data entry via the web
Input terminal	Personal computer available at study sites

19.1 Data to be collected in CRF

The data to be collected in the CRFs is shown below.

19.1.1 Participants assigned to treatment

1) Date of written informed consent
2) Visit dates
3) Participant demographics
4) Major therapies received for SSc in the past
5) Inclusion and exclusion criteria
6) Complications
7) Concomitant Medications/Concomitant Therapies
8) Patient-reported Outcomes
9) Global improvement rating
10) mRSS
11) The number of digital ulcers
12) Respiratory function test
13) Electrocardiogram
14) Echocardiography
15) HRCT
16) Severity of pulmonary lesions
17) ACR-CRISS
18) Vital signs
19) Body weight
20) Laboratory tests
21) Biomarkers
22) Serum nemolizumab levels
23) Immunogenicity measurement
24) Comprehensive measurements of autoantibodies
25) CyTOF measurement
26) Dosing status of IP
27) Adverse events

    Information on outcome of an adverse event is to be collected until the follow-up visit.
28) The details of adverse events of atopic dermatitis and skin symptoms with edematous erythema or

scaling as well as the basis for determining the causal relationship with the IP

29) Malfunction of DCS

30) Status of study entry after screening, enrollment, completion/discontinuation of the study
completion status of study entry after screening, completion status of enrollment, study completion status, date of completion, date and reason for discontinuation if discontinued, and impact of COVID-19

31) Follow-up visit
Whether there was a follow-up visit or not, date of follow-up visit, date of determination and reason if no follow-up visit, and impact of COVID-19

32) Others
   a) Comment on each assessment
   b) Unscheduled visits

19.1.2 Participants Who Discontinue the Study before study entry after screening and those Who Discontinue the Study before enrollment

The following data will be collected and documented in the CRF for respective participants:

1) to 6) for participants having discontinued the study before study entry after screening

1) to 6) and 7) to 16) for participants having discontinued the study before enrollment

1) Date of written informed consent
2) Visit dates
3) Participant demographics
4) Inclusion and exclusion criteria
5) Adverse events
6) Date of and reason for discontinuation
7) mRSS
8) The number of digital ulcers
9) Respiratory function test
10) Vital signs
11) Body weight
12) Severity of pulmonary lesions
13) HRCT
14) Echocardiography
15) Electrocardiograms
16) Laboratory tests

19.2 Source Data for Information Entered in Case Report Form

Source data for information entered in the case report forms are as follows:

1) Medical records
2) Laboratory test slips
3) Serious Adverse Event Report (copy)
4) Serious Adverse Event and Device Malfunction Report (copy)
5) Informed consent forms
6) Participant screening logs
7) IP accountability records
8) ECG measurement results

9） Respiratory function test
10） Patient QOL questionnaire (paper)

19.3 Information in the Case Report Forms Treated as Source Data

Any information of the following items described only in the CRF will be treated as the original data.

1） Presence or absence of data for each item
2） Indication of drug/therapy
3） Seriousness and severity of adverse event, causality of adverse event to IP, and presence or absence of abnormal laboratory changes
4） Date of and reason for study discontinuation
5） All comments

19.4 Guidelines for Preparation of Case Report Form

The investigator, subinvestigator involved in CRF preparation, and CRCs will have to receive training before preparing CRFs. The sponsor will create an account management table to specify the authority given to each person in the place of a list of signatures/seals.

1） The investigator or subinvestigator will accurately prepare CRFs based on the source documents of enrolled participants according to the “Guidance for CRF Preparation.”
2） The investigator or subinvestigator will promptly prepare the CRF once the evaluation of the participant at each visit is completed.
3） CRCs may fill out or transcript and correct CRFs on the basis of the source documents. The investigator will review the entries, transcriptions, and corrections made by CRCs and electronically sign the CRFs.
4） The investigator will review the CRFs prepared at the study site and electronically sign the CRFs.
5） The investigator will submit the CRFs to the sponsor. In addition, the investigator will obtain a copy of the CRFs from the sponsor at the end of the study and retain them electronically.
6） If data in the CRF shows a discrepancy with the source document, the investigator will prepare a document explaining the discrepancy and submit it to the sponsor. The investigator will also retain a copy of the record.

19.5 Modification and Amendment to Case Report Forms

1） The investigator, subinvestigator, or CRCs will amend the CRFs according to the “Guidance for CRF Preparation” provided by the sponsor.
2） The investigator will review the modifications or amendments made by the subinvestigator or, CRCs and electronically sign the CRF.

20. Follow-up report of adverse events of special interest

For adverse events of interest falling under those specified in Section 11.6 1) which are “not recovered/not resolved” at the time of physical examination on the day of follow-up visit, the investigator will report their following information from after the physical examination of the follow-up visit to the time of obtaining the final outcome in the format separately specified by the sponsor.

1） Outcome and date of outcome/date of outcome obtained
2） Drugs used for the adverse event
3） Therapies performed for the adverse event

21. Direct Access to Source Documents

The investigator, subinvestigator, and the head of the study site will allow study monitoring, the sponsor's audit, and inspections by the IRB and regulatory authorities, and their direct access to all study-related documents, including the source documents.
When regulations on direct access are stipulated at the study site, they will be followed.

22. Quality Control and Quality Assurance

Risk management of this study will be performed based on the risk management plan prepared according to the standard operating procedures of [redacted]

1) Monitoring
The CRA will request the investigator and subinvestigator, etc. to comply with the GCP, related regulatory notifications, and study protocol throughout the study period, and will then assess their compliance. If any deviation from the GCP, related regulatory notifications, and the study protocol is found by monitoring, the CRA will inform the investigator immediately and the head of the study site as necessary and take appropriate measures to prevent the recurrence of the deviation. Furthermore, on the basis of direct access to the source documents, the CRA will verify whether the CRFs are completed accurately and are consistent with the source documents.

2) Quality control
a) Standardization of assessments
Prior to the start of the study, the sponsor will explain the standards of the assessment and the protocol to the investigator and subinvestigator, etc.

3) Quality control of CRF data
The quality control of CRF data will be performed according to the SOPs of Maruho Co., Ltd. When necessary, a case review meeting may be held by the medical expert and the sponsor to determine the handling of individual cases.

4) Audit
The auditor will assess whether the study is being conducted in accordance with GCP, the protocol, and relevant operating procedures separately and independently from the monitoring and quality control activities performed by the clinical study department. The auditor will also assess whether the study is being conducted properly and that the reliability of the study data is being maintained by direct access to study-related documents and records or other methods.

23. Completion, Discontinuation, or Interruption of the Study

23.1 Completion of the Study

Upon the completion of the study, the investigator will report the completion and a summary of study results in writing to the head of the study site. Once receiving the report of study completion from the investigator, the head of the study site will notify the IRB and the sponsor of the fact the summary of study results.

23.2 Discontinuation or Interruption of the Study

The investigator will, when interrupting or discontinuing the study at his/her own discretion, promptly report it and the reason in writing to the head of the study site. Once receiving the report of study discontinuation

or interruption from the investigator, the head of the study site will promptly notify the IRB and the sponsor of the fact and the reason in writing.
The sponsor will, when deciding the discontinuation or interruption of the study or the termination of development of the IP, promptly notify the head of the study site of the fact and the reason in writing. Once receiving a notification of interruption or discontinuation of the study or the termination of development from the sponsor, the head of the study site will promptly notify the investigator and the IRB of the fact and the reason in writing.

24. Archiving of Records

1) Study site
The head of the study site should retain the documents and records related to this study to be archived at the study site (hereinafter, the study-related records) until the elapse of 15 years after either the date of the marketing approval of the investigational drug or the date of decision of discontinuation of the development of the investigational drug.
For archiving the study-related records, the head of the study site will assign a storage manager. The head of the study site and the storage manager must take necessary measures so that these records are not lost or disposed of during the retention period and that they can be presented at the request of the sponsor, regulatory authorities, etc.
When the retention period of records to be archived at the study site expires, the sponsor will promptly notify the head of the study site of the fact.

2) Sponsor
The sponsor should retain the study-related records to be archived at the sponsor site until the elapse of 15 years after either the date of the marketing approval of the investigational drug or the date of the decision of discontinuation of the development of the investigational drug.

25. Publication Policy

1) The study site may not disclose or divulge data on the study provided by the sponsor or information such as study results to any third party without prior permission of the sponsor. If intending to publish the information obtained from the study to external parties such as academic conferences, the study site must obtain prior permission from the sponsor.
2) The founder of the IRB shall accept the sponsor's request (if any) for prior checking of a summary of the meeting minutes specified in Article 28, Paragraph 2-6 of the GCP to ensure the summary does not include the description infringing on the sponsor's intellectual property rights. When necessary, the founder may publish the summary after taking appropriate measures such as data masking.
3) The sponsor may freely use information obtained from this study for application for marketing approval for the test drug, product summary, promotional materials, publications, presentations at academic societies, and other materials to be submitted to the Ministry of Health, Labour, and Welfare.
4) When publishing information, sufficient attention must be paid to participant privacy.

26. Use of study-related data

1) The sponsor may use information obtained from this study (the study-related data) for application for marketing approval for the test drug, product summary, promotional materials, publications, presentations at academic societies, and other materials to be submitted to the Ministry of Health, Labor, and Welfare.
2) The sponsor may use the study-related data for the research and development of other than the test

drug and otherwise academic research when considered necessary.

27. Ethics

27.1 Institutional Review Board

Prior to the execution of the clinical study agreement, the IRB will review the contents of the protocol, informed consent form, and other explanatory documents, as well as the appropriateness of conducting the study. After the execution of the clinical study agreement, the IRB will continuously review the appropriateness of continuing the study.

27.2 Ethical Conduct of the Study

This study shall be conducted in compliance with the Ministerial Ordinance on Good Clinical Practice for Drugs and related notifications, the ethical principles based on the Declaration of Helsinki, and the protocol.

27.3 Protection of Participants' Confidentiality

To protect the participants' confidentiality, the investigator or subinvestigator will use participant identification codes instead of names to identify participants when completing CRFs and reporting adverse events and other study-related data to the sponsor. The sponsor's CRA and auditors will similarly protect any confidential participant information obtained during the course of the study in accordance with the provisions of Article 80-2, Paragraph 10 of the Act on Securing Quality, Efficacy, and Safety of Products Including Pharmaceuticals".

27.4 Participant Selection and Informed Consent

27.4.1 Participant Selection

During the selection of participants, the investigator or subinvestigator should carefully consider the advisability of asking for a patient to participate in the study taking into consideration the health condition, symptoms, age, sex, ability to consent, dependency on the investigator or subinvestigator, and status of participation in other clinical studies from the viewpoints of human rights protection and based on the protocol-specified inclusion and exclusion criteria. If a patient who is visiting another hospital is enrolled in the study, the investigator or subinvestigator will consider eligibility for study participation after examining the details of the medical treatment.

27.4.2 Informed Consent

1) Prior to the assessment for study participation, the investigator or subinvestigator will fully explain the study to each participant by using the informed consent form and other explanatory documents that describe the items provided in "27.4.3 Explanations to Participants." After this explanation, written voluntary consent to participate in the study will be obtained from the participant personally.
2) In cooperation with the sponsor, the investigator will prepare the informed consent and other explanatory documents that will be used to obtain the participants' consent to participate in the study and revise them as needed. The prepared or revised informed consent form and other explanatory documents should be approved by the IRB before use.
3) The investigator will comply with the ethical principles when preparing or revising the informed consent form and other explanatory documents.
4) The investigator or subinvestigator who provided the explanation, and the participant will each sign and date on the informed consent form. If a CRC makes a supplemental explanation, the CRC will also sign and date on the form.
5) The investigator or subinvestigator will provide the participant with the signed and dated informed

consent form (copy), and other explanatory documents before the participant participates in the study.

6) The investigator, subinvestigator, and CRC should not put pressure or unjustified influence on the participants to participate or continue participating in the study.
7) The informed consent form and other explanatory documents for the participants or information provided orally when explaining the study must not contain any words or suggestions that cause the participants to relinquish their rights. Furthermore, the consent materials and explanation must not contain any words or suggestions that absolve the investigator, subinvestigator, CRC, study site, or sponsor of their legal responsibilities.
8) Nontechnical vocabulary that the participants can understand should be used as much as possible during the verbal explanation and in written explanation and the informed consent form.
9) The investigator or subinvestigator will provide the participant with the opportunity to ask questions and sufficient time to decide whether to participate in the study before obtaining the participant's consent. The investigator, subinvestigator, or CRC (as someone providing additional explanation) must answer all questions to the satisfaction of the participant.
10) If information is obtained that could potentially affect the participants' willingness to continue participating the study, the investigator or subinvestigator must promptly give the information to the participants and ask whether the participants are willing to continue participating the study. In such cases, the fact that this information has been given to the participants will be recorded in the source documents.
11) If significant new information that may be related to the participants' consent is obtained, the investigator should promptly revise the informed consent form and other explanatory documents for the participants on the basis of this information.
12) When the informed consent form and other explanatory documents for participants are revised, the investigator or subinvestigator will promptly give the information which the amendment is based on to participants and ask whether the participants are willing to continue participation in the study. Furthermore, the investigator or subinvestigator will again explain the study using the revised informed consent form and other explanatory documents for participants and obtain voluntary written informed consent to continue participation in the study from each participant. The investigator or subinvestigator will provide the participants with the newly signed and dated revised informed consent form (copy) and the other explanatory documents.

27.4.3 Explanations to Participants

1) This study is being conducted for the purpose of investigation (i.e., this study involves research).
2) Study objective
3) Name, job title, and contact information of the investigator.
4) The study method (including the investigative aspect of the study, the participant inclusion criteria, and the probability of being assigned to each treatment)
5) The expected benefits to the participant's physical and mental health and the expected disadvantages to the participant of the IP
6) The presence or absence of other treatments available to the participant and the expected important benefits and risks of the treatments
7) The participant's scheduled duration of participation in the study
8) Participation in the study is voluntary, and the participant can refuse or withdraw consent to participate in the study at any time.
9) The participant will not undergo any disadvantages as a result of refusing or withdrawing consent to

participate in the study, and the participant will not lose any benefits that the participant should receive if he or she does not participate in the study.

10) The CRAs, auditors, and the IRB which deliberated the protocol, and regulatory authorities will have direct access to medical records and similar documents on the condition that the participant's confidentiality will be protected. At such times, the participant's confidentiality will be protected. The participant allows direct access to such materials by signing the informed consent form.
11) The participant's confidentiality will be protected if the study results are published.
12) The consultation service to the study site where the participant should make inquiries or should contact if the participant desires further information regarding the study or participant's rights or if study-related injury occurs.
13) The compensation and treatment available to the participant in the event of study-related injury.
14) The types of IRBs that review the appropriateness of the study, the matters reviewed by each IRB, and other matters related to the IRBs involved in this study.
15) Matters to be communicated to participants on this study
    - The planned number of participants in the study
    - If information is obtained that could potentially affect the participant's willingness to continue participating the study, that information will be promptly reported to the participant.
    - The conditions or reasons to withdraw participants from the study
    - Information for the financial responsibility of the participant in the study
    - Information related to payments to the participant
    - Instructions to be followed by the participant
    - Study staff will obtain medical information from other physicians with the consent of the participant.

28. Payments

Measures taken to reduce the participant's financial burden resulting from participation in the study (if any) should be stipulated in writing after a discussion with the study site. Provisions for other necessary expenses will also be stipulated in writing after another discussion with each study site.

29. Compensation for Injuries

If a participant suffers from an injury attributable to the study and seeks compensation from the study site, the sponsor shall be fully responsible for the compensation unless the injury is due to an intentional error or a medical error by the study site. Prior to conducting the study, the sponsor will purchase product liability insurance for the IP as a measure to compensate for injuries.

30. Responses to COVID-19

Definitions of confirmed COVID-19 patients (including asymptomatic pathogen carriers), suspected COVID-19 patients, and persons in close contact with such patient follow the latest edition of the Treatment Guidelines for New Coronavirus Infections (COVID-19).

30.1 COVID-19-related instructions to participants

The investigator or subinvestigator will instruct the participants in this study to promptly contact the study site if they are found to have confirmed COVID-19 (including asymptomatic pathogen carriers) or suspected COVID-19, or found to have been in close contact with a confirmed or suspected COVID-19 patient.

30.2 When found to have confirmed COVID-19 (including asymptomatic pathogen carriers) or suspected COVID-19, or found to have been in close contact with a confirmed or suspected COVID-19 patient

30.2.1 When participants are found to have confirmed COVID-19 (including asymptomatic pathogen carriers) or suspected COVID-19, or found to have been in close contact with a confirmed or suspected COVID-19 patient

(1) Visits for the study

1) The investigator or subinvestigator will instruct the participant not to visit the study site during the period shown in Table 30 1, ask their safety by telephone, e-mail, online medical examination, or other means (hereinafter referred to as telephone contact, etc.), and record their status in the source document.

2) After ensuring that the participant does not in the period shown in Table 10-1, Scoring the degree of skin thickening by two-step pinching method, the investigator or subinvestigator will urge the participant to visit the study site, ask whether the participant is willing to continue participating in the study, and determine whether or not the participant can continue the study.

Table 30-1 Period of prohibition to visit the study site due to the impact of COVID-19

Category	Period of prohibited visits to the study site
Patients with confirmed COVID-19 (including asymptomatic pathogen carriers)	Until meeting the criteria for discharge or termination of care at designated facilities, etc. in the Treatment Guidelines for New Coronavirus Infections (COVID-19).
Patients with suspected COVID-19	Until being confirmed not to meet any of the criteria of patients with suspected COVID-19 in the Treatment Guidelines for New Coronavirus Infections (COVID-19).
Participants having been in close contact with a confirmed or suspected COVID-19 patient	From the day of contact (Day 0) to the day 14 days have elapsed from contact

(2) Administration of investigational product

1) The investigator or subinvestigator should not administer the IP unless it is confirmed that the participant meets the following criteria on the day of administration:

a) For participants who have confirmed (including asymptomatic pathogen carriers) or suspected COVID-19

- At least 20 days after the onset of symptoms and 72 hours after the symptoms have resolved: or
- The symptoms have resolved, and the participant has been confirmed not to carry the pathogen.

b) For participants having been in close contact with a confirmed or suspected COVID-19 patient

- At least 15 days after close contact

2) When the participant infected with COVID-19 visits the study site according to (1) continues the study, the investigator or subinvestigator will determine whether the IP can be administered to the participant by interview with him/her, etc. When it is considered administration is possible through consultation with the sponsor, the investigator or subinvestigator will administer the IP to the participant

30.2.2 When staff at the study site who may have close contact with participants have confirmed COVID-19 (including asymptomatic pathogen carriers) or suspected COVID-19.

(1) The investigator or subinvestigator will inform the participants in the study that staff at the study site who may have close contact with them are (or may be) infected with COVID-19, ask the safety of the subjects by telephone or other contact means, and document the result in the source documents. The investigator or subinvestigator will also provide response and instruction to the participants according to the instructions of the study site.

(2) The investigator or subinvestigator will promptly inform the sponsor that staff at the study site who may have close contact with participants are (or may be) infected with COVID-19.

30.3 Discontinuation of the study due to the influence of COVID-19

If the study has been discontinued due to the influence of COVID-19, the investigator or subinvestigator will record in the source document and the CRF that the study was discontinued due to COVID-19.

30.4 Deviations from the protocol due to the influence of COVID-19

If a protocol deviation has occurred due to the influence of COVID-19, the investigator or subinvestigator will keep a record in the source document so as to make it clear that the deviation occurred due to the influence of COVID-19.

31. Study Period

December 2021 to October 2023

32. Administrative Structure

32.1 Sponsor

[redacted] Representative Director, President & CEO, Maruho Co., Ltd.
[redacted], Osaka [redacted]

32.2 Sponsor Organization

1) Head of Clinical Trial

[redacted], General Manager, Clinical Development Department, Maruho Co., Ltd

Major roles:

a) [redacted]

b) [redacted]

c) [redacted]

2) Clinical Trial Supervisor

[redacted], Clinical Development Department, Maruho Co., Ltd.

