Protocol

Protocol Number: MT-7117-G02

A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate Efficacy, Safety, and Tolerability of MT-7117 in Subjects With Diffuse Cutaneous Systemic Sclerosis

Version Number: Version 5.0
Date: 03 November 2021
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STUDY PROTOCOL

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IND Number:	143973
EudraCT number:	2020-000134-17
Investigational Medicinal Product:	MT-7117
Indication:	Treatment of diffuse cutaneous systemic sclerosis
Development Phase:	Phase 2
Sponsor:	Mitsubishi Tanabe Pharma Development America, Inc. (MTDA) 525 Washington Boulevard, Suite 400 Jersey City, New Jersey 07310, USA
Sponsor's EU Representative:	EU Legal Representative for Clinical Trials Mitsubishi Tanabe Pharma GmbH Willstätterstraße 30, 40549 Düsseldorf Germany
Sponsor's UK Representative:	Mitsubishi Tanabe Pharma Europe Ltd Dashwood House 69 Old Broad Street London, EC2M 1QS, UK
Protocol Version and Date:	Version 5.0, 03 November 2021

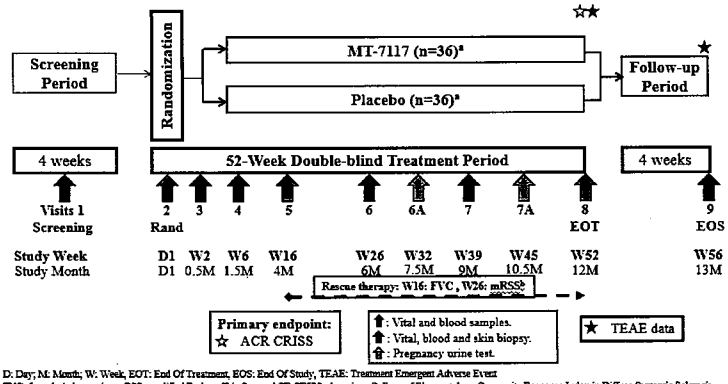
Protocol/ Amendment History of MT-7117-G02 study:

	Name	Version	Date	Comment
	MT-7117-G02 protocol	1.0	5-Mar-20	Original protocol
Amendment 1	MT-7117-G02 protocol	2.0	13-Jul-20	Global Master Protocol
Amendment 2	MT-7117-G02 protocol	3.0	12-Oct-20	Global Master Protocol
	Country Specific Protocol Amendment for the UK	3.1	27-Oct-20	The UK country specific
Amendment 3	MT-7117-G02 protocol	4.0	23-Dec-20	Global Master