Major roles:

[redacted]

3) Medical Safety Officer

[redacted], MD, PhD, Senior Medical Director, Maruho Co., Ltd.

Major roles:

a)

b)

4) Clinical Research Associate Leader

Clinical Development Department, Maruho Co., Ltd.

Major roles:

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32.3 Study Sites and Investigators

Study Center : The University of , Tokyo

Investigator :

32.4 Medical Expert

Shinichi Sato

Professor, Department of Dermatology, , The University of

32.5 Contract Research Organization

1) Clinical Testing Laboratory

Corporation, Tokyo

2) Biomarker Measurement Institution

Corporation, Tokyo

3) Anti-Drug Antibody Measurement Institution

Corporation, Tokyo

4) Drug Concentration Measurement Institution

Laboratories, Ltd., Tokyo

5) Autoantibody Measurement Institution

Corporation, Tokyo

6) CyTOF Measurement Institution

, Inc., Tokyo

33. Contact Information

33.1 Contact Information

[redacted] Clinical Development Department, Maruho Co., Ltd.
[redacted] Kyoto [redacted]
TEL [redacted] (dial in)
FAX [redacted]

33.2 Emergency Contact (Saturdays and Sundays, National Holidays, Nights)

[redacted] Clinical Development Department, Maruho Co., Ltd. TEL [redacted]
[redacted], Clinical Development Department, Maruho Co., Ltd. TEL [redacted]

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Project
M5250C

Protocol
M525101-21

A Phase II Study of Nemolizumab in Patients with Systemic Sclerosis

Single-arm multiple-dose study

Protocol

Version 1.0

Maruho Co., Ltd.

Date of Preparation: October 22, 2021

List of Definitions of Abbreviations and Technical Terms

Acronym/Abbreviation/ Technical term	Full text/Definition
ACR-CRISS	American College of Rheumatology Combined Response Index in diffuse cutaneous Systemic Sclerosis
ADL	Activities of daily living
AE	Adverse events
AIDS	Acquired immunodeficiency syndrome
ALB	Albumin
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma/serum concentration-time curve
$AUC_{0\text{-}28day}$	Area under the serum concentration-time curve 0-28day
AUC_{last}	Area under the serum concentration-time curve from zero to last observed concentration time point
A/G ratio	Albumin-Globulin ratio
BLQ	Below the lower limit of quantification
CBA	Cell-based assay
CK	Creatine kinase
C_{max}	Maximum concentration in plasma/serum
COVID-19	Coronavirus disease 2019
CREA	Creatinine
CRP	C reactive protein
CTCAE	Common terminology criteria for adverse events
CyTOF	Cytometry by time of flight
D-Bil	Direct bilirubin
DCS	Dual chamber syringe
dcSSc	Diffuse cutaneous SSc
DLco	Diffusing capacity of lung for carbon monoxide
ECG	Electrocardiogram
ECL	Electro Chemi Luminescence
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
EULAR	European League Against Rheumatism
FAS	Full analysis set
FACIT-Fatigue	Functional assessment of chronic illness therapy-Fatigue
FEV_1	Forced expiratory volume in one second
FSSG	Frequency Scale for the Symptoms of GERD
FU	Follow up
FVC	Forced vital capacity
GCP	Good clinical practice

Acronym/Abbreviation/ Technical term	Full text/Definition
γ-GT	γ-Glutamyl transpeptidase
HAQ-DI	Health assessment questionnaire disability index
Hb	Hemoglobin
HBc antibody	Hepatitis B core antibody
HBs antigen	Hepatitis B surface antigen
HBV	Hepatitis B virus
hCG	human chorionic gonadotrophin
HCV	Hepatitis C virus
HDL-C	High-density lipoprotein cholesterol
HIV	Human immunodeficiency virus
HRCT	High-resolution computed tomography
Ht	Hematocrit
IL	Interleukin
IL-31RA	Interleukin-31 receptor A
IP	Investigational product
IRB	Institutional review board
JCOG	Japan clinical oncology group
KL-6	Krebs von den lungen-6
lcSSc	Limited cutaneous SSc
LDH	Lactic acid dehydrogenase
LDL-C	Low density lipoprotein cholesterol
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA/J	Medical dictionary for regulatory activities / Japanese edition
mRSS	Modified rodman total skin thickness score
nemolizumab	Humanized anti-human interleukin-receptor A (IL-31RA) monoclonal antibody
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
PAH	Pulmonary arterial hypertension
PGA	Physician’s global assessment
Plt	Platelet
PT	Preferred term
PtGA	Patient’s global assessment
QFT-3G	QuantiFERON-TB Gold
RBC	Red blood cell
SAE	Serious adverse event
SP-D	Surfactant protein D
SOC	System organ class
SSc	Systemic sclerosis
TARC	Thymus and activation-regulated chemokine

Acronym/Abbreviation/ Technical term	Full text/Definition
T-Bil	Total-bilirubin
TC	Total cholesterol
TG	Triglyceride
TLC	Total lung capacity
t_{max}	Time to reach the maximum concentration in plasma/serum
TP	Total protein
T-SPOT	T-SPOT®.TB
UA	Uric acid
UN	Urea nitrogen
VAS	Visual analogue scale
WBC	White blood cell

Protocol Synopsis

1. Study objectives

1.1 Primary Objective

To exploratorily evaluate the efficacy of nemolizumab in systemic sclerosis (SSc) patients with moderate to severe skin thickening

1.2 Secondary Objective

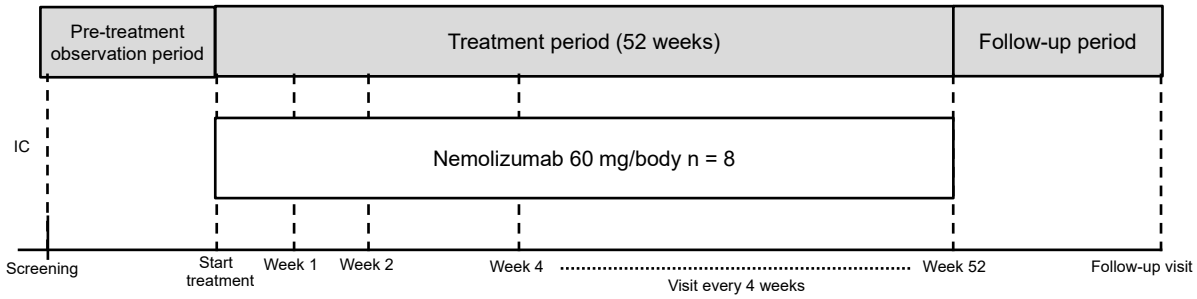
To evaluate the safety and pharmacokinetics of nemolizumab in SSc patients with moderate to severe skin thickening

2. Study Design

This is a phase II, single-arm, multiple-dose study consisting of a pre-treatment observation period (1-4 weeks) and a treatment period (52 weeks). The pre-treatment observation period is from the day of screening to the day of study treatment initiation, and participants will visit the site a total of twice, for screening and for study treatment initiation. Treatment period is from the day of study treatment initiation and every 4 weeks thereafter. Participants having received study treatment will be followed up 84 days after the day of the last dose of study treatment. Follow-up period is from Visit17 (Week 52) or the day of discontinuation visit to the day of follow-up visit.

Study phase: Phase II
Study type: Open-label, single-arm, multiple-dose study
Participants: SSc patients with moderate to severe skin thickening
Target Sample Size: 8 participants

Figure 2-1: Study Schema



1) Pre-treatment observation period

The investigator or subinvestigator will make observations and assessments at the screening visit specified in Table 4-1 after obtaining informed consent from the participant.

2) Treatment period

The investigator or subinvestigator will administer the investigational product (IP) (nemolizumab, 60 mg/body) every 4 weeks (Q4W) at visits until Week 48 after making observations and assessments on the day of study treatment initiation specified in Table 4-1. In addition, the investigator or subinvestigator will make perform observations and assessments at each visit specified in Table 4-1.

3） Follow-up period

All participants having received the IP will be scheduled to visit for follow-up 12 weeks after the day of the last dose of study treatment (the day of follow-up visit). On the day of the follow-up visit, the investigator or subinvestigator will evaluate the safety and efficacy after completion of study treatment for all participants.

3. Target Indication and Inclusion and Exclusion Criteria for Patients

3.1 Target Indication

SSc

3.2 Inclusion Criteria

Participants must meet all of the following criteria for study entry:

Inclusion Criteria	Assessment timing		
	Day of Informed Consent	Day of Screening	Day of treatment start
1） Patients aged 20 to 70 years at the time of informed consent	X	–	–
2） Patients meeting the classification criteria for SSc in ACR and EULAR 2013	X	–	–
3） Patients with systemic sclerosis who have moderate to severe skin thickening, with mRSS of 10 to 22 on both the screening and treatment initiation dates	–	X	X
4） Patients considered by the investigator or subinvestigator to be competent to perform the protocol-specified self-assessment	X	X	X

3.3 Exclusion Criteria

Participants who meet any of the following criteria will be excluded from study entry:

Exclusion Criteria	Confirmation timing		
	Day of informed consent	Day of Screening	Day of treatment start
1） Patients complicated with diseases considered inappropriate for participation in clinical trials, such as serious* cardiac/hepatic/renal/pulmonary/hematologic disease *Refer to the Criteria for Seriousness Classification of Adverse Drug Reactions. (PAB/SD Notification No.80 by the Director of Safety Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare dated June 29, 1992) and the Common Terminology Criteria for Adverse Events v 5.0 Japanese JCOG version (CTCAE v 5.0-JCOG).	X	X	X
2） Patients complicated with congestive heart failure [New York Heart Association (NYHA) Functional Class III or IV]	X	X	X
3） Patients having any of the following complications or concomitant/concurrent diseases: a） Severe chronic pulmonary disease (including %FVC < 60%, or %DLco < 40% on the day of screening, calculated from the New Reference Values for Spirometry in Japanese adults calculated with the LMS	X	X	X

Exclusion Criteria	Confirmation timing		
	Day of informed consent	Day of Screening	Day of treatment start
Method (the Japanese Respiratory Society)" b) Serious complications associated with SSc other than interstitial lung disease* (e.g., renal crisis) * Interstitial lung disease is excluded if it falls under Item a) of 3) c) Poorly controlled asthma that requires steroids (systemic), intravenous infusion of aminophylline, subcutaneous injection of adrenaline 0.1%, oxygen inhalation, or antibody drugs d) Diseases to affect the assessment of SSc			
4) Patients with a history of malignant tumor, who are receiving no treatment and have had no recurrence /relapse for ≥5 years at the time of informed consent, or patients with a history of radical treatment for cervical intraepithelial neoplasia at the time of informed consent may be included in the study	X	X	X
5) Patients with Immune deficiency (e.g., congenital immunodeficiency, AIDS, or HIV).	X	X	X
6) Patients with a history or current hypersensitivity (including anaphylaxis) to immunoglobulin products (plasma-derived preparations or genetic recombinant monoclonal antibodies)	X	X	X
7) Patients weighing < 30.0 kg or > 120 kg on the day of study treatment initiation	–	–	X
8) Patients whose laboratory test values on the day of screening meet any of the following criteria: a) AST or ALT > 2 times the upper limit of normal b) Serum creatinine ≥2.0 mg/dL c) WBC <3000 cells/μL	–	–	X
9) Patients infected with hepatitis B virus (HBV) or hepatitis C virus (HCV) (Positive for HBs antigen or HBc antibody on the day of screening, positive for anti-HCV antibody on the day of screening) The allowed exceptions are as follows: ・ Patients confirmed not to be infected with HBV at the time of the HBV-DNA test performed before study treatment initiation in the case of negative for HBs antigen and positive for HBc antibody in the hepatitis B test performed on the day of screening. ・ Patients confirmed not to be infected with HCV at the time of the HCV-RNA test performed before study treatment initiation in the case of positive for anti-HCV antibody in the hepatitis C test performed on the day of screening	–	–	X
10) Patients with latent or active tuberculosis based on the result of the screening TB test. The allowed exception is patients deemed not to be infected with tuberculosis according to the "Guidelines for the use of interferon-γ release assay (Prevention Committee of the Japanese Society for Tuberculosis).	–	–	X
11) Patients with either of the following infectious diseases: ・ Recurrent/chronic infections or other active infections	X	X	X

Exclusion Criteria		Confirmation timing		
		Day of informed consent	Day of Screening	Day of treatment start
deemed by the investigator to possibly aggravated by participating in the study. ・ Infections (including skin infections) requiring systemic antibiotics, antivirals, or antifungals within 7 days prior to the day of study treatment initiation.				
12) Patients who have received oral steroids (> 10 mg/day of prednisolone or equivalent), dosage of receiving oral steroids have been changed (from ≤ 10 mg/day of prednisolone or equivalent), or newly treated with oral steroids, within 14 days before the day of study treatment initiation		–	–	X
13) Patients who have received any of the following therapies within the indicated period prior to the day of study treatment initiation		–	(X)*	X
a) Within 365 days	Cyclophosphamide			
b) Within 120 days or 5 times the elimination half-life of the drug, whichever is longer	Antibody drugs			
c) Within 28 days	・ Live vaccines ・ The following systemic medications: – Antifibrotic drugs (e.g., pirfenidone, nintedanib) – Immunosuppressants (e.g., cyclosporine, tacrolimus, azathioprine, mycophenolate mofetil, mizoribine, sulfasalazine, leflunomide, methotrexate, hydroxychloroquine, D-penicillamine, sirolimus) – Tyrosine kinase inhibitors (e.g., imatinib) – JAK inhibitors (e.g., tofacitinib, upadacitinib) – Endothelin receptor agonists (e.g., bosentan, ambrisentan, macitentan) – Phosphodiesterase-5 inhibitors (e.g., sildenafil, tadalafil) – Prostaglandin analogue (e.g., alprostadil, epoprostenol) – Riociguat ・ Injections of corticosteroids (excluding joint injections) ・ Phototherapy			

Exclusion Criteria	Confirmation timing		
	Day of informed consent	Day of Screening	Day of treatment start
・ High-dose intravenous immunoglobulin therapy			
14） Patients who are within 120 days from the end of participation in other clinical trials or post-marketing clinical studies (i.e., the last day of administration of another IP or post-marketing clinical study drug) until the day of study treatment initiation, or participating in other clinical trials or post-marketing clinical studies	–	(X)*	X
15） Women who are pregnant, breastfeeding, possibly pregnant, or unwilling to use appropriate contraception measures as instructed by the investigator during the study period	X	X	X
16） Patients who meet any of the following criteria: a） Having not met eligibility for participation when participating in this study in the past d） Having previously received nemolizumab (including placebo)	X	X	X
17） Patients with confirmed or suspected COVID-19	–	X	X
18） Patients with a history of confirmed or suspected COVID-19 excluding those meeting any of the following criteria: • At least 20 days after the onset of symptoms and at least 72 hours after the resolution of symptoms. • Confirmed not to carry SARS-Cov-2.	–	X	X
19） Patients found to have close contacts with COVID-19 patients within 14 days before the day of study treatment initiation	–	–	X
20） Other patients who are considered ineligible for the study by the investigator	X	X	X

*The exclusion criteria will be assessed with the expected date of study treatment initiation as the starting point.

4. Schedule of Study Procedures and Assessments

Table 4-1 Schedule of Study Procedures and Assessments

Visit	1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17/ discont	FU
Visit name	IC day	Screening	Treatment initiation	W 1	W 2	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 52 or discont	FU[i]
Reference day	-	-14	1	8	15	29	57	85	113	141	169	197	225	253	281	309	337	365/ discont	Day of last dose +84
Visit window	-	-16/+9	-	±2	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7/ day of discon+14	±7
Screening/management																			
Informed consent	X[a]																		
Physician examinations	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient Background	X	X	X																
Body weight		X	X			X	X	X	X	X	X	X	X	X	X	X	X		
Registration		X 1st	X 2nd															X Time of discont	
Efficacy evaluation																			
mRSS[b]		X	X			X		X			X			X				X	X
Respiratory function test[C]		X						X			X							X	
Chest HRCT[d]		X									X							X	
Severity classification of the lung		X									X							X	

Visit	1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17/ discont	FU
Visit name	IC day	Screening	Treatment initiation	W 1	W 2	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 52 or discont	FU[i]
ACR-CRISS								X			X							X	
Number of digital ulcers		X	X					X			X			X				X	
Physician's Global Assessment			X					X			X			X				X	
HAQ-DI			X					X			X			X				X	
FACIT-Fatigue			X					X			X			X				X	
FSSG			X					X			X			X				X	
Patient's Global Assessment			X					X			X			X				X	
Safety evaluation																			
Vital signs		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Echocardiography		X									X							X	
Electrocardiogram		X									X							X	
Photography[e]			X																
Laboratory tests																			
Hematology Blood chemistry TARC Urinalysis		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy[f] and TB[g] tests		X																	
Hepatitis B and C tests		X																	
Antinuclear antibodies test			X																
PK analysis and immunogenicity																			

Visit	1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17/ discont	FU
Visit name	IC day	Screening	Treatment initiation	W 1	W 2	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 52 or discont	FU[i]
Serum nemolizumab concentrations			X	X	X	X	X	X	X	X	X			X				X	X
Anti-nemolizumab antibody assay			X								X			X				X	X
Biomarkers																			
IL-31			X			X	X	X	X	X	X			X				X	
KL-6, SP-D, NT-proBNP			X			X		X			X			X				X	
Exploratory biomarkers			X					X			X							X	
Investigational product administration																			
Administration[h]			X			X	X	X	X	X	X	X	X	X	X	X	X		
Others																			
Comprehensive measurement of autoantibodies			X								X							X	
CyTOF measurement			X								X							X	
Adverse Events		→																	
Concomitant medications and therapies		→																	

[a] To be obtained before the observation/tests for the study, and may be obtained on the same day as the day of screening
[b] In principle, the same investigator or subinvestigator will evaluate each participant throughout the study.
[c] If the %FVC decreases by ≥ 15% from baseline, %FVC will be measured again within 1 month.
[d] If having been performed within 1 month of the specified timepoint, not necessary to be performed at the specified timepoint, and the results within 1 month will be substituted.

[e] Not to be performed if refused by the participant.
If any of the following treatment-emergent adverse events occurs, photographs of the affected skin areas of the adverse event should be taken while the event (at least once) is occurring and at the final outcome evaluation, in addition to the scheduled visit (i.e., the day of study treatment initiation).
• Atopic dermatitis
• Adverse events with skin symptoms of edematous erythema or scaling
• Any other adverse event for which the investigator or subinvestigator considers that photography is necessary.

[f] To be performed on female participants excluding those who never become pregnant.

[g] May be conducted on another day after the day of screening before the day of study treatment initiation

[h] To be administered after all observation/tests are performed. If the IP cannot be administered within the window indicated, the next dose should be administered 14 days or later after the day of the previous dose.

[i] Participants who discontinued the study will visit the site 84 days (±7 days) after the day of the last dose of study treatment for observation/tests at FU shown in Table 4-1. Participants discontinued the study before study treatment initiation need not to undergo observation/tests scheduled on the day of visit for discontinuation.

5. Treatment Method

5.1 Method of Administration

The investigator or subinvestigator will slowly administer the IP, nemolizumab (one DCS [0.6 ml]) subcutaneously to the upper arm, abdomen, or thigh of the participants. The IP may be administered by a person qualified to administer it under the instruction of the investigator or subinvestigator.

5.2 Treatment Period

52 weeks

All participants who have received at least one dose of the IP will visit the site 12 weeks after the day of the last dose of study treatment for follow-up.

5.3 Concomitant Medications and Therapies

5.3.1 Restricted Concomitant Medications

The following medications may be continued at a stable dose if used for at least 14 days before the day of study treatment initiation. However, the dose may be reduced at the discretion of the investigator or subinvestigator, and after dose reduction, the dose may be increased up to that used at the day of study treatment initiation.

・Oral steroids (≤ 10 mg/day of prednisolone or equivalent)

5.3.2 Prohibited Concomitant Medications and Therapies

Concomitant use of medications and therapies listed below is prohibited in this study.

- From the day of study treatment initiation to Week 52 or to the physical examination on the day of visit for discontinuation

1） The following systemic medications:
   a） Antifibrotic drugs (e.g., pirfenidone, nintedanib)
   b） Immunosuppressants (e.g., cyclophosphamide, cyclosporine, tacrolimus, azathioprine, mycophenolate mofetil, mizoribine, sulfasalazine, leflunomide, methotrexate, hydroxychloroquine, D-penicillamine, sirolimus)
   c） Tyrosine kinase inhibitors (e.g., imatinib)
   d） JAK inhibitors (e.g., tofacitinib, upadacitinib)
   e） Endothelin receptor agonists (e.g., bosentan, ambrisentan, macitentan)
   f） Phosphodiesterase-5 inhibitors (e.g., sildenafil, tadalafil)
   g） Prostaglandin analogues (e.g., alprostadil, epoprostenol)
   h） Riociguat
2） Injections of corticosteroids (excluding joint injections)
3） Phototherapy
4） High-dose intravenous immunoglobulin therapy
5） Antibody drugs
6） Live vaccines

- From the day of study treatment initiation to the day of follow-up visit

1） Other drugs and medical devices under development

6. Study Discontinuation of Individual Participants

6.1 Discontinuation Criteria

1) Use of other antibody drugs by Week 52 visit
2) Use of live vaccines by Week 52 visit
3) The investigator or subinvestigator determined that an adverse event which would prevent the continuation of the study has occurred.
4) The participant is found to fail to meet any of the inclusion criteria or to meet any of the exclusion criteria.
5) The participant is found to be pregnant.
6) The investigator or subinvestigator has determined that the participant should be withdrawn from the study due to inadequate response to the IP.
7) The participant requests to withdraw from the study.
8) The participant no longer visits the medical institution, and the study cannot be continued.
9) The participant has died.
10) The sponsor has determined the participant discontinuation from the study due to significant protocol deviations.
11) The sponsor has prematurely terminated the study.
12) The investigator or subinvestigator has determined to withdraw the participant from the study for any other reasons.

7. Efficacy Evaluation

7.1 Primary Endpoint

Change from baseline in mRSS at Week 24

7.2 Other Endpoints

1) Change from baseline in mRSS at Week 52
2) Change from baseline in HAQ-DI at Week 52
3) Change from baseline in HAQ-DI at Week 24
4) Change from baseline in %FVC at Week 52
5) Change from baseline in %FVC at Week 24
6) Change from baseline in DLco at Week 52
7) Change from baseline in DLco at Week 24
8) Change from baseline in PGA at Week 52
9) Change from baseline in PGA at Week 24
10) Change from baseline in PtGA at Week 52
11) Change from baseline in PtGA at Week 24
12) ACR-CRISS at Week 52
13) ACR-CRISS at Week 24
14) Change from baseline in the number of digital ulcers at Week 52
15) Change from baseline in the number of digital ulcers at Week 24
16) Time-course change in the following items:
    a) HAQ-DI
    b) FACIT-Fatigue
    c) FSSG
    d) FVC

e） %FVC
f） DLco
g） %DLco
h） TLC
i） FEV_1
j） Severity evaluation of lung lesion
k） PGA
l） PtGA
m） ACR-CRISS
n） The number of digital ulcers

8. Safety Evaluation

8.1 Assessments for Safety Evaluations

1） Adverse events
   a） Symptoms and signs
   b） Abnormal laboratory test values
   c） Abnormal vital signs
   d） Abnormal electrocardiograms
2） Laboratory test values
3） Vital signs
4） Electrocardiogram
5） Echocardiography

9. Target Sample Size

8 participants

10. Study Period

December 2021 to October 2023

Table of Contents

1. Introduction

1.1 Background of Development

1.1.1 Pathophysiology and epidemiology of systemic sclerosis

Systemic scleroderma (SSc) is a systemic autoimmune disease characterized by fibrosis and vasculopathy of skin and various internal organs such as lung and classified as a connective tissue disease. Skin fibrosis, a common symptom in patients with SSc, is considered to be excessive deposition of the extracellular matrix mainly composed of collagen. [1)] In Japan, SSc is designated as an intractable disease; according to the information of the Japan Intractable Diseases Information Center, the number of SSc patients is about 20,000. [2)] The male-to-female ratio of patients is 1:12 and is more prevalent in women between the ages of 30 and 50 years.

SSc is classified as either diffuse cutaneous systemic scleroderma (dcSSc) in which skin thickening extends to the proximal extremities (i.e. the upper arms and the thighs) or the trunk or limited cutaneous systemic scleroderma (lcSSc) in which skin thickening is limited to the distal extremities (i.e. the forearms and the lower legs) and the face.[3)] In dcSSc patients, as skin thickening progresses, visceral involvement such as in the lungs, gastrointestinal tract, kidneys, and heart, and joint flexion contracture progress. In dcSSc in particular, it is widely recognized that the degree of skin thickening correlates with that of fibrotic lesions in internal organs, and higher severity of skin thickening has been reported to be associated with higher rates of visceral involvement including in the lungs and lower survivals. [4), 5), 6)] In addition, fibrosis of internal organs, as well as skin thickening, develops at an early stage, in which slight tissue damage accumulates and progresses to irreversible organ damage. Therefore, treatment should be initiated as early as possible, especially in patients in whom the condition is predicted to become severe. In lcSSc patients, on the other hand, skin thickening progresses slowly and are not eligible for aggressive treatment. However, lcSSc with the possibility of rapid and widespread progression of skin thickening may be eligible for treatment.[7)]

1.1.2 Therapeutic treatment of systemic sclerosis and its issues

The etiology of SSc has not been clarified, and the main treatment methods are symptomatic treatments and disease-modifying drugs that inhibit disease progression. The progression and sites of involvement of SSc are different for each patient, and accordingly, the treatment method is selected based on the symptom of each patient.

Diagnostic Criteria, Severity Classification and Guidelines of Systemic Sclerosis[7)] state that oral corticosteroids are thought to be empirically valid for patients with progressing skin thickening at an early stage but that they have risk factors for inducing renal crisis. Cyclophosphamide is the most recommended treatment option for both skin thickening and interstitial lung disease in patients with SSc; however, it has a problem of difficulty in long-term administration because of its carcinogenicity, immunosuppression, and side effects of drug such as hemorrhagic cystitis. Other drugs for SSc symptoms are prostacyclin, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors for the treatment of pulmonary hypertension, calcium channel blockers for the treatment of cardiac involvement, intravenous prostaglandin E1 or prostacyclin for the treatment of disturbed blood flow in the fingers, and proton pump inhibitors for the treatment of reflux esophagitis. However, due to limited efficacy or safety issues of these therapeutic agents, the disease burden remains high and there is a great unmet medical need.

1.1.3 Summary description and significance of the development of nemolizumab

Nemolizumab is a monoclonal antibody that recognizes interleukin-31 receptor A (IL-31RA) in humans, which competitively inhibits the binding of interleukin-31 (IL-31) to its receptor, thereby blocking subsequent signal transduction into the cells. Nemolizumab was initially developed by [redacted] Co., Ltd.; the worldwide development and marketing rights, except in Japan and Taiwan,

were granted to [redacted] in 2016, while the development and marketing rights in the field of skin diseases in Japan were granted to [redacted].

IL-31 is a cytokine produced mainly from activated T cells. IL-31 is present at higher levels in serum in SSc than in healthy individuals; IL-31 positive cells were identified in inflammatory infiltrates in fibrotic lesions in the skin and lungs[8]. Moreover, an *in vitro* study with dermal fibroblasts from healthy individuals showed IL-31 increased collagen production in these cells, and IL-31 administration to mice induced skin and lung fibrosis in an *in vivo* study, suggesting that IL-31 induces skin and lung fibrosis via inducing collagen production in fibroblasts[8].These results indicate that IL-31 is a key cytokine involved in the development of SSc, and therefore, nemolizumab is expected to inhibit the progression of or ameliorate of skin and pulmonary fibrosis in SSc.

From the above, nemolizumab is considered to be a possible new treatment option for SSc. Thus, this study has been developed to explore the efficacy and safety of nemolizumab in SSc patients.

1.2 Guidelines, Consultation with Pharmaceuticals and Medical Devices Agency (PMDA), etc., Referenced for Study Planning

This study has been planned in reference to the “Diagnostic criteria, severity classification and guidelines of systemic sclerosis.”

2. Study objectives

2.1 Primary Objective

To exploratorily evaluate the efficacy of nemolizumab in systemic sclerosis (SSc) patients with moderate to severe skin thickening

2.2 Secondary Objective

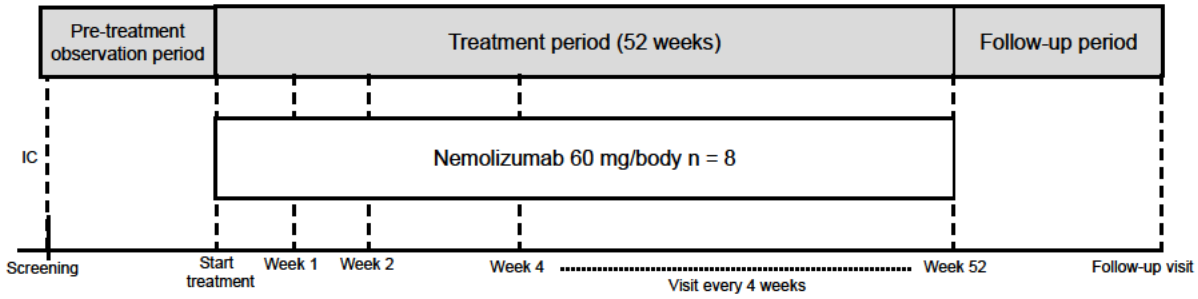
To evaluate the safety and pharmacokinetics of nemolizumab in SSc patients with moderate to severe skin thickening

3. Study Design

This is a phase II, single-arm, multiple-dose study consisting of a pre-treatment observation period (1-4 weeks) and a treatment period (52 weeks). The pre-treatment observation period is from the day of screening to the day of study treatment initiation, and participants will visit the site a total of twice, for screening and for study treatment initiation. The treatment period is from the day of study treatment initiation to Visit 17 (Week 52), during which participants will visit a total of 15 times: Week1,2 and 4, and every four weeks thereafter. Participants having received study treatment will be followed up 84 days after the day of the last dose of study treatment. Follow-up period is from Visit17 (Week 52) or the day of discontinuation visit to the day of follow-up visit.

Study phase: Phase II
Study type: Open-label, single-arm, multiple-dose study
Participants: SSc patients with moderate to severe skin thickening
Target Sample Size: 8 participants

Figure 3-1: Study Schema



1) Pre-treatment observation period
The investigator or subinvestigator will make observations and assessments at the screening visit specified in Table 9-1 after obtaining informed consent from the participant.

2) Treatment period
The investigator or subinvestigator will administer the investigational product (IP) (nemolizumab, 60 mg/body) every 4 weeks (Q4W) at visits until Week 48 after making observations and assessments on the day of study treatment initiation specified in Table 9-1. In addition, the investigator or subinvestigator will make perform observations and assessments at each visit specified in Table 9-1.

3) Follow-up period

All participants having received the IP will be scheduled to visit for follow-up 12 weeks after the day of the last dose of study treatment (the day of follow-up visit). On the day of the follow-up visit, the investigator or subinvestigator will evaluate the safety and efficacy after completion of study treatment for all participants.

4. Target Indication and Inclusion and Exclusion Criteria for Participants

The investigator or subinvestigator will ensure before enrollment that all inclusion criteria are met and none of the exclusion criteria are met.

4.1 Target Indication

SSc

4.2 Inclusion Criteria

Participants must meet all of the following criteria for study entry:

Inclusion Criteria	Assessment timing		
	Day of Informed Consent	Day of Screening	Day of treatment start
1) Patients aged 20 to 70 years at the time of informed consent	X	–	–
2) Patients meeting the classification criteria for SSc in ACR and EULAR 2013	X	–	–
3) Patients with systemic sclerosis who have moderate to severe skin thickening, with mRSS of 10 to 22 on both the screening and treatment initiation dates	–	X	X
4) Patients considered by the investigator or subinvestigator to be competent to perform the protocol-specified self-assessment	X	X	X

・ Rationale for inclusion criteria

1)	Established for safety consideration and to select patients with a sufficient capacity for judgment
2)	Established to standardize the diagnostic criteria for SSc for participants
3)	Established to include only patients with moderate to severe symptoms who are considered to be target patients for this drug.
4)	Established to select patients who can comply with the protocol-specified activities.

4.3 Exclusion criteria

Participants who meet any of the following criteria will be excluded from study entry:

Exclusion Criteria	Confirmation timing		
	Day of informed consent	Day of Screening	Day of treatment start
1) Patients complicated with diseases considered inappropriate for participation in clinical trials, such as serious* cardiac/hepatic/renal/pulmonary/hematologic disease *Refer to the Criteria for Seriousness Classification of Adverse Drug Reactions. (PAB/SD Notification No.80 by the Director	X	X	X

Exclusion Criteria	Confirmation timing		
	Day of informed consent	Day of Screening	Day of treatment start
of Safety Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare dated June 29, 1992) and the Common Terminology Criteria for Adverse Events v 5.0 Japanese JCOG version (CTCAE v 5.0-JCOG).			
2) Patients complicated with congestive heart failure [New York Heart Association (NYHA) Functional Class III or IV]	X	X	X
3) Patients having any of the following complications or concomitant/concurrent diseases: a) Severe chronic pulmonary disease (including %FVC < 60%, or %DLco < 40% on the day of screening, calculated from the New Reference Values for Spirometry in Japanese adults calculated with the LMS Method (the Japanese Respiratory Society)" b) Serious complications associated with SSc other than interstitial lung disease* (e.g., renal crisis) * Interstitial lung disease is excluded if it falls under Item a) of3) c) Poorly controlled asthma that requires steroids (systemic), intravenous infusion of aminophylline, subcutaneous injection of adrenaline 0.1%, oxygen inhalation, or antibody drugs d) Diseases to affect the assessment of SSc	X	X	X
4) Patients with a history of malignant tumor, who are receiving no treatment and have had no recurrence /relapse for ≥5 years at the time of informed consent, or patients with a history of radical treatment for cervical intraepithelial neoplasia at the time of informed consent may be included in the study	X	X	X
5) Patients with Immune deficiency (e.g., congenital immunodeficiency, AIDS, or HIV).	X	X	X
6) Patients with a history or current hypersensitivity (including anaphylaxis) to immunoglobulin products (plasma-derived preparations or genetic recombinant monoclonal antibodies)	X	X	X
7) Patients weighing < 30.0 kg or > 120 kg on the day of study treatment initiation	–	–	X
8) Patients whose laboratory test values on the day of screening meet any of the following criteria: a) AST or ALT > 2 times the upper limit of normal b) Serum creatinine ≥2.0 mg/dL c) WBC <3000 cells/μL	–	–	X
9) Patients infected with hepatitis B virus (HBV) or hepatitis C virus (HCV) (Positive for HBs antigen or HBc antibody on the day of screening, positive for anti-HCV antibody on the day of screening) The allowed exceptions are as follows: ・ Patients confirmed not to be infected with HBs at the time of the HBV-DNA test performed before study treatment initiation in the case of negative for HBs antigen and positive for HBc antibody in the hepatitis B test	–	–	X

Exclusion Criteria		Confirmation timing		
		Day of informed consent	Day of Screening	Day of treatment start
performed on the day of screening. ・ Patients confirmed not to be infected with HCV at the time of the HCV-RNA test performed before study treatment initiation in the case of positive for anti-HCV antibody in the hepatitis C test performed on the day of screening				
10) Patients with latent or active tuberculosis based on the result of the screening TB test. The allowed exception is patients deemed not to be infected with tuberculosis according to the "Guidelines for the use of interferon-γ release assay (Prevention Committee of the Japanese Society for Tuberculosis).		–	–	X
11) Patients with either of the following infectious diseases: ・ Recurrent/chronic infections or other active infections deemed by the investigator to possibly aggravated by participating in the study ・ Infections (including skin infections) requiring systemic antibiotics, antivirals, or antifungals within 7 days prior to the day of study treatment initiation.		X	X	X
12) Patients who have received oral steroids (> 10 mg/day of prednisolone or equivalent), dosage of receiving oral steroids have been changed (from ≤ 10 mg/day of prednisolone or equivalent), or newly treated with oral steroids, within 14 days before the day of study treatment initiation		–	–	X
13) Patients who have received any of the following therapies within the indicated period prior to the day of study treatment initiation		–	(X)*	X
a) Within 365 days	Cyclophosphamide			
b) Within 120 days or 5 times the elimination half-life of the drug, whichever is longer	Antibody drugs			
c) Within 28 days	i. Live vaccines ii. The following systemic medications: – Antifibrotic drugs (e.g., pirfenidone, nintedanib) – Immunosuppressants (e.g., cyclosporine, tacrolimus, azathioprine, mycophenolate mofetil, mizoribine, sulfasalazine, leflunomide, methotrexate, hydroxychloroquine, D-penicillamine, sirolimus) – Tyrosine kinase inhibitors (e.g., imatinib)			

Exclusion Criteria	Confirmation timing		
	Day of informed consent	Day of Screening	Day of treatment start
– JAK inhibitors (e.g., tofacitinib, upadacitinib) – Endothelin receptor agonists (e.g., bosentan, ambrisentan, macitentan) – Phosphodiesterase-5 inhibitors (e.g., sildenafil, tadalafil) – Prostaglandin analogue (e.g., alprostadil, epoprostenol) – Riociguat iii. Injections of corticosteroids (excluding joint injections) iv. Phototherapy v. High-dose intravenous immunoglobulin therapy			
14) Patients who are within 120 days from the end of participation in other clinical trials or post-marketing clinical studies (i.e., the last day of administration of another IP or post-marketing clinical study drug) until the day of study treatment initiation, or participating in other clinical trials or post-marketing clinical studies	–	(X)*	X
15) Women who are pregnant, breastfeeding, possibly pregnant, or unwilling to use appropriate contraception measures as instructed by the investigator during the study period	X	X	X
16) Patients who meet any of the following criteria: a) Having not met eligibility for participation when participating in this study in the past b) Having previously received nemolizumab (including placebo)	X	X	X
17) Patients with confirmed or suspected COVID-19	–	X	X
18) Patients with a history of confirmed or suspected COVID-19 excluding those meeting any of the following criteria: • At least 20 days after the onset of symptoms and at least 72 hours after the resolution of symptoms. • Confirmed not to carry SARS-Cov-2.	–	X	X
19) Patients found to have close contacts with COVID-19 patients within 14 days before the day of study treatment initiation	–	–	X
20) Other patients who are considered ineligible for the study by the investigator	X	X	X

*The exclusion criteria will be assessed with the expected date of study treatment initiation as the starting point.

・ Rationale for exclusion criteria

1) to 6), 8) to 11), 15), and 17) to 19)	Established considering the safety of participants
7)	Since the dose in this study is 60 mg/body, the upper body weight limit was set not to be lower than the dose (0.5 mg/kg) proven effective in the studies conducted to date in patients with atopic dermatitis, in view of efficacy. The lower

	limit of body weight was set to ensure the safety of participants so that the exposure does not exceed that at the maximum dose (2.0 mg/kg) confirmed to be tolerated after repeated administration of IP.
12)	Established considering the impact on the efficacy of the IP and to ensure the safety of the participants.
13) a), b), c) ii), iii), v),14)	Established considering the impact on the efficacy and safety evaluation of the IP. The period was considered necessary for washout based on the duration of treatment effect and half-live of each drug and therapy.
13) c), i)	Established considering the impact on the safety evaluation of the IP. The period was considered necessary for washout based on the duration of treatment effect and half-live of each drug
13) c), iv)	Established considering the impact on the efficacy evaluation of the IP. The period was considered necessary for washout based on the duration of treatment effect and half-live of each therapy.
16)	1) Established to exclude patients ineligible for this study 2) Established to exclude the impact on the evaluation of efficacy and safety
20)	Established as a general criterion to exclude patients considered ineligible for this study by the investigator or subinvestigator.

5. Study Discontinuation of Individual Participants

The investigator or subinvestigator will withdraw the participant signing informed consent from the study and take appropriate measures if participant meets any of the following discontinuation criteria before observation/tests at Visit 17 (Week 52). Even if the participant requests withdrawal from the study, the participant's data will be used.

5.1 Discontinuation criteria

1) Use of other antibody drugs by Week 52 visit
2) Use of live vaccines by Week 52 visit
3) The investigator or subinvestigator determined that an adverse event which would prevent the continuation of the study has occurred.
4) The participant is found to fail to meet any of the inclusion criteria or to meet any of the exclusion criteria.
5) The participant is found to be pregnant.
6) The investigator or subinvestigator has determined that the participant should be withdrawn from the study due to inadequate response to the IP.
7) The participant requests to withdraw from the study.
8) The participant no longer visits the medical institution, and the study cannot be continued
9) The participant has died.
10) The sponsor has determined the participant discontinuation from the study due to significant protocol deviations.

The sponsor has prematurely terminated the study.
The investigator or subinvestigator has determined to withdraw the participant from the study for any other reasons.

・ Rationale for discontinuation criteria

1) to 3), 5)	Established considering the safety of the participants
4)	Established because the participants are considered ineligible for the study
6)	Established to reduce disadvantages for the participants

7)	Established because it is considered the rights of participants
8) to 11)	Established for contingencies
12)	Established to allow participant discontinuation from the study at the discretion of the investigator or subinvestigator.

5.2 Procedure for Discontinuation

5.2.1 Discontinuation before Enrollment

1) For the participant not led to enrollment because of not satisfying the inclusion criteria, meeting any of the exclusion criteria or other reasons, the investigator or subinvestigator will explain the reason to withdraw the participant from the study, take appropriate action for the participant. The investigator or subinvestigator will ascertain and record the date of discontinuation and the reason for discontinuation in the source documents. A visit for discontinuation and observation/tests scheduled on the day of visit for discontinuation will not be performed.
2) The investigator, subinvestigator, or CRC will record the data for the items described in Section 19.1.2 in the CRF.

5.2.2 Discontinuation after Enrollment

1) The investigator or subinvestigator will explain the reason to withdraw the participant from the study and take appropriate action, ascertain and record the reason for discontinuation in the source documents.
2) The investigator or subinvestigator will perform the observation/tests scheduled on the day of visit for discontinuation. When determining to discontinue the study on a day other than the day of the visit, the investigator or subinvestigator will instruct the participant to come to the study site as early as possible. However, if the day of visit for discontinuation is on or after 77 days from the last dose of study treatment.
3) The investigator, subinvestigator, or CRC will record the data of the items described in Section 19.1.1 in the CRF.

5.3 Handling of Participants Who Fail to Visit the Study Site

5.3.1 Participants Discontinuing Study Site Visit Between the Day of Informed Consent and the Day of Enrollment

When a participant discontinues visiting the study site after the day of informed consent but before enrollment, the investigator or subinvestigator will perform follow-up of the participant through contact with him/her by telephone, letter or other means to record the method and the result of follow-up, reason(s) for not visiting with the date of such information obtained, presence or absence of adverse events, and other information obtained in the source document.

5.3.2 Participants Discontinuing Study Site Visit in the Period after the Enrollment up to Visit 17 (Week 52)

If a participant discontinues visiting the study site after assigned to treatment, the investigator or subinvestigator will identify the whereabouts of the participant as far as possible and encourage him/her to visit the study site. If the participant dose not visit the study site, the investigator or subinvestigator will perform follow-up of the participant through contact with him/her by telephone, letter, or other means to document the method of follow-up, reason(s) for not visiting with the date of such information obtained, presence or absence of adverse events, and other information obtained.

5.3.3 Participants Discontinuing Study Site Visit during the Follow-up Period

The participant who cannot visit the study site within the window of the follow-up visit will be encouraged to visit the study site on the nearest day to the window. If the participant does not visit the study site, the investigator or subinvestigator will perform follow up of the participant through contact with him/her by telephone, letter, and other means to document the method of follow-up, reason(s) for not visiting with the

date of such information obtained, the presence or absence of adverse events, and other information obtained.

6. Participant Enrollment

6.1 Informed Consent

The investigator or subinvestigator will fully explain the study to participants who are considered eligible for the study and obtain written consent before the procedures for the study (see Section 27.4 for the method and points to note for obtaining informed consent).
The investigator or subinvestigator will record the participant information on the participant screening log and provide the participant identification code. The participant identification will be AF001-XXX and will be coded in order of informed consent acquisition. Each participant will use the same participant identification code from informed consent to completion of the study.

6.2 Notification when the Participant is Treated by Another Doctor

The investigator or subinvestigator will ask participants whether or not they are being treated by another doctor. When a participant is being treated by another doctor, the investigator or subinvestigator will notify the doctor of his/her participation in the study after obtaining his/her consent. In addition, the investigator or subinvestigator will record this notification to the doctor in the medical record, etc.

6.3 Enrollment Procedure of Participants

1) For first and second registration.
   For participants considered eligible for the study on the day of screening and on the day of study treatment initiation, the investigator or subinvestigator will enter the necessary information in the source documents, and then fill out a registration form and fax it to the sponsor. The registration form should be filled out and faxed after the source documents have been prepared, which can be performed by the CRC.

2) For discontinuation before assigned to treatment
   For participants discontinued from the study after informed consent but before second registration, the investigator or subinvestigator will enter the necessary information in the source documents, and then fill out a registration form and fax it to the sponsor. The registration form should be filled out and faxed after the source documents have been prepared, which can be performed by the CRC.

3) Correction of entries in the source documents
   When an error is found in the information registered, the investigator or subinvestigator will correct the data in the source document and enter the necessary information in a registration form as needed, and then fax it to the sponsor to correct such data. The registration form should be filled out and faxed after the source documents have been corrected, which can be performed by the CRC.

7. Investigational Product

7.1 Name, Dosage Form, and Strength of the IP

Name, dosage form, and strength of the IPs are indicated in Table 7-1.

Table 7-1 Name, dosage form and strength of investigational product

Name of investigational product	Formulation	Active ingredient and strength (Per DCS)	Storage condition (Before preparation)
Nemolizumab	Injection (DCS)	nemolizumab 75 mg (lyophilized) Nemolizumab is overfilled to ensure injectable nemolizumab 60 mg from one DCS in consideration of the loss of the prepared drug solution during administration. The active ingredient level after preparation is 100 mg/mL.	2°C to 8°C Protection from light

7.2 Packaging and Labeling

7.2.1 Packaging

One DCS of the IP is contained in a small box.

7.2.2 Labeling

The small box is labeled with a statement for clinical study use only, the name and address of the sponsor, identification number, lot number, and storage method.

7.3 Storage and Management of Investigational Products

The investigational product manager at each study site will store and manage the IPs according to the "Operating Procedure for Investigational Product Management" prepared by the sponsor and other procedures specified at each site.

8. Treatment Method

8.1 Dispensing of Investigational Products

The investigator or subinvestigator will dispense one DCS of the IP at the following visits:
<Dispensing visits>
Day of study treatment initiation, Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48

8.2 Preparation of Investigational Products

The investigator or subinvestigator, the investigational product manager or the person in charge of preparation of the IP will prepare injection solutions of IPs according to the "Standard Operating Procedure for Investigational Product Management."

8.3 Method of Administration

On the days of administration (see Table 9-1: Schedule), the investigator or subinvestigator will subcutaneously inject one DCS (0.6-mL) of nemolizumab slowly to the participant either in the upper arm, abdomen, or thigh. The IP may be administered by a person qualified to administer it under the instruction of the investigator or subinvestigator.

・ Precautions
  - The IP will be administered after all observation/tests scheduled at the visit have been completed.
  - The IP will be administered within the window of the specified visit. However, if the IP cannot be administered within the window, the next dose should be administered 14 days or later after the

previous dose.

- If the participant's body weight is lower than 30.0 kg on the day of administration, the IP must not be administered.

・ Rationale for selection>

1） Dosage: 60 mg/body Q4W

A phase III study in Japanese patients with atopic dermatitis has demonstrated the long-term safety of nemolizumab 60 mg/body Q4W. This study has been designed to exploratorily evaluate the efficacy of nemolizumab in SSc patients at 60 mg/body Q4W which has shown the long-term efficacy in SSc patients.

2） Treatment Period

The treatment period has been set at 52 weeks because long-term observation is required to evaluate the efficacy of nemolizumab on skin thickening in SSc patients in an exploratory manner.

3） Day of Follow-up Visit

Considering the serum elimination half-life after a single dose of nemolizumab ranges from 12.6 to 14.6 days in patients with atopic dermatitis, the day of follow-up visit has been set to collect information such as the occurrence of adverse events on the day of 5 times the elimination half-life (84 days ± 7 days) from the day of the last dose.

8.4 Concomitant Medications and Therapies

8.4.1 Restricted Concomitant Medications

The following medications may be continued at a stable dose if used for at least 14 days before the day of study treatment initiation. However, the dose may be reduced at the discretion of the investigator or subinvestigator, and after dose reduction, the dose may be increased up to that used at the day of study treatment initiation.

・Oral steroids (≤ 10 mg/day of prednisolone or equivalent)

8.4.2 Duration and Method of Inspection

The investigator or subinvestigator will collect the information of concomitant medications/therapies by interviewing participants according to Section.9.3.2

8.4.3 Prohibited Concomitant Medications and Therapies

Concomitant use of medications and therapies listed below is prohibited in this study.

- From the day of study treatment initiation to Week 52 or to the physical examination on the day of visit for discontinuation

1） The following systemic medications:

a） Antifibrotic drugs (e.g., pirfenidone, nintedanib)

b） Immunosuppressants (e.g., cyclophosphamide, cyclosporine, tacrolimus, azathioprine, mycophenolate mofetil, mizoribine, sulfasalazine, leflunomide, methotrexate, hydroxychloroquine, D-penicillamine, sirolimus)

c） Tyrosine kinase inhibitors (e.g., imatinib)

d） JAK inhibitors (e.g., tofacitinib, upadacitinib)

e） Endothelin receptor agonists (e.g., bosentan, ambrisentan, macitentan)

f） Phosphodiesterase-5 inhibitors (e.g., sildenafil, tadalafil)

g） Prostaglandin analogues (e.g., alprostadil, epoprostenol)
h） Riociguat

2） Injections of corticosteroids (excluding joint injections)
3） Phototherapy
4） High-dose intravenous immunoglobulin therapy
5） Antibody drugs
6） Live vaccines

・ Rationale for selection

1) 2) 4) 5)	Established considering the impact on the efficacy of the IP and the safety of participants
3)	Established considering the impact on the efficacy evaluation of the IP
6)	Established considering the safety of participants

- From the day of study treatment initiation to the day of follow-up visit

1） Other drugs and medical devices under development

・ Rationale for selection

1)	Established considering the safety of participants and the impact on the efficacy of the IP.

8.4.4 Instructions to participants

The investigator or subinvestigator will examine the implementation status of the treatment of SSc at each visit and give instructions to the participants on treatment of SSc according to the therapeutic guidance specified in Sections 8.4.1 and 8.4.3.

9. Study Procedures and Assessments and the Schedule

9.1 Schedule of Study Procedures and Assessments

Observation, tests and sample collection will be performed according to the schedule shown in Table 9-1.

Table 9-1: Schedule

Visit	1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17/ discont	FU
Visit name	IC day	Screening	Treatment initiation	W 1	W 2	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 52 or discont	FU[i]
Reference day	-	-14	1	8	15	29	57	85	113	141	169	197	225	253	281	309	337	365/ discont	Day of last dose +84
Visit window	-	-16/+9	-	±2	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7/ day of discon+14	±7
Screening/management																			
Informed consent	X[a]																		
Physical examinations	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Demographics	X	X	X																
Body weight		X	X			X	X	X	X	X	X	X	X	X	X	X	X		
Registration		X 1st	X 2nd															X Time of discont	
Efficacy evaluation																			
mRSS[b]		X	X			X		X			X			X				X	X
Respiratory function test[C]		X						X			X							X	
Chest HRCT[d]		X									X							X	

Visit	1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17/ discont	FU
Visit name	IC day	Screening	Treatment initiation	W 1	W 2	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 52 or discont	FU[i]
Severity classification of the lung		X									X							X	
ACR-CRISS								X			X							X	
Number of digital ulcers		X	X					X			X			X				X	
Physician's Global Assessment			X					X			X			X				X	
HAQ-DI			X					X			X			X				X	
FACIT-Fatigue			X					X			X			X				X	
FSSG			X					X			X			X				X	
Patient's Global Assessment			X					X			X			X				X	
Safety evaluation																			
Vital signs		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Echocardiography		X									X							X	
Electrocardiogram		X									X							X	
Photography[e]			X																
Laboratory tests																			
Hematology Blood chemistry TARC Urinalysis		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy[f] and TB[g] tests		X																	
Hepatitis B and C tests		X																	
Antinuclear antibodies test			X																

Visit	1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17/ discont	FU
Visit name	IC day	Screening	Treatment initiation	W 1	W 2	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 52 or discont	FU[i]
PK analysis and immunogenicity																			
Serum nemolizumab concentrations			X	X	X	X	X	X	X	X	X			X				X	X
Anti-nemolizumab antibody assay			X								X			X				X	X
Biomarkers																			
IL-31			X			X	X	X	X	X	X			X				X	
KL-6, SP-D, NT-proBNP			X			X		X			X			X				X	
Exploratory biomarkers			X					X			X							X	
Investigational product administration																			
Administration[h]			X			X	X	X	X	X	X	X	X	X	X	X	X		
Others																			
Comprehensive measurement of autoantibodies			X								X							X	
CyTOF measurement			X								X							X	
Adverse Events		→																	
Concomitant medications and therapies		→																	

[a] To be obtained before the observation/tests for the study, and may be obtained on the same day as the day of screening
[b] In principle, the same investigator or subinvestigator will evaluate each participant throughout the study.
[c] If the %FVC decreases by ≥ 15% from baseline, %FVC will be measured again within 1 month.
[d] If having been performed within 1 month of the specified timepoint, not necessary to be performed at the specified timepoint, and the results within 1 month will be substituted.

[e] Not to be performed if refused by the participant.
If any of the following treatment-emergent adverse events occurs, photographs of the affected skin areas of the adverse event should be taken while the event (at least once) is occurring and at the final outcome evaluation, in addition to the scheduled visit (i.e., the day of study treatment initiation). The photography on the scheduled visit (day of study treatment initiation) will be performed according to Section 9.3.5.4
• Atopic dermatitis
• Adverse events with skin symptoms of edematous erythema or scaling
• Any other adverse event for which the investigator or subinvestigator considers that photography is necessary.

[f] To be performed on female participants excluding those who never become pregnant.

[g] May be conducted on another day after the day of screening before the day of study treatment initiation

[h] To be administered after all observation/tests are performed. If the IP cannot be administered within the window indicated, the next dose should be administered 14 days or later after the day of the previous dose.

[i] Participants who discontinued the study will visit the site 84 days (±7 days) after the day of the last dose of study treatment for observation/tests at FU shown in Table 4-1. Participants discontinued the study before study treatment initiation need not to undergo observation/tests scheduled on the day of visit for discontinuation.

9.2 Definition of the Days of Observation, Tests, and Sample Collection

The days of observation, tests, and sample collection will be defined as follows. Table 9-1 shows the visit window of the assessment day.

9.2.1 Day of Informed Consent

The day when informed consent is obtained from the participant is defined as the day of informed consent.

9.2.2 Day of screening

The day of screening is defined as the day of first registration after completion of protocol-specified assessments. The day of informed consent may be the same day as the day of screening.
All observation/tests scheduled for the day of screening must be performed on the same day. The tuberculosis test may be performed after the day of screening; however, the test result should be reviewed before the day of study treatment initiation.

9.2.3 Day of Study Treatment Initiation

The day of study treatment initiation is defined as the day when the participant is enrolled after completion of protocol-specified assessments. All assessments scheduled for the day of study treatment initiation must be performed on the same day.
The day of study treatment initiation is Day 1, and the day before the day of study treatment initiation is Day -1.

9.2.4 Day of Assessment (Weeks 1, 2, 4, 8, 12, through 52)

Week 1 through Week 52 are days when participants visit the study site for protocol-specified observation/tests.

9.2.5 Day of Study Treatment

The day of study treatment is defined as the day when the IP is administered to the participant according to the schedule of Table 9-1 after the protocol-specified assessments are implemented.

9.2.6 Day of Discontinuation

The day of discontinuation is defined as the day when the investigator or subinvestigator determines to withdraw the participant from the study.

9.2.7 Day of Discontinuation Visit

The day of visit for discontinuation is defined as the day when the protocol-specified observation/tests scheduled for discontinuation are performed for the participant who is determined to be withdrawn from the study after study treatment initiation and visit the study site for the procedure.

9.2.8 Day of Follow-up Visit

The day of follow-up visit is defined as the day when the protocol-specified observation/tests are performed for the participant who visits the study site 84 days (±7 days) after the day of the last dose of study treatment.

9.3 Observation, Tests and Sample Collection

9.3.1 Participant Demographics

The investigator or subinvestigator will perform following assessments on the day of informed consent, the day of screening and the day of study treatment initiation.

1） Assessments on the day of informed consent
- Primary disease (diagnosis)
- Time of onset of primary disease
- Classification of primary disease (diffuse cutaneous SSc [dcSSc] or limited cutaneous SSc [lcSSc])
- Main therapy given for SSc in the past
- Date of birth
- Sex
- Complication (any disease which is ongoing at the time of informed consent)
- Race
- Inclusion and exclusion criteria (see “4. Target Indication and Inclusion and Exclusion Criteria for Participants”)

2） Assessments on the day of screening
- Inclusion and exclusion criteria (see “4. Target Indication and Inclusion and Exclusion Criteria for Participants”)
- Height

3） Assessments on the day of study treatment initiation
- Inclusion and exclusion criteria (see “4. Target Indication and Inclusion and Exclusion Criteria for Participants”)

9.3.2 Prior and Concomitant Medications and Therapies
9.3.2.1 Prior and concomitant medications
The investigator or subinvestigator will review the following medications for each participant:

1） Medications intended to treat SSc
- Used from 28 days before the day of study treatment initiation to the physical examination at the follow-up visit

2） Medications intended to treat adverse events

a） Medications intended to treat adverse events of special interest defined in Section 11.6 :
Used from the day of study treatment initiation (after initiating study treatment) to the final outcome evaluation.

b） Medications intended to treat adverse events except for 1):
Used from the day of study treatment initiation (after initiating study treatment) to the physical examination at the follow-up visit.

3） All concomitant medications other than 1), and 2)
- Used from the day of study treatment initiation (after initiating study treatment) to Week 52 or the day of discontinuation visit.

Information to be obtained	Presence or absence of concomitant medications, and the drug name, dosage, drug use classification, start and end dates of use, and indication for use of each concomitant medication
Notes	The following information is not required to be collected: ・Diagnostic agents, infusions, fluid replacement, nutritional agents, disinfectants, anesthetics for surgery, laxatives and suppository for barium examination (unless these drugs were used for treatment or are included in the prohibited concomitant medications) ・Dosage of 3) ・Among medications of 1), those newly used in participants who discontinued

	from the study on or after the physical examination at the discontinuation visit.

9.3.2.2 Prior and concomitant therapies

The investigator or subinvestigator will collect the data of the following therapies:

1) Therapies to treat SSc
   - Performed from 28 days before the day of study treatment initiation to the physical examination at the follow-up visit.
2) Concomitant therapies intended to treat adverse events
   a) Concomitant therapies intended to treat adverse events of special interest defined in Section 11.6
      - Performed from the day of study treatment initiation (after initiating study treatment) to the final outcome evaluation.
   b) Concomitant therapies intended to treat adverse events except for 1)
      - Performed from the day of study treatment initiation (after initiating study treatment) to the physical examination at the follow-up visit.
   c) Prohibited concomitant therapies
      - Performed from the day of study treatment initiation (after initiating study treatment) to Week 52 or the day of discontinuation visit.

Information to be obtained	Presence or absence of therapy, and the name of therapy, site to which concomitant therapy is applied, start and end dates of application and purpose of use of concomitant therapy
Notes	Among therapies of 1), those newly performed to participants who discontinued from the study on or after the physical examination at the discontinuation visit are not required.

9.3.3 Body Weight

The investigator or subinvestigator will measure the body weight of participants at the following timepoints:

Data to be obtained	Body weight
Time points	Day of screening, Day of study treatment initiation, Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48
Notes	・On the days of study treatment, measurement will be performed, and the results will be reviewed before administration of IP. ・Participants weighing less than 30.0 kg on the day of study treatment are not allowed to receive study treatment.

9.3.4 Efficacy Evaluation

9.3.4.1 Evaluation of Skin Findings

The investigator or subinvestigator will perform the following assessments:

Assessment	mRSS
Time points	Day of screening, Day of study treatment initiation, Week 4, 12, 24, and 36, Week 52 or Day of discontinuation visit, Day of follow-up visit
Notes	・On the day of study treatment, assessment will be performed before the treatment. ・mRSS assessment will be performed by a skilled physician experienced in scoring skin sclerosis. ・In principle, the same investigator or subinvestigator will perform assessment throughout the study period for each participant in order to minimize inter-assessor variability.

9.3.4.2 Respiratory function test

Spirometry will be performed according to the separately specified procedure.

Assessment	• Forced vital capacity (FVC) and %FVC • Diffusing capacity of lung for carbon monoxide (DLco) and % DLco • Total lung capacity (TLC) and forced expiratory volume in one second (FEV_1)
Time points	Day of screening, Week 12, and 24, Week 52 or Day of discontinuation visit
Notes	• If the %FVC decreases by ≥ 15% from baseline, %FVC will be measured again within 1 month to examine whether the %FVC decreases by ≥ 15% from baseline or not.

9.3.4.3 Chest HRCT

HRCT will be performed according to the regulations or procedures or the test manual of the study site.

Time points	• Day of screening, Week 24, Week 52 or Day of discontinuation visit
Notes	If having been performed within 1 month of the specified timepoint, it is not necessary to be performed at the specified timepoints, and the results within 1 month will be substituted.

9.3.4.4 Severity of pulmonary lesions

The investigator or subinvestigator will evaluate the severity of pulmonary lesions based on the results of respiratory function test and chest HRCT according to 10.1.4 .

Time points	Day of screening, Week 24, Week 52 or Day of discontinuation visit

9.3.4.5 ACR-CRISS

The investigator or subinvestigator will assess whether the participant fall under the following criteria:

Evaluations	• Onset of scleroderma renal crisis • Interstitial lung disease with a decline in %FVC ≥15% (requiring reconfirmation within 1 month), and %FVC of 80% or less • Onset of left ventricular failure requiring treatment (defined as left ventricular ejection fraction ≤45%) * • Onset of pulmonary arterial hypertension requiring right heart catheterization * *Caused by SSc
Time points	Week 12 and 24, Week 52 or Day of discontinuation visit

9.3.4.6 The Number of Digital Ulcers

The investigator or subinvestigator will count the number of digital ulcers.

Time points	• Day of screening, Day of study treatment initiation, Week 12, 24 and 36, Week 52 or Day of discontinuation visit
Notes	• In principle, the same investigator or subinvestigator will perform assessment throughout the study period for each participant in order to minimize inter-assessor variability.

9.3.4.7 Patient-reported outcome

The participants will perform the following assessments:

Evaluations	HAQ-DI, FACIT-Fatigue and FSSG
Time points	Day of study treatment initiation, Week 12, 24, and 36, Week 52 or Day of discontinuation visit
Notes	• The participants will perform each assessment before receiving the examination and evaluation by the physician at the above visits. • The investigator or subinvestigator must not attend the assessments by the participants.

9.3.4.8 Global improvement rating

9.3.4.8.1 Patient's Global Assessment (PtGA)

The participants will assess the overall condition of SSc using a visual analog scale (VAS).

Time points	Day of study treatment initiation, Week 12, 24, and 36, Week 52 or Day of discontinuation visit
Notes	• The participants will perform each assessment before receiving the examination and evaluation by the physician at the above visits. • The investigator or subinvestigator must not attend the assessments by the participants.

9.3.4.8.2 Physician's Global Assessment (PGA)

The investigator or subinvestigator will assess the overall condition of SSc of each participant using a VAS.

Time points	Day of study treatment initiation, Week 12, 24, and 36, Week 52 or Day of discontinuation visit
Notes	• In principle, the same investigator or subinvestigator will perform assessment throughout the study period for each participant in order to minimize inter-assessor variability.

9.3.5 Safety Evaluation

9.3.5.1 Vital signs

The investigator or subinvestigator will perform the following measurements:

Measurements	Body temperature, pulse rate, and blood pressure (systolic/diastolic)
Time points	Day of screening, Day of study treatment initiation, Week 1, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48, Week 52 or Day of discontinuation visit, Day of follow-up visit
Notes	• On the day of study treatment, measurements will be performed, and the results will be reviewed before the treatment. • The vital signs will be measured at rest in the sitting position.

9.3.5.2 ECG

The investigator or subinvestigator will perform the following measurements:

Measurements	PR interval, QRS interval, QT interval, heart rate and presence or absence of abnormalities
Time points	Day of screening, Week 24, Week 52 or Day of discontinuation visit

Notes	・ On the day of study treatment, measurements will be performed, and the results will be reviewed before the treatment. ・ The same electrocardiograph will be used for each participant at each measurement whenever possible. ・ ECG will be performed at rest in the supine position.

9.3.5.3 Echocardiography

Echocardiography will be performed according to the regulations, procedures, or the test manual of the study site.

Time points	Day of screening, Week 24, Week 52 or Day of discontinuation visit
Notes	・ On the day of study treatment, measurements will be performed, and the results will be reviewed before the treatment.

9.3.5.4 Photography

The investigator or subinvestigator will perform photography according to the separately specified procedure.

Sites to be Photographed	1） Anterior and dorsal views of the upper body (excluding the face) 2） Skin appearance of adverse events
Time points	1） Day of study treatment initiation 2） Duration of the following adverse events (at least once occurrence) after study treatment initiation and at the final outcome evaluation: ・ Atopic dermatitis ・ Adverse events with skin symptoms accompanied by edematous erythema or scaling ・ Any other adverse event for which the investigator or subinvestigator considers that photography is necessary.
Notes	1) and 2): ・ The photos will be retained by the study site and collected by the sponsor. When personal information can be identified from the photos, the photos must be collected with the personal information being masked. ・ Photography will not be performed if refused by the participant.

9.3.6 Laboratory tests

Laboratory tests will be performed at the central laboratory. The investigator or subinvestigator will collect blood and urine samples from participants before study treatment initiation and submit them to the central laboratory. Tuberculosis test may be performed in an in-hospital laboratory.

1） Hematology and serum chemistry tests
2） Immunological tests (thymus and activation-regulated chemokines [TARC])
3） Urinalysis

Time points	Day of screening, Day of study treatment initiation, Week 1, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48, Week 52 or Day of discontinuation visit, Day of follow-up visit
Notes	1) 2) and 3): ・ On the day of study treatment, blood and urine will be collected before the treatment. ・ The test result should be reviewed before the next study treatment. 1) and 2): ・ When aggregation or coagulation is observed in “Plt” because of a reason other than manual technique, blood will be collected into a blood collecting tube containing 3.2% sodium citrate in addition to a conventional blood collection tube from the next visit.

4） Pregnancy test

Time points	Day of screening
Notes	• The test will be performed on female participants. However, those who are considered unable to become pregnant (e.g., menopausal women* and women who have had total hysterectomy) will be excluded. *: Defined as those who are amenorrhea for at least 12 months without any medical reason.

5） Tuberculosis test

Time points	Day of screening
Notes	• If the test cannot be performed on the day of screening, it may be performed on another day after the day of screening but before study treatment initiation. In such cases, the rest results should be reviewed before administration of IP on the day of study treatment initiation.

6） Hepatitis B and C tests

Time points	Day of screening
Notes	The participants who test negative for HBs antigen and positive for HBc antibody on the day of screening will undergo HBV-DNA measurement before the day of study treatment initiation. The participants who test positive for anti-HCV antibody on the day of screening will undergo HCV-RNA measurement before the day of study treatment initiation.

7） Antinuclear antibodies test

Time points	Day of study treatment initiation
Notes	• Blood will be collected before administration of IP on the day of study treatment initiation

Table 9-2: Clinical Laboratory Assessments

Laboratory tests	Parameters
Hematology	Hb, Ht, Plt, RBC, WBC, differential leukocyte count, MCV, MCH, and MCHC
Serum chemistry	Na, K, Cl, UN, CREA, Ca, T-Bil, D-Bil, TP, ALB, ALT (GPT), AST (GOT), ALP, P, LDH, CK, UA, TC, LDL-C, HDL-C, TG, A/G ratios, γ-GTs, and CRP
Immunology	TARC
Urinalysis	Protein, occult blood, urinary sugar, and urobilinogen
Pregnancy	Urine hCG
Tuberculosis	Interferon gamma release assay (Central measurement: T-SPOT, in-house examination: T-SPOT or QFT-3G)
Hepatitis B and C	HBs antigen, HBc antibody, HBV-DNA, Anti-HCV antibody, and HCV-RNA
Antinuclear antibodies	Anti-Scl-70 antibodies, anti-centromere antibodies, and anti-RNA polymerase-III antibodies

9.3.7 Pharmacokinetics

The investigator or subinvestigator will collect blood samples for central measurement of serum drug concentrations.

To be measured	Serum concentration of nemolizumab
Time points	Day of study treatment initiation, Week 1, 2, 4, 8, 12, 16, 20, 24, and 36, Week 52 or Day of discontinuation visit, Day of follow-up visit
Notes	• On the day of study treatment, blood will be collected before the treatment.

9.3.8 Immunogenicity

The investigator or subinvestigator will collect blood samples for central measurement of serum anti-nemolizumab antibodies and neutralizing antibodies.

To be measured	Serum anti-nemolizumab antibodies and neutralizing antibodies
Time points	Day of study treatment initiation, Week 24 and 36, Week 52 or Day of discontinuation visit, Day of follow-up visit
Notes	• On the day of study treatment, blood will be collected before the treatment.

9.3.9 Biomarker measurement

The investigator or subinvestigator will collect blood samples for central measurement of serum biomarkers.

To be measured	1) IL-31 2) KL-6, SP-D, NT-proBNP 3) Exploratory biomarkers
Time points	1) Day of study treatment initiation, Week 4, 8, 12, 16, 20, 24, and 36, Week 52 or Day of discontinuation visit 2) Day of study treatment initiation, Week 4, 12, 24, and 36, Week 52 or Day of discontinuation visit 3) Day of study treatment initiation, Week 12 and 24, Week 52 or Day of discontinuation visit
Notes	1) 2) 3) :

	On the day of study treatment, blood will be collected before the treatment

9.3.10 Comprehensive measurement of autoantibodies

The investigator or subinvestigator will collect blood samples for comprehensive measurement of autoantibodies. The measurement will be performed centrally.

Time points	Day of study treatment initiation, Week 24, Week 52 or Day of discontinuation visit
Notes	• On the day of study treatment, blood will be collected before the treatment.

9.3.11 CyTOF measurement

The investigator or subinvestigator will collect blood samples for central measurement of CyTOF.

Time points	Day of study treatment initiation, Week 24, Week 52 or Day of discontinuation visit
Notes	• On the day of study treatment, blood will be collected before the treatment.

9.3.12 Assessment of Adverse Events

The investigator or sub-investigator will assess the adverse events according to the procedure described in "11.4 Review and reporting of adverse events."

9.3.13 Investigation of Malfunction of DCS

The investigator or subinvestigator will investigate malfunction of DCS according to "11.11 Malfunctions of DCS."

9.3.14 Amount of Blood and Urine Samples to be Collected

In principle, the amounts of blood and urine samples to be collected on each assessment day will follow Table 9-3 unless additional tests are required.

Table 9-3: Amount of blood and urine samples to be collected

1)		Day of screening*	Day of treatment initiation	Week 1	Week 2	Week 4	Week 8, 16 and 20	Week 12**	Week 24**, and Week 52 or Day of discontinuation visit	Week 28, 32, 40, 44 and 48**	Week 36	FU**
Amount of blood collected	Laboratory tests	17 mL	6 mL	6 mL	-	6 mL	6 mL	6 mL	6 mL	6 mL	6 mL	6 mL
	Serum nemolizumab concentration	-	3 mL	3 mL	3 mL	3 mL	3 mL	3 mL	3 mL	-	3 mL	3 mL
	Anti-nemolizumab antibody	-		-	-	-	-	-		-	-	
	Antinuclear antibodies test	-	6 mL	-	-	-	-	-	-	-	-	-
	Biomarker measurement	-	12 mL	-	-	9 mL	3 mL	12 mL	12 mL	-	9 mL	-
	Comprehensive measurement of autoantibodies	-	5 mL	-	-	-	-	-	5 mL	-	-	-
	CyToF measurement	-	5 mL	-	-	-	-	-	5 mL	-	-	-
Total amount of blood collected		17 mL	37 mL	9 mL	3 mL	18 mL	12 mL	21 mL	31 mL	6 mL	18 mL	9 mL
Amount of urine collected		10 mL	10 mL	10 mL	-	10 mL	10 mL	10 mL	10 mL	10 mL	10 mL	10 mL

* : The participants found to require measurement of HBV-DNA or HCV-RNA as a result of the hepatitis B and hepatitis C tests performed on the day of screening will need an additional 5 mL of blood to be drawn before the day of study treatment initiation.

** : The participants enrolled through HBV-DNA or HCV-RNA will need an additional 5 mL of blood to be drawn on Week 12, 24, 36 and 48, and on the day of follow up visit.

10. Efficacy Evaluation

10.1 Efficacy Assessments

10.1.1 Assessment of Skin Findings

1) Modified Rodnan Total Skin Thickness Score (mRSS)

The investigator or subinvestigator will assess the degree of skin thickening for each of 17 sites (fingers of both hands, dorsum of both hands, both forearms, both upper arms, face, anterior chest, abdomen, both thighs, both lower legs, and dorsum of both feet) with a 4-point scale from 0 to 3 according to Table 10-1 on each specified day of assessment. Total score will be 0 to 51.

Table 10-1 Scoring the degree of skin thickening by two-step pinching method

Score	Skin thickening	Broad pinching	Slight pinching	Skin thickness when pinched broadly
0	Normal	Possible	Possible	Not thick
1	Mild	Possible	Possible	Thick
2	Moderate	Possible	Impossible	Thicker
3	Severe	Impossible	Impossible	–

10.1.2 Respiratory Function Test

Spirographic examinations, including the flow-volume curve, lung volume measurements, and diffusing lung capacity for carbon monoxide (DL_{CO}) will be performed on each specified day of testing.

10.1.3 Chest HRCT

Chest HRCT will be performed to obtain visually the approximate ratios (HRCT extent) of interstitial opacities (ground-glass opacities, reticular shadows, honeycomb pattern and cystic shadows) with five slides of a) upper aortic arch, b) carina, c) pulmonary vein confluence point, d) midway between c) and e), and e) immediately above the right diaphragm, and their mean will be calculated.

The investigator or subinvestigator will assess in which of the following ranges the ratios are included; 20% or less (≤ 20%), more than 20% to 70% or less (> 20% to ≤ 70%), or more than 70% (>70%). In addition, in combination with FVC, each severity classification of lung disease will be determined according to 10.1.4 Severity Classification of Lung Lesion.

10.1.4 Severity Classification of Lung Lesion

The investigator or subinvestigator will assess the severity of lung lesions using the severity classification of lung lesions specified in the Guidelines for Diagnostic Criteria, Severity Classification and Clinical Practice of Systemic Sclerosis 2016[7] (see Figure 10-2). Respiratory function test results obtained according to Section 10.1.2 and chest CT images obtained according to Section10.1.3 will be used for this assessment.

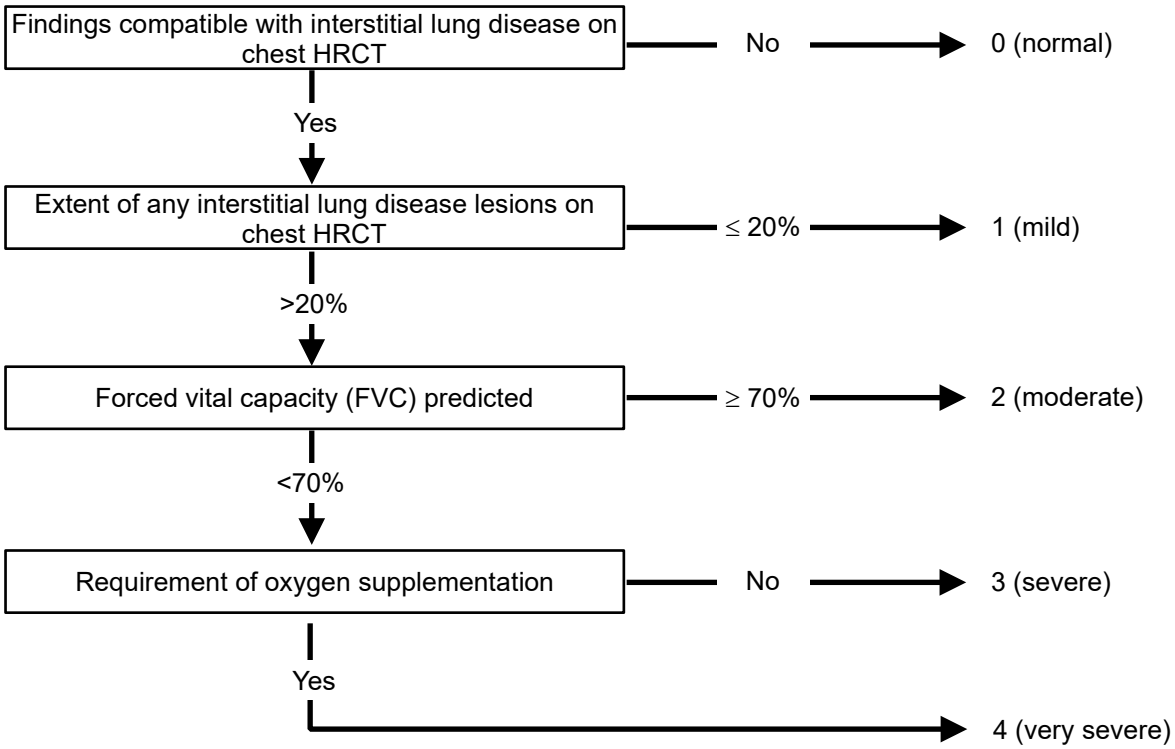


Figure 10-1　Severity classification of lung lesion

10.1.5 ACR-CRISS

ACR-CRISS is a composite outcome measure that is calculated as an index taking a value ranging from 0 to 1 for the probability of improving for participants based on the presence or absence of renal, pulmonary, and cardiac impairments and changes in the 5 core set items (mRSS, %FVC, PGA, PtGA, and HAQ-DI). Participants are considered improved and not improved when their ACR-CRISS is ≥ 0.6 and < 0.6, respectively. If participants meet any of the following criteria, the probability of improving is 0.0. The investigator or subinvestigator will assess whether participants met or not met the following criteria at specified visits. If patients do not meet any of the following criteria, an ACR-CRISS score will be calculated using the formula shown in 17.3.2 2).

- Onset of scleroderma renal crisis
- Decline in FVC% ≥15% (requiring reevaluation within 1 month), and %FVC of 80% or less
- Onset of left ventricular failure requiring treatment (defined as left ventricular ejection fraction ≤45%) *
- Onset of pulmonary arterial hypertension requiring right heart catheterization *

* Caused by SSc

10.1.6 The Number of Digital Ulcers

The investigator or subinvestigator will count the number of digital ulcers.

10.1.7 Patient-reported outcome

1）HAQ-DI

Participants will assess the degree of their difficulty in performing actions of eight functional categories (dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities) using HAQ-DI (Health assessment questionnaire disability index, Japanese version)[9] on a 4-point scale of 0 (Without any difficulty), 1 (Without some difficulty), 2 (Without much difficulty), and 3 (Unable to do).

2） FACIT-Fatigue

Participants will assess their fatigue over the past 7 days using FACIT-Fatigue Scale, Japanese version [10] on a 5-point scale from 0 (not at all) to 4 (very much).

3） FSSG.

Participants will assess their gastroesophageal reflux disease using Frequency Scale for the Symptoms of GERD (FSSG) [11] on a 5-point scale from 0 (never) to 4 (always).

10.1.8 Global improvement rating

1） PtGA

Participants will assess their general health status associated with SSc at visit using a 10-cm visual analog scale (VAS) from 0 (the best status) to 10 (the worst status) [12]. The investigator or subinvestigator or the clinical trial collaborator will measure the length (cm) from the left end to the first decimal place and record it.

2） PGA

The investigator or subinvestigator will assess participants' general health status associated with SSc in terms of Severity, Damage, and Overall disease using a 10-cm VAS from 0 (the best status) to 10 (the worst status) [12]. The investigator (or subinvestigator) or the clinical trial collaborator will measure and record the length (cm) from the left end to the first decimal place.

10.2 Efficacy Endpoints

10.2.1 Primary Endpoint

Change from baseline in mRSS at Week 24

10.2.2 Other Endpoints

1） Change from baseline in mRSS at Week 52
2） Change from baseline in HAQ-DI at Week 52
3） Change from baseline in HAQ-DI at Week 24
4） Change from baseline in %FVC at Week 52
5） Change from baseline in %FVC at Week 24
6） Change from baseline in DLco at Week 52
7） Change from baseline in DLco at Week 24
8） Change from baseline in PGA at Week 52
9） Change from baseline in PGA at Week 24
10） Change from baseline in PtGA at Week 52
11） Change from baseline in PtGA at Week 24
12） ACR-CRISS at Week 52
13） ACR-CRISS at Week 24
14） Change from baseline in the number of digital ulcers at Week 52

15） Change from baseline in the number of digital ulcers at Week 24
16） Time-course changes in the following parameters:
  a） HAQ-DI
  b） FACIT-Fatigue
  c） FSSG
  d） FVC
  e） %FVC
  f） DLco
  g） %DLco
  h） TLC
  i） FEV_1
  j） Severity assessment of lung lesion
  k） PGA
  l） PtGA
  m） ACR-CRISS
  n） The number of digital ulcers

10.3 Rationale for Efficacy Endpoints

1） mRSS

mRSS is used internationally to assess severity of SSc[13), 14)]. Moreover, mRSS is generally considered to be correlated with visceral involvement, etc. and change over a relatively short period of time by receiving treatment, etc. Therefore, change from baseline in mRSS at Week 24 has been selected as primary endpoint to evaluate the efficacy of this drug on SSc. Since SSc has a chronic course, change from baseline in mRSS at Week 52 has been also selected as an efficacy endpoint to discuss the clinical significance of this drug.

2） Respiratory Function Test

FVC in respiratory function tests has been shown to be a useful indicator for predicting vital prognosis in interstitial lung disease associated with SSc[15)] . %FVC and %DLco are useful parameters for screening pulmonary hypertension associated with SSc[16)]. Therefore, this test has been selected to evaluate the efficacy of this drug on lung lesion in an exploratory manner and to ensure the safety of participants.

3） Chest HRCT

Interstitial lung disease in SSc patients has been reported to be detected 50% to 60% by HRCT[17)]. Interstitial lung disease is the most common cause of death in SSc patients[18)]. Interstitial lung disease often occurs from the early stage of SSc, and therefore, it is useful to predict prognosis and determine whether the treatment is feasible for the patient. Moreover, the guidelines recommend to predict the risk of progression to end-stage pulmonary disease and determine whether the treatment is feasible for the patient by the fibrotic finding in HRCT and the extent of the lesion or of the entire lesion in conjunction with FVC-predicted values in respiratory function tests[7)]. Based on the above, this test has been selected to evaluate the efficacy of this drug on lung lesion in an exploratory manner and to ensure the safety of participants.

4） Severity Classification of Lung Lesion

The Guidelines for Diagnostic Criteria, Severity Classification and Clinical Practice of Systemic Sclerosis recommend to predict the risk of progression to end-stage pulmonary disease and determine whether the treatment is feasible for the patient by the fibrotic finding in HRCT, the extent of the lesion or of the entire lesion and FVC predictive value in respiratory function tests[7]. This parameter has been selected to evaluate the efficacy of this drug on lung lesion in an exploratory manner and to ensure the safety of participants.

5) ACR-CRISS

ACR-CRISS is a composite response index for clinical trials in early diffuse cutaneous SSc [19], which is generally used in clinical trials in SSc patients. This index has been selected to evaluate the efficacy of this drug on SSc in an exploratory manner.

6) The number of digital ulcers

Ulcers of the fingers and toes are complications of vascular disorder, one of the conditions of SSc, which occur frequently (35-60%) and arise from the early stage of the disease; therefore, they are considered to reflect the condition of SSc. Moreover, the ulcers are often refractory and recurrent, which is directly related to participants' activities of daily living (ADL) and decreased QOL. Accordingly, this parameter has been selected to evaluate the efficacy of this drug on SSc in an exploratory manner.

7) HAQ-DI

HAQ is a convenient self-administered questionnaire assessing physical function for activities of daily living. It was originally developed to evaluate the effect of rheumatoid arthritis on activities of daily living; however, it has been reported that HAQ-DI correlates with the degree of skin thickening, cardiac involvement, renal involvement, etc., also in SSc[20]. Moreover, along with mRSS, it is a widely used standard method to evaluate SSc. Based on the above, HAQ-DI has been selected to evaluate the efficacy of this drug on SSc in an exploratory manner.

8) FACIT-Fatigue

FACIT-Fatigue is a health-related quality of life that assesses fatigue and its impact on daily activities and functions in chronic diseases. Shortness of breath and fatigue occur in interstitial lung disease and pulmonary hypertension associated with SSc. FACIT-Fatigue has been proven to be reliable and useful in various diseases including SSc[10]. Thus, FACIT-Fatigue has been selected to evaluate the effects of this drug on fatigue and on daily living and functions in SSc, a chronic disease, in an exploratory manner.

9) FSSG

FSSG is a useful questionnaire to objectively assess the symptoms of Japanese participants with gastroesophageal reflux disease[11]. In SSc, esophageal involvement is complicated at a high rate from the early stage of the disease, and 80% to 90% of SSc patients have reflux esophagitis [1]. Esophageal involvements are also associated with the extent and duration of thickening[1]. Based on the above, FSSG has been selected to evaluate the efficacy of this drug on reflux esophagitis in SSc patients in an exploratory manner.

10) Global improvement rating (PtGA, PGA)

Global improvement rating is a widely used method to assess disease activity in clinical trials such as

in rheumatoid arthritis. This rating has been selected to evaluate the efficacy of this drug on SSc in an exploratory manner.

11. Safety Evaluation

11.1 Assessments for Safety Evaluations

1) Adverse events
   a) Symptoms and signs
   b) Abnormal laboratory test values
   c) Abnormal vital signs
   d) Abnormal electrocardiograms
2) Laboratory test values
3) Vital signs
4) Electrocardiograms
5) Echocardiography

11.2 Definition of Adverse Events

1) Adverse events (AEs)

An AE in the study will be defined as any undesirable or unexpected sign, symptom, disease, or aggravation of an existing condition occurring in a participant who is given an IP on or after the time of informed consent regardless of whether there is a causal relationship to the IP. The aggravation of diseases or symptoms that have occurred before the time of informed consent are also considered an AE.

The following events are not considered AE:

- Events for which medical treatment had been scheduled before the time of informed consent
- Aggravation of primary disease

2) Serious adverse events (SAEs)
   a) Results in death
   b) Is life-threatening
   c) Requires or prolongs inpatient hospitalization*

      *Excluding the following events;
      - Any hospitalization that had been scheduled before the time of informed consent (e.g., hospitalization for surgeries and detailed examinations)
      - Any hospitalization for examinations without any treatment (including bed rest treatment).
   d) Results in persistent or significant disability/incapacity
   e) Is a congenital anomaly/birth defect
   f) Is another medically important condition*

      *An important medical event that may not be immediately life-threatening or does not result in death or hospitalization but may jeopardize the safety of the patient or may require treatments to prevent one of the other outcomes listed in a) to e) above.

      e.g., bronchospasm requiring intensive care at an emergency room, blood dyscrasias or convulsions not leading to hospitalization, drug dependence, or drug abuse

3) Adverse events of special interest (AESIs)

AESIs in this study are defined as the following treatment-emergent events:

   a) AEs requiring discontinuation of study treatment

b） Injection-related reactions (including local and systemic injection site reactions)
Injection-related reactions are defined as AEs which develop within 24 hours after administration of IP.

c） Asthma

d） Atopic dermatitis

e） Skin symptoms with edematous erythema or scales

f） Skin infections

g） Non-skin infections

h） Suspected infection of infectious pathogen from the IP

・ Rationale for selection

b), c), d), f), and g)	These events should be monitored carefully because of being included in “important potential risks” in nemolizumab.
e)	These are events of interest closely monitored by the sponsor based on the results of clinical studies of nemolizumab in patients with atopic dermatitis
h)	The event should be carefully investigated in biological products in general.

11.3 Definitions of Safety Endpoints

1） Adverse events

a） Symptoms and signs
The investigator or subinvestigator will assess symptoms and signs in participants after the time of informed consent through the time of physical examination on the day of follow-up visit based on interview results and complaints from participants.

b） Abnormal laboratory test values
The investigator or subinvestigator will treat laboratory test results collected after the time of informed consent through the day of follow-up visit as AEs if the results meet any of the following criteria:

i. Accompanied with clinical symptoms
ii. Resulted in any change of study treatment (e.g., interruption or discontinuation of the IP).
iii. Resulted in medical treatment (including change of concomitant medications/therapies).
iv. Considered clinically significant by the investigator or subinvestigator.
v. Total bilirubin is >2-fold the upper limit of the reference value, and ALT or AST is >3-fold the upper limit of the reference value
vi. ALT or AST is >3-fold the upper limit of the reference value with clinical jaundice

Individual abnormal changes in laboratory test findings will be reported as individual AEs in principle. However, a single abnormal laboratory test finding or two or more abnormal laboratory test findings that are related to each other may be reported collectively as a single event under a single diagnosis if it is considered appropriate by the investigator or sub-investigator. If individual abnormal changes in laboratory test findings are regarded by the investigator or subinvestigator as manifestations of a symptom or a sign reported as an AE, the changes may be reported collectively with the AE of the symptom or sign.

Laboratory values may change depending on interindividual factors, such as sex, age, and lifestyle, and intraindividual factors, such as diurnal fluctuation, diet, exercise, body positioning, and sexual cycle. Therefore, the investigator or subinvestigator will determine whether the change in each laboratory test findings is a physiological change or an abnormal change after sufficiently taking into

consideration the demographics of each participant, such as the underlying disease and complication, baseline values, and the changes specific to each participant who have any periodic laboratory test before study participation.

c) Abnormal vital signs

The investigator or subinvestigator will treat measurement results collected after the time of informed consent through the day of follow-up visit as AEs if the results meet any of the following criteria:

i. Accompanied with clinical symptoms
ii. Resulted in any change of study treatment (e.g., interruption or discontinuation of the IP).
iii. Resulted in medical treatment (including change of concomitant medications/therapies).
iv. Considered clinically significant by the investigator or subinvestigator.

d) Abnormal electrocardiograms

The investigator or subinvestigator will assess AEs based on the results collected after the time of informed consent through the day of follow-up visit

e) Echocardiography

Echocardiographic images will be assessed for cardiac morphology, cardiac motion and blood flow during cardiac contraction and relaxation, and other parameters. The investigator or subinvestigator will record the presence or absence of abnormalities in the source documents.

11.4 Review and reporting of adverse events

The investigator or subinvestigator will assess the items shown in Table 11-1 regarding AEs occurring from after obtaining informed consent to the day of follow-up visit and fill the necessary information in the case report forms (CRFs).

The investigator or subinvestigator will report the SAEs according to Section 11.5 and the AESIs according to Section 11.6 to the sponsor. The investigator or subinvestigator will promptly report the other AEs to the sponsor.

Table 11-1 Assessments for adverse events

Assessments	Details of assessment	
Name of adverse event	Disease name/symptom, classification of the site of occurrence of adverse events	
Onset date	Classification of onset date, Onset date	
Action on investigational product	Treatment discontinuation, Treatment interruption, Dose reduction, No dose change, Not applicable, Unknown	
Treatment for the event	Presence or absence of treatment	
Outcomes and Date of outcome/Date of outcome obtained	Recovered/Resolved, Recovering/Resolving, Not Recovered/Not Resolved, Recovered/Resolved with sequelae, Death, and Unknown End date of AE, whether the AE is ongoing or not	
Severity	Mild	Transient, requiring minimal treatment and not interfering with daily life
	Moderate	Specified treatments relieve symptoms and do not result in permanent or significant disability but interfere with daily life
	Severe	Significant effect on advanced clinical condition or requiring intensive care or no longer allowing daily life.
Seriousness	Serious/Non-serious	
Definition of serious adverse events in Section 13.2	1. Results in death	
	2. Life-threatening	
	3. Requires or prolongs inpatient hospitalization	
	4. Results in persistent or significant disability/incapacity	
	5. Is a congenital anomaly/birth defect	
	6. Is another medically important condition	
Causal relationship with investigational product	Causality classification (according to the following causality classification), and rationale	
Causality classification*	Not related	Causal relationship is unlikely because the adverse event has no plausible temporal relationship to administration of IP, or the event can be explained by another factor. The rationale for no causal relationship is required to be described.
	Related	Causal relationship is presumed because there is a plausible temporal relationship between the onset of the adverse event and administration of investigational drug, and the event cannot be readily explained by another factor. The rationale for the causal relationship should be described if it is necessary to be explained.

*The following guidance can be taken into consideration on causality assessment: resolution of the event after discontinuation of IP; recurrence after restarting of IP; established causal relationship with IP or similar drugs; no confounding risk factors; consistency with the amount and duration of exposure to IP; almost clearly explainable involvement of the IP based on the correct past medical history; no reasonable possibility of causal relationship with concomitant therapy, etc.

11.5 Review and reporting of serious adverse events

1) The investigator will report any serious adverse events to the sponsor within 24 hours of getting to know the occurrence of the event. The investigator will report detailed information to the sponsor by using the “Report of Serious Adverse Events” form within 2 days of getting to know the occurrence of the event (the date the event was known is regarded as day 0). The study site’s own form may be used instead of the "Report of Serious Adverse Events". For additional reporting, new serious information (e.g., change in the name of the adverse event, causal relationship, outcome information, the severity category, etc.) should be reported to the sponsor according to the above rules when it becomes known.
2) The investigator will report the event to the study site according to the study site’s operating procedures.
3) The investigator will provide any additional information (e.g., autopsy reports, late-stage medical records, and other necessary information) on reported serious adverse events, as requested by the sponsor.

11.6 Reporting of adverse events of special interests (AESIs)

The investigator should report to the sponsor promptly when an AESI is noted. For atopic dermatitis and skin symptoms with edematous erythema or scaling, the necessary information (details of the symptoms/signs and the basis for determining the causal relationship with the IP) should be stated in the CRF. Any additional information should be provided, as requested by the sponsor.

At the time of physical examination on the day of follow-up visit, the final outcome of any AESI “not recovered/not resolved” falling under 1) below should be obtained according to 2). Concomitant medications and therapies will also be collected according to Sections 9.3.2.1 and 9.3.2.2 .

1) AESIs to be obtained
   a) AEs requiring discontinuation of study treatment
   b) Asthma
   c) Atopic dermatitis
   d) Skin symptoms with edematous erythema or scales
2) Period to obtain AESIs

   AESIs should be collected until the earlier of the following dates to obtain the final outcome information (the outcome and the date of outcome/outcome obtained).

   • Date of recovering or recovered
   • Date 6 months after the last dose of IP

11.7 Photography

Among AESIs, "atopic dermatitis" and "skin symptoms with edematous erythema or scales" will be photographed to examine the detailed skin findings of the events. Other adverse events of which the principal investigator or subinvestigator considers it necessary to take photographs will also be photographed.

The photographs taken will be used as a record of the occurrence of adverse event and a reference for safety evaluation.

11.8 Reporting of the Pregnancy of the Participant

1) If obtaining the information on the pregnancy of the participant who received the IP, the investigator or subinvestigator must immediately discontinue study treatment and take appropriate action for the participant, and follow up the participant until the completion of the pregnancy (e.g., delivery).
2) The investigator or subinvestigator will also report detailed information to the sponsor by using the “Report for Pregnancies during the Study” form.
3) Participant pregnancies are not regarded as adverse events.

11.9 Rationale for Safety Endpoints

1) In terms of safety protection of participants, it is considered decided that the echocardiography should be carried out periodically. Echocardiography is a useful examination for screening of pulmonary arterial hypertension caused by SSc, and the Guidelines for Diagnostic Criteria, Severity Classification and Clinical Practice of Systemic Sclerosisits recommends performing echocardiography. Pulmonary arterial hypertension caused by SSc has a poor prognosis and requires early detection

11.10 Follow-up of Adverse Events

For all adverse events developing during the study period (from the time of informed consent to the day of follow-up visit), the investigator or subinvestigator will provide appropriate treatments, and follow up until the event recovers to normal condition (within the reference ranges for laboratory test values), to the level before the consent was obtained, or until the investigator or subinvestigator considers that medical follow-up is no longer required. However, AESIs defined in Section 11.6 1) should be obtained according to Section11.6 even if the investigator or subinvestigator considers that their follow-up is not medically necessary.

11.11 Malfunctions of DCS

11.11.1 Reporting of Malfunctions of DCS

In the event of a malfunction of DCS, the principal investigator or subinvestigator will promptly report it to the sponsor according to the "Procedures for the Management of Investigational Products."

11.11.2 Collection and Reporting of Malfunction Information on DCS occurring at the Stage of Use on Participants

The principal investigator or subinvestigator will obtain the information shown in Table 11-2 on DCS malfunctions occurring after prescription to participants and record them in the CRFs

Table 11-2 Information to be obtained for DCS Malfunction Occurring after Prescription to Participants

Information	Details
Details of malfunction	Structural, material, functional defects, etc.
Presence or absence of SAEs (including possibility)	Presence or absence of SAEs or possibility of occurring SAEs due to malfunction
Date of incident	Date of incident
Presence or absence of AEs associated with the malfunction of DCS	Presence or absence of adverse events occurring associated with the malfunction of DCS

If a SAE occurs or may occur associated with a DCS malfunction, the SAE information together with the detailed information of the SAE will be sent to the sponsor in a "Serious Adverse Event and Malfunction Report" form to according to the procedures described in "11.5 Collection and Reporting of Serious Adverse Events." The "Serious Adverse Event and Malfunction Report" may be used in the form of the medical institution.

11.11.3 Storage of Malfunctioning DCS

The IP manager shall store malfunctioning DCSs appropriately at the study site, not discarding them.

11.12 Anticipated Adverse Drug Reactions

See the investigator's brochure of nemolizumab for anticipated adverse drug reactions of nemolizumab.

12. Biomarkers

12.1 Measurements of Biomarkers

1) Variable to be measured
   a) IL-31
   b) KL-6, SP-D, NT-proBNP
   c) Exploratory biomarkers

2) Collection of blood samples
   a) Blood samples will be collected on the day of study treatment initiation, at Week 4, 8, 12, 16, 20, 24, and 36, and Week 52 or on the day of visit for discontinuation. On the days of study treatment, blood samples will be collected before administration of IP.
   b) Blood samples will be collected on the day of study treatment initiation, at Week 4, 12, 24, and 36, and Week 52 or the day of visit for discontinuation. On the days of study treatment, blood samples will be collected before administration of IP.
   c) Blood samples will be collected on the day of study treatment initiation, at Week 12, 24, and Week 52 or the day of visit for discontinuation. On the days of study treatment, blood samples will be collected before administration of IP.

   The collected blood samples will be centrifuged to separate the serum, and the serum samples will be stored frozen until measured. The amount of blood collected, centrifugal conditions, and storage conditions are specified in a separate operating procedure.

12.2 Blood Biomarker Outcome Measures

1) Serum IL-31 level
   - Rationale for selection
     Since IL-31 is one of the cytokines considered to be involved in the disease state of SSc[8],this has been selected to evaluate the changes after administration of nemolizumab.

2) KL-6 and SP-D
   - Rationale for selection
     KL-6 and SP-D have been used as sensitive markers for interstitial pneumonitis in examination and measuring of disease progression or as a prognostic predictor in clinical practice. Moreover, increased levels of these have been reported to be associated with inflammatory pathological conditions such as ground-glass opacities on HRCT and elevated proportions of inflammatory cells in bronchoalveolar lavage fluid [21]. Based on the above, these have been selected in terms of safety protection of participants.

3) NT-proBN
   - Rationale for selection
     NT-proBNP is critical as a serological marker of pulmonary hypertension because it elevates in correlation with its severity in patients with SSc-PAH[22]. It is also important as a serological marker for overall some sort of because it elevates in the presence of any myocardial damage even without pulmonary hypertension[23]. Therefore, it has been set in terms of ensuring safety of participants.

4) Exploratory biomarkers

As exploratory biomarkers, IL-1α, IL-4, IL-6, IL-8, IL-13, IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, IL-17F, and IL-23 levels will be measured; however, cytokines for which adequate performance of the assay methods could not be validated will not be measured.

・ Rationale for selection

The major cytokines considered to be involved in pathological conditions of SSc have been selected to evaluate the changes after nemolizumab administration.

12.3 Measurement Method and Reporting of Results

1) Measurement methods

a) IL-31 and exploratory biomarkers will be measured using the Enzyme-Linked Immuno Sorbent Assay (ELISA) method. The measurements will be performed by [redacted] Corporation according to its assay protocol.

b) KL-6, SP-D and NT-proBNP will be measured by [redacted] Corporation according to its assay protocol.

c) Exploratory biomarkers will be measured using the Electro Chemi-Luminescence (ECL) method. The measurements will be performed by [redacted] Corporation according to its assay protocol.

2) Report of measurement results

a) IL-31, KL-6, SP-D, NT-proBNP and exploratory biomakers

[redacted] Corporation will prepare and submit a report of analysis results to the sponsor.

13. Pharmacokinetics

13.1 Pharmacokinetic Measurements

1) Variable to be measured

Serum concentration of nemolizumab

2) Collection of blood samples

Blood samples will be collected on the day of study treatment initiation, at Week 1, 2, 4, 8, 12, 16, 20, 24, and 36, Week 52 or on the day of visit for discontinuation, and on the day of follow up. On the days of study treatment, blood samples will be collected before administration of IP.

The collected blood samples will be centrifuged to separate the serum, and the serum samples will be stored frozen until measured. The amount of blood collected, centrifugal conditions, and storage conditions are specified in a separate operating procedure.

13.2 Pharmacokinetic Outcome Measures

1) Serum concentration of nemolizumab

2) Pharmacokinetic parameters: C_{max}、t_{max}、$AUC_{0\text{-}28day}$、AUC_{last}

・ Rationale for selection

Parameters necessary and evaluable to examine pharmacokinetics of nemolizumab have been selected in reference to “Clinical pharmacokinetic studies on drugs (PFSB/ELD No.796 of June 1, 2001).”

13.3 Measurement Method and Reporting of Results

1) Measurement method

Serum concentration of nemolizumab will be measured using the ELISA method. The measurements will be performed by [redacted] Laboratories, Ltd. according to its assay protocol.

2） Report of measurement results

[redacted] Laboratories, Ltd. will prepare and submit a report of analysis results to the sponsor.

14. Immunogenicity

14.1 Immunogenicity Measurements

1） Variable be measured

Serum anti-nemolizumab antibody

2） Collection of blood samples

Blood samples will be collected on the day of study treatment initiation, at Week 24 and 36, Week 52 or on the day of visit for discontinuation, and on the day of follow up. On the days of study treatment, blood samples will be collected before administration of IP.

The collected blood samples will be centrifuged to separate the serum, and the serum samples will be stored frozen until measured. The amount of blood collected, centrifugal conditions, and storage conditions are specified in a separate operating procedure.

14.2 Immunogenicity Outcome Measures

1） Serum anti-nemolizumab antibody

2） Neutralizing antibody concentrations

・ Rationale for selection

The variables have been selected to evaluate the effects of the development of anti-nemolizumab antibodies to efficacy and safety in participants.

14.3 Measurement Method and Reporting of Results

1） Measurement method

The serum anti-nemolizumab antibody will be measured using the ECL method. When anti-nemolizumab antibodies are detected, their characteristics will be determined using the cell-based assay (CBA) method. The measurement will be performed by [redacted] Corporation according to its assay protocol.

2） Report of measurement results

[redacted] Corporation will prepare and submit a report of analysis results to the sponsor.

15. Comprehensive Measurement of Autoantibodies

Comprehensive measurement of autoantibodies will be performed to determine the disease state of SSc and explore the patient-group for whom nemolizumab is effective.

15.1 Measurement Method and Reporting of Results

1） Collection of blood samples

Blood samples will be collected on the day of study treatment initiation, at Week 24, and Week 52 or on the day of visit for discontinuation. On the days of study treatment, blood samples will be collected before administration of IP.

The collected blood samples will be centrifuged to separate the serum, and the serum samples will be stored frozen until measured. The amount of blood collected, centrifugal conditions, and storage

conditions are specified in a separate operating procedure.

2) Measurement method
Autoantibodies will be measured comprehensively using HuPEX™ protein array. The measurement will be performed by [redacted] Corporation according to its assay protocol.

3) Report of measurement results
[redacted] Corporation will prepare and submit a report of analysis results to the sponsor. Measurement results will not be included in the clinical study report and will be summarized in a separate report.

16. CyTOF measurement

CyTOF measurement will be performed to explore the mechanism of action of nemolizumab in SSc.

16.1 Measurement Method and Reporting of Results

1) Collection of blood samples
Blood samples will be collected on the day of study treatment initiation, at Week 24, and Week 52 or on the day of visit for discontinuation. On the days of study treatment, blood samples will be collected before administration of IP.
PBMC preparation of collected blood samples will be performed by the day following sample collection. The amount of blood to be collected and storage conditions are specified in a separate operating procedure.

2) Measurement method
Measurement will be performed by [redacted], Inc. according to its assay protocol.

3) Report of measurement results
[redacted], Inc. will prepare and submit a report of analysis results to the sponsor. Measurement results will not be included in the clinical study report and will be summarized in a separate report.

17. Statistical Analysis

The major plans for statistical analyses are presented below. The details are provided in the Statistical Analysis Plan. This plan will be fixed prior to database lock on through discussions on data review etc.

17.1 Analysis Sets

17.1.1 Efficacy Analysis Set (Full Analysis Set: FAS)

The efficacy analysis set includes all participants assigned to treatment except for those who meet any of the following criteria:

1) Participants who are found not to have SSc
2) Participants who have received no dose of nemolizumab at all after assigned to treatment
3) Participants with no efficacy data at all after assigned to treatment

17.1.2 Safety Analysis Set

The safety analysis set includes all participants assigned to treatment except for those who meet any of the following criteria:

a） Participants who have received no dose of nemolizumab at all after assigned to treatment

2） Participants with no safety data at all after assigned to treatment

17.1.3 Pharmacokinetics Analysis Set

The pharmacokinetics analysis set includes all participants assigned to treatment except for those who meet any of the following criteria:

1) Participants who have received no dose of nemolizumab at all after assigned to treatment

2) Participants with no pharmacokinetic data at all after assigned to treatment

17.1.4 Biomarker Analysis Set

The biomarker analysis set includes all participants assigned to treatment except for those who meet any of the following criteria:

1) Participants who have received no dose of nemolizumab at all after assigned to treatment

2) Participants with no biomarker data at all after assigned to treatment

17.2 Data Handling

17.2.1 Common Rules

a） Handling of missing values

The missing values will not be imputed.

2） Handling of data on the day of visit for discontinuation

The data measured or evaluated on the day of visit for discontinuation will be handled as the data of the relevant evaluation period if the visit is within the allowance of any visit for evaluation period. However, such data will not be included in the analysis if another data has been obtained in the relevant evaluation period.

17.2.2 Data Handling on Pharmacokinetics

1) Handling of values below the lower limit of quantification (BLQ) and missing values for serum drug concentration data

Values BLQ will be handled as follows and missing values will not be imputed.

a) Tabulation: They will be reported as BLQ.

b) Changes over time and profiles and summary statistics: They will be replaced by 0. However, if the number of participants with BLQ values exceeds half number of participants in pharmacokinetic analysis set, the summary statistics of serum drug concentrations at that time point will not be calculated and reported as N.C. (not calculated).

2) Handling of pharmacokinetic parameters not calculable

Parameters not calculable should be handled as follows:

a) Tabulation: They will be reported as N.C.

b) Summary statistic: They will be left missing. However, if the number of unevaluable participants for a pharmacokinetic parameter exceeds half of participants to be evaluated, the summary statistic of the parameter will not be calculated and reported as N.C.

17.3 Statistical Analysis Plan

The statistical analysis plan is described below. Unless otherwise stated, continuous variables are summarized by number of participants, mean and its standard deviation, minimum value, 25% percentile, median value, 75% percentile, and maximum value, while categorical variables are summarized by the number and percentage of participants in each category.

17.3.1 Demographic and Other Baseline Characteristics, and Severity of Primary Disease

Demographic and other baseline characteristics and severity of primary disease will be summarized, or the summary statistics will be calculated on the FAS.

17.3.2 Efficacy Analysis

This study will be conducted to evaluate the efficacy of nemolizumab in SSc patients with moderate to severe skin thickening in an exploratory manner.

1) Analysis of the primary endpoint: Change from baseline in mRSS at Week 24
   Summary statistics will be calculated for mRSS at Week 24 and the change from baseline.

2) Summary of continuous data
   The following analyses will be performed on the FAS:
   - Summary statistics will be calculated for the following variables and indicators at each time point.
   - The scores or measurements of the following variables will be used to create a spaghetti plot for each participant

Variable	Indicator
mRSS Physician's Global Assessment Patient 's Global Assessment	Score Changes from baseline Percent change from baseline
HAQ-DI FACIT-Fatigue FSSG FVC % FVC DLco %DLco TLC FEV_1 The number of digital ulcers	Score or measurement Change from baseline
ACR-CRISS (Only Week 12, 24 and 52) Severity Classification of Lung Lesion (Figure 10-1)	Score

ACR CRISS is calculated using the following formula.:

$$\frac{\exp\left(-5.54 - 0.81 \times \Delta_{\mathrm{mRSS}} + 0.21 \times \Delta_{\mathrm{FVC\%}} - 0.40 \times \Delta_{\mathrm{pt-glob}} - 0.44 \times \Delta_{\mathrm{MD-glob}} - 3.41 \times \Delta_{\mathrm{HAQ-DI}}\right)}{1 + \exp\left(-5.54 - 0.81 \times \Delta_{\mathrm{mRSS}} + 0.21 \times \Delta_{\mathrm{FVC\%}} - 0.40 \times \Delta_{\mathrm{pt-glob}} - 0.44 \times \Delta_{\mathrm{MD-glob}} - 3.41 \times \Delta_{\mathrm{HAQ-DI}}\right)}$$

Δ_{mRSS}: mRSS change
$\Delta_{\mathrm{FVC\%}}$: Percent FVC change
$\Delta_{\mathrm{pt-glob}}$, $\Delta_{\mathrm{MD-glob}}$: Patient's / Physician's Global assessment change (cm)
$\Delta_{\mathrm{HAQ-DI}}$: HAQ-DI Score change

The score of participants occurring any of the following events is 0:
・Onset of scleroderma renal crisis
・Decline in FVC% ≥15% (requiring reevaluation within 1 month), and %FVC of 80% or less
・Onset of left ventricular failure requiring treatment (defined as left ventricular ejection fraction ≤45%) *
・Onset of pulmonary arterial hypertension requiring right heart catheterization *
*Caused by SSc

17.3.3 Safety Analysis

The following variables will be summarized on the safety analysis set:

1) Adverse events

The following data will be collected and tabulated for AEs and separately for the treatment-related AEs.

a) The number of participants included in the safety analysis set, and the number of participants with, and the number of occurrences of AEs, AEs by severity (mild, moderate, and severe), SAEs (total, fatal, and non-fatal), and AESIs will be calculated.
b) The number of participants with AEs will be calculated by SOC and PT using MedDRA/J.
c) For AESIs, the number of participants with AESIs, the number of participants with AESIs by PT will be calculated by the category.

2) Laboratory test values

a) Laboratory test values throughout the treatment period

For the continuous variables, summary statistics will be calculated by laboratory parameter and time point. For the categorical variables, the number of participants will be calculated by category. The percentage of participants will be calculated using the number of observed participants at each time point.

b) Changes in individual participants during the treatment period

A spaghetti plot will be created for each participant using individual test values by laboratory parameter of continuous variables.

3) Vital signs, physical findings, and other assessments related to safety

a) Vital signs, electrocardiogram and echocardiography throughout the study period

For the continuous variables, summary statistics will be calculated by vital sign, electrocardiogram parameter, and echocardiography parameter. For the categorical variables, the number and percentage of participants will be calculated by category. The percentage of participants will be calculated using the number of observed participants at each time point.

17.3.4 Analyses of Drug Concentrations and Pharmacokinetic Parameters

The following variables will be summarized on the pharmacokinetic analysis set.

1) Serum concentrations of nemolizumab

a) Summary statistics including coefficient of variation and geometric mean of serum nemolizumab concentrations will be calculated by time point.
b) The serum nemolizumab concentration-time profile will be created using mean serum drug concentrations and their standard deviations.
c) The serum nemolizumab concentration-time profile will be created by participant.
d) The serum nemolizumab concentration-time profile will be created by participant where participants who tested positive for the first time after study treatment (in blue), those who had tested positive since before treatment (in red), and those who tested negative at all time points (in black) for anti-nemolizumab antibodies in serum in the confirmatory test will be identified by color.

2) Pharmacokinetic parameters (C_{max}, t_{max}, $AUC_{0\text{-}28Day}$, and AUC_{last})

Summary statistics including coefficient of variation and geometric mean of parameters will be calculated.

17.3.5 Analysis of Immunogenicity

The following variables will be tabulated from the pharmacokinetics analysis set.

1) Serum anti-nemolizumab antibody
   a) The percentage of participants with positive serum anti-nemolizumab antibodies will be calculated by test (Screening, Confirmatory, and Neutralizing) and time point. The positive rate in the Confirmatory test and the Neutralizing test is based on the number of participants having undergone the screening test.
   b) The number of and the percentage of participants who tested positive for anti-nemolizumab antibodies will be determined in this study. According to Shankar's definition,[24] among participants who tested positive for anti-nemolizumab antibodies for the first time after study treatment or both before and after study treatment, a positive participant is defined as a participant with a ≥ 4-fold increase in difference in antibody titer.

17.3.6 Analysis of Biomarker

Details will be described in the Statistical Analysis Plan.

17.4 Determination of Sample Size

17.4.1 Target Sample Size

The target sample size for this study is 8 participants.

17.4.2 Rationale for Sample Size

The number of participants required to determine the efficacy of this drug for SSc was set at 8. Since no statistical evaluation is planned, the number is not based on the level of significance and power.

17.5 Data Review

Data review will be performed before data fixation. In the data review, the appropriateness of data handling and analysis methods, etc., will be examined, and analysis sets, data handling, and an analysis plan will be determined. If a change in the statistical analysis plan is required after data review, the statistical analysis plan will be revised and documented.

18. Agreement on the Protocol and Protocol Deviation/Amendment

18.1 Agreement of and Compliance with the Protocol

The investigator will, before the sponsor requests to conduct the study at the study site, agree in writing with the sponsor on the contents of the protocol and conducting the study in compliance with the protocol. The investigator will do the same when the protocol is revised through discussion with the sponsor or according to the instructions of the head of the study site on the basis of the opinion of the institutional review board (IRB).

18.2 Protocol Deviation/Amendment

1) The investigator or subinvestigator should not deviate from or amend the protocol without prior written agreement with the sponsor and without written approval based on a prior review by the IRB. However, the investigator or subinvestigator may deviate from or amend the protocol without prior agreement with the sponsor or without prior approval from the IRB in the following cases where:
    a) it is medically unavoidable to avoid immediate danger to a participant
    b) it is on administrative matters of the study (e.g., change of the name of study site, change of the address or phone number of study site, and change of job title of the investigator)

2) The investigator or subinvestigator will record all deviations from the protocol. The investigator will prepare a document only for deviations from the protocol to avoid immediate danger to the participant with the reason for deviation or for other medically unavoidable reasons and immediately submit it to the sponsor and the head of the study site. The investigator will also submit the document to the IRB via the head of the study site, obtain approval from the IRB, and obtain in writing approval of the head of the study site and agreement of the sponsor.

3) If the protocol amendment is appropriate when the investigator is unable to comply with the protocol to avoid any immediate hazard to participants or due to other unavoidable medical reasons, the investigator will submit a draft amendment to the protocol to the sponsor as soon as possible to obtain written approval of the sponsor. Furthermore, the investigator will submit a draft amendment to the protocol to the head of the study site, obtain approval from the IRB and the head of the study site.

19. Case Report Form

The EDC system (Table 19-1) will be used in this study. The original CRFs will be those generated in the EDC system. The validated EDC system will be used in this study.

The data and audit trails entered in EDC system by the investigator, subinvestigator involved in CRF preparation, and CRCs are stored in the EDC server.

Table 19-1 EDC system

Name of EDC system	[redacted]
Name of EDC system development Company	[redacted].
Input method	Data entry via the web
Input terminal	Personal computer available at study sites

19.1 Data to be collected in CRF

The data to be collected in the CRFs is shown below.

19.1.1 Participants assigned to treatment

1) Date of written informed consent
2) Visit dates
3) Participant demographics
4) Major therapies received for SSc in the past
5) Inclusion and exclusion criteria
6) Complications
7) Concomitant Medications/Concomitant Therapies
8) Patient-reported Outcomes
9) Global improvement rating
10) mRSS
11) The number of digital ulcers
12) Respiratory function test
13) Electrocardiogram
14) Echocardiography
15) HRCT
16) Severity of pulmonary lesions
17) ACR-CRISS
18) Vital signs
19) Body weight
20) Laboratory tests
21) Biomarkers
22) Serum nemolizumab levels
23) Immunogenicity measurement
24) Comprehensive measurements of autoantibodies
25) CyTOF measurement
26) Dosing status of IP
27) Adverse events

    Information on outcome of an adverse event is to be collected until the follow-up visit.
28) The details of adverse events of atopic dermatitis and skin symptoms with edematous erythema or

scaling as well as the basis for determining the causal relationship with the IP

29) Malfunction of DCS

30) Status of study entry after screening, enrollment, completion/discontinuation of the study
completion status of study entry after screening, completion status of enrollment, study completion status, date of completion, date and reason for discontinuation if discontinued, and impact of COVID-19

31) Follow-up visit
Whether there was a follow-up visit or not, date of follow-up visit, date of determination and reason if no follow-up visit, and impact of COVID-19

32) Others
   a) Comment on each assessment
   b) Unscheduled visits

19.1.2 Participants Who Discontinue the Study before study entry after screening and those Who Discontinue the Study before enrollment

The following data will be collected and documented in the CRF for respective participants:

1) to 6) for participants having discontinued the study before study entry after screening

1) to 6) and 7) to 16) for participants having discontinued the study before enrollment

1) Date of written informed consent
2) Visit dates
3) Participant demographics
4) Inclusion and exclusion criteria
5) Adverse events
6) Date of and reason for discontinuation
7) mRSS
8) The number of digital ulcers
9) Respiratory function test
10) Vital signs
11) Body weight
12) Severity of pulmonary lesions
13) HRCT
14) Echocardiography
15) Electrocardiograms
16) Laboratory tests

19.2 Source Data for Information Entered in Case Report Form

Source data for information entered in the case report forms are as follows:

1) Medical records
2) Laboratory test slips
3) Serious Adverse Event Report (copy)
4) Serious Adverse Event and Device Malfunction Report (copy)
5) Informed consent forms
6) Participant screening logs
7) IP accountability records
8) ECG measurement results

9） Respiratory function test
10） Patient QOL questionnaire (paper)

19.3 Information in the Case Report Forms Treated as Source Data

Any information of the following items described only in the CRF will be treated as the original data.

1） Presence or absence of data for each item
2） Indication of drug/therapy
3） Seriousness and severity of adverse event, causality of adverse event to IP, and presence or absence of abnormal laboratory changes
4） Date of and reason for study discontinuation
5） All comments

19.4 Guidelines for Preparation of Case Report Form

The investigator, subinvestigator involved in CRF preparation, and CRCs will have to receive training before preparing CRFs. The sponsor will create an account management table to specify the authority given to each person in the place of a list of signatures/seals.

1） The investigator or subinvestigator will accurately prepare CRFs based on the source documents of enrolled participants according to the “Guidance for CRF Preparation.”
2） The investigator or subinvestigator will promptly prepare the CRF once the evaluation of the participant at each visit is completed.
3） CRCs may fill out or transcript and correct CRFs on the basis of the source documents. The investigator will review the entries, transcriptions, and corrections made by CRCs and electronically sign the CRFs.
4） The investigator will review the CRFs prepared at the study site and electronically sign the CRFs.
5） The investigator will submit the CRFs to the sponsor. In addition, the investigator will obtain a copy of the CRFs from the sponsor at the end of the study and retain them electronically.
6） If data in the CRF shows a discrepancy with the source document, the investigator will prepare a document explaining the discrepancy and submit it to the sponsor. The investigator will also retain a copy of the record.

19.5 Modification and Amendment to Case Report Forms

1） The investigator, subinvestigator, or CRCs will amend the CRFs according to the “Guidance for CRF Preparation” provided by the sponsor.
2） The investigator will review the modifications or amendments made by the subinvestigator or, CRCs and electronically sign the CRF.

20. Follow-up report of adverse events of special interest

For adverse events of interest falling under those specified in Section 11.6 1) which are “not recovered/not resolved” at the time of physical examination on the day of follow-up visit, the investigator will report their following information from after the physical examination of the follow-up visit to the time of obtaining the final outcome in the format separately specified by the sponsor.

1） Outcome and date of outcome/date of outcome obtained
2） Drugs used for the adverse event
3） Therapies performed for the adverse event

21. Direct Access to Source Documents

The investigator, subinvestigator, and the head of the study site will allow study monitoring, the sponsor's audit, and inspections by the IRB and regulatory authorities, and their direct access to all study-related documents, including the source documents.
When regulations on direct access are stipulated at the study site, they will be followed.

22. Quality Control and Quality Assurance

Risk management of this study will be performed based on the risk management plan prepared according to the standard operating procedures of [redacted].

1) Monitoring
The CRA will request the investigator and subinvestigator, etc. to comply with the GCP, related regulatory notifications, and study protocol throughout the study period, and will then assess their compliance. If any deviation from the GCP, related regulatory notifications, and the study protocol is found by monitoring, the CRA will inform the investigator immediately and the head of the study site as necessary and take appropriate measures to prevent the recurrence of the deviation. Furthermore, on the basis of direct access to the source documents, the CRA will verify whether the CRFs are completed accurately and are consistent with the source documents.

2) Quality control
a) Standardization of assessments
Prior to the start of the study, the sponsor will explain the standards of the assessment and the protocol to the investigator and subinvestigator, etc.

3) Quality control of CRF data
The quality control of CRF data will be performed according to the SOPs of Maruho Co., Ltd. When necessary, a case review meeting may be held by the medical expert and the sponsor to determine the handling of individual cases.

4) Audit
The auditor will assess whether the study is being conducted in accordance with GCP, the protocol, and relevant operating procedures separately and independently from the monitoring and quality control activities performed by the clinical study department. The auditor will also assess whether the study is being conducted properly and that the reliability of the study data is being maintained by direct access to study-related documents and records or other methods.

23. Completion, Discontinuation, or Interruption of the Study

23.1 Completion of the Study

Upon the completion of the study, the investigator will report the completion and a summary of study results in writing to the head of the study site. Once receiving the report of study completion from the investigator, the head of the study site will notify the IRB and the sponsor of the fact the summary of study results.

23.2 Discontinuation or Interruption of the Study

The investigator will, when interrupting or discontinuing the study at his/her own discretion, promptly report it and the reason in writing to the head of the study site. Once receiving the report of study discontinuation

or interruption from the investigator, the head of the study site will promptly notify the IRB and the sponsor of the fact and the reason in writing.
The sponsor will, when deciding the discontinuation or interruption of the study or the termination of development of the IP, promptly notify the head of the study site of the fact and the reason in writing. Once receiving a notification of interruption or discontinuation of the study or the termination of development from the sponsor, the head of the study site will promptly notify the investigator and the IRB of the fact and the reason in writing.

24. Archiving of Records

1) Study site
   The head of the study site should retain the documents and records related to this study to be archived at the study site (hereinafter, the study-related records) until the elapse of 15 years after either the date of the marketing approval of the investigational drug or the date of decision of discontinuation of the development of the investigational drug.
   For archiving the study-related records, the head of the study site will assign a storage manager. The head of the study site and the storage manager must take necessary measures so that these records are not lost or disposed of during the retention period and that they can be presented at the request of the sponsor, regulatory authorities, etc.
   When the retention period of records to be archived at the study site expires, the sponsor will promptly notify the head of the study site of the fact.
2) Sponsor
   The sponsor should retain the study-related records to be archived at the sponsor site until the elapse of 15 years after either the date of the marketing approval of the investigational drug or the date of the decision of discontinuation of the development of the investigational drug.

25. Publication Policy

1) The study site may not disclose or divulge data on the study provided by the sponsor or information such as study results to any third party without prior permission of the sponsor. If intending to publish the information obtained from the study to external parties such as academic conferences, the study site must obtain prior permission from the sponsor.
2) The founder of the IRB shall accept the sponsor's request (if any) for prior checking of a summary of the meeting minutes specified in Article 28, Paragraph 2-6 of the GCP to ensure the summary does not include the description infringing on the sponsor's intellectual property rights. When necessary, the founder may publish the summary after taking appropriate measures such as data masking.
3) The sponsor may freely use information obtained from this study for application for marketing approval for the test drug, product summary, promotional materials, publications, presentations at academic societies, and other materials to be submitted to the Ministry of Health, Labour, and Welfare.
4) When publishing information, sufficient attention must be paid to participant privacy.

26. Use of study-related data

1) The sponsor may use information obtained from this study (the study-related data) for application for marketing approval for the test drug, product summary, promotional materials, publications, presentations at academic societies, and other materials to be submitted to the Ministry of Health, Labor, and Welfare.
2) The sponsor may use the study-related data for the research and development of other than the test

drug and otherwise academic research when considered necessary.

27. Ethics

27.1 Institutional Review Board

Prior to the execution of the clinical study agreement, the IRB will review the contents of the protocol, informed consent form, and other explanatory documents, as well as the appropriateness of conducting the study. After the execution of the clinical study agreement, the IRB will continuously review the appropriateness of continuing the study.

27.2 Ethical Conduct of the Study

This study shall be conducted in compliance with the Ministerial Ordinance on Good Clinical Practice for Drugs and related notifications, the ethical principles based on the Declaration of Helsinki, and the protocol.

27.3 Protection of Participants' Confidentiality

To protect the participants' confidentiality, the investigator or subinvestigator will use participant identification codes instead of names to identify participants when completing CRFs and reporting adverse events and other study-related data to the sponsor. The sponsor's CRA and auditors will similarly protect any confidential participant information obtained during the course of the study in accordance with the provisions of Article 80-2, Paragraph 10 of the Act on Securing Quality, Efficacy, and Safety of Products Including Pharmaceuticals".

27.4 Participant Selection and Informed Consent

27.4.1 Participant Selection

During the selection of participants, the investigator or subinvestigator should carefully consider the advisability of asking for a patient to participate in the study taking into consideration the health condition, symptoms, age, sex, ability to consent, dependency on the investigator or subinvestigator, and status of participation in other clinical studies from the viewpoints of human rights protection and based on the protocol-specified inclusion and exclusion criteria. If a patient who is visiting another hospital is enrolled in the study, the investigator or subinvestigator will consider eligibility for study participation after examining the details of the medical treatment.

27.4.2 Informed Consent

1) Prior to the assessment for study participation, the investigator or subinvestigator will fully explain the study to each participant by using the informed consent form and other explanatory documents that describe the items provided in "27.4.3 Explanations to Participants." After this explanation, written voluntary consent to participate in the study will be obtained from the participant personally.
2) In cooperation with the sponsor, the investigator will prepare the informed consent and other explanatory documents that will be used to obtain the participants' consent to participate in the study and revise them as needed. The prepared or revised informed consent form and other explanatory documents should be approved by the IRB before use.
3) The investigator will comply with the ethical principles when preparing or revising the informed consent form and other explanatory documents.
4) The investigator or subinvestigator who provided the explanation, and the participant will each sign and date on the informed consent form. If a CRC makes a supplemental explanation, the CRC will also sign and date on the form.
5) The investigator or subinvestigator will provide the participant with the signed and dated informed

consent form (copy), and other explanatory documents before the participant participates in the study.

6) The investigator, subinvestigator, and CRC should not put pressure or unjustified influence on the participants to participate or continue participating in the study.
7) The informed consent form and other explanatory documents for the participants or information provided orally when explaining the study must not contain any words or suggestions that cause the participants to relinquish their rights. Furthermore, the consent materials and explanation must not contain any words or suggestions that absolve the investigator, subinvestigator, CRC, study site, or sponsor of their legal responsibilities.
8) Nontechnical vocabulary that the participants can understand should be used as much as possible during the verbal explanation and in written explanation and the informed consent form.
9) The investigator or subinvestigator will provide the participant with the opportunity to ask questions and sufficient time to decide whether to participate in the study before obtaining the participant's consent. The investigator, subinvestigator, or CRC (as someone providing additional explanation) must answer all questions to the satisfaction of the participant.
10) If information is obtained that could potentially affect the participants' willingness to continue participating the study, the investigator or subinvestigator must promptly give the information to the participants and ask whether the participants are willing to continue participating the study. In such cases, the fact that this information has been given to the participants will be recorded in the source documents.
11) If significant new information that may be related to the participants' consent is obtained, the investigator should promptly revise the informed consent form and other explanatory documents for the participants on the basis of this information.
12) When the informed consent form and other explanatory documents for participants are revised, the investigator or subinvestigator will promptly give the information which the amendment is based on to participants and ask whether the participants are willing to continue participation in the study. Furthermore, the investigator or subinvestigator will again explain the study using the revised informed consent form and other explanatory documents for participants and obtain voluntary written informed consent to continue participation in the study from each participant. The investigator or subinvestigator will provide the participants with the newly signed and dated revised informed consent form (copy) and the other explanatory documents.

27.4.3 Explanations to Participants

1) This study is being conducted for the purpose of investigation (i.e., this study involves research).
2) Study objective
3) Name, job title, and contact information of the investigator.
4) The study method (including the investigative aspect of the study, the participant inclusion criteria, and the probability of being assigned to each treatment)
5) The expected benefits to the participant's physical and mental health and the expected disadvantages to the participant of the IP
6) The presence or absence of other treatments available to the participant and the expected important benefits and risks of the treatments
7) The participant's scheduled duration of participation in the study
8) Participation in the study is voluntary, and the participant can refuse or withdraw consent to participate in the study at any time.
9) The participant will not undergo any disadvantages as a result of refusing or withdrawing consent to

participate in the study, and the participant will not lose any benefits that the participant should receive if he or she does not participate in the study.

10) The CRAs, auditors, and the IRB which deliberated the protocol, and regulatory authorities will have direct access to medical records and similar documents on the condition that the participant's confidentiality will be protected. At such times, the participant's confidentiality will be protected. The participant allows direct access to such materials by signing the informed consent form.
11) The participant's confidentiality will be protected if the study results are published.
12) The consultation service to the study site where the participant should make inquiries or should contact if the participant desires further information regarding the study or participant's rights or if study-related injury occurs.
13) The compensation and treatment available to the participant in the event of study-related injury.
14) The types of IRBs that review the appropriateness of the study, the matters reviewed by each IRB, and other matters related to the IRBs involved in this study.
15) Matters to be communicated to participants on this study
    - The planned number of participants in the study
    - If information is obtained that could potentially affect the participant's willingness to continue participating the study, that information will be promptly reported to the participant.
    - The conditions or reasons to withdraw participants from the study
    - Information for the financial responsibility of the participant in the study
    - Information related to payments to the participant
    - Instructions to be followed by the participant
    - Study staff will obtain medical information from other physicians with the consent of the participant.

28. Payments

Measures taken to reduce the participant's financial burden resulting from participation in the study (if any) should be stipulated in writing after a discussion with the study site. Provisions for other necessary expenses will also be stipulated in writing after another discussion with each study site.

29. Compensation for Injuries

If a participant suffers from an injury attributable to the study and seeks compensation from the study site, the sponsor shall be fully responsible for the compensation unless the injury is due to an intentional error or a medical error by the study site. Prior to conducting the study, the sponsor will purchase product liability insurance for the IP as a measure to compensate for injuries.

30. Responses to COVID-19

Definitions of confirmed COVID-19 patients (including asymptomatic pathogen carriers), suspected COVID-19 patients, and persons in close contact with such patient follow the latest edition of the Treatment Guidelines for New Coronavirus Infections (COVID-19).

30.1 COVID-19-related instructions to participants

The investigator or subinvestigator will instruct the participants in this study to promptly contact the study site if they are found to have confirmed COVID-19 (including asymptomatic pathogen carriers) or suspected COVID-19, or found to have been in close contact with a confirmed or suspected COVID-19 patient.

30.2 When found to have confirmed COVID-19 (including asymptomatic pathogen carriers) or suspected COVID-19, or found to have been in close contact with a confirmed or suspected COVID-19 patient

30.2.1 When participants are found to have confirmed COVID-19 (including asymptomatic pathogen carriers) or suspected COVID-19, or found to have been in close contact with a confirmed or suspected COVID-19 patient

(1) Visits for the study

1) The investigator or subinvestigator will instruct the participant not to visit the study site during the period shown in Table 30 1, ask their safety by telephone, e-mail, online medical examination, or other means (hereinafter referred to as telephone contact, etc.), and record their status in the source document.

2) After ensuring that the participant does not in the period shown in Table 10-1, Scoring the degree of skin thickening by two-step pinching method, the investigator or subinvestigator will urge the participant to visit the study site, ask whether the participant is willing to continue participating in the study, and determine whether or not the participant can continue the study.

Table 30-1 Period of prohibition to visit the study site due to the impact of COVID-19

Category	Period of prohibited visits to the study site
Patients with confirmed COVID-19 (including asymptomatic pathogen carriers)	Until meeting the criteria for discharge or termination of care at designated facilities, etc. in the Treatment Guidelines for New Coronavirus Infections (COVID-19).
Patients with suspected COVID-19	Until being confirmed not to meet any of the criteria of patients with suspected COVID-19 in the Treatment Guidelines for New Coronavirus Infections (COVID-19).
Participants having been in close contact with a confirmed or suspected COVID-19 patient	From the day of contact (Day 0) to the day 14 days have elapsed from contact

(2) Administration of investigational product

1) The investigator or subinvestigator should not administer the IP unless it is confirmed that the participant meets the following criteria on the day of administration:

a) For participants who have confirmed (including asymptomatic pathogen carriers) or suspected COVID-19

- At least 20 days after the onset of symptoms and 72 hours after the symptoms have resolved: or
- The symptoms have resolved, and the participant has been confirmed not to carry the pathogen.

b) For participants having been in close contact with a confirmed or suspected COVID-19 patient

- At least 15 days after close contact

2) When the participant infected with COVID-19 visits the study site according to (1) continues the study, the investigator or subinvestigator will determine whether the IP can be administered to the participant by interview with him/her, etc. When it is considered administration is possible through consultation with the sponsor, the investigator or subinvestigator will administer the IP to the participant

30.2.2 When staff at the study site who may have close contact with participants have confirmed COVID-19 (including asymptomatic pathogen carriers) or suspected COVID-19.

(1) The investigator or subinvestigator will inform the participants in the study that staff at the study site who may have close contact with them are (or may be) infected with COVID-19, ask the safety of the subjects by telephone or other contact means, and document the result in the source documents. The investigator or subinvestigator will also provide response and instruction to the participants according to the instructions of the study site.

(2) The investigator or subinvestigator will promptly inform the sponsor that staff at the study site who may have close contact with participants are (or may be) infected with COVID-19.

30.3 Discontinuation of the study due to the influence of COVID-19

If the study has been discontinued due to the influence of COVID-19, the investigator or subinvestigator will record in the source document and the CRF that the study was discontinued due to COVID-19.

30.4 Deviations from the protocol due to the influence of COVID-19

If a protocol deviation has occurred due to the influence of COVID-19, the investigator or subinvestigator will keep a record in the source document so as to make it clear that the deviation occurred due to the influence of COVID-19.

31. Study Period

December 2021 to October 2023

32. Administrative Structure

32.1 Sponsor

[redacted], Representative Director, President & CEO, Maruho Co., Ltd.
[redacted] Osaka [redacted]

32.2 Sponsor Organization

1) Head of Clinical Trial

[redacted], General Manager, Clinical Development Department, Maruho Co., Ltd

Major roles:

a) [redacted]

b) [redacted]

c) [redacted]

2) Clinical Trial Supervisor

[redacted] Clinical Development Department, Maruho Co., Ltd.

Major roles:

[redacted]

3) Medical Safety Officer

[redacted] MD, PhD, Senior Medical Director, Maruho Co., Ltd.

Major roles:

a) [redacted]

b) [redacted]

4) Clinical Research Associate Leader

[redacted], Clinical Development Department, Maruho Co., Ltd.

Major roles:

[redacted].

32.3 Study Sites and Investigators

Study Center：The University of [redacted] Tokyo [redacted]

Investigator：[redacted]

32.4 Medical Expert

Shinichi Sato

Professor, Department of Dermatology, [redacted], The University of [redacted]

32.5 Contract Research Organization

1) Clinical Testing Laboratory

[redacted] Corporation, [redacted] Tokyo [redacted]

2) Biomarker Measurement Institution

[redacted] Corporation, [redacted] Tokyo [redacted]

3) Anti-Drug Antibody Measurement Institution

[redacted] Corporation, [redacted], Tokyo [redacted]

4) Drug Concentration Measurement Institution

[redacted] Laboratories, Ltd., [redacted] Tokyo [redacted]

5) Autoantibody Measurement Institution

[redacted] Corporation, [redacted], Tokyo [redacted]

6) CyTOF Measurement Institution

[redacted], Inc., [redacted], Tokyo [redacted]

33. Contact Information

33.1 Contact Information

[redacted], Clinical Development Department, Maruho Co., Ltd.
[redacted] Kyoto [redacted]
TEL [redacted] (dial in)
FAX [redacted]

33.2 Emergency Contact (Saturdays and Sundays, National Holidays, Nights)

[redacted], Clinical Development Department, Maruho Co., Ltd. TEL [redacted]
[redacted], Clinical Development Department, Maruho Co., Ltd. TEL [redacted]

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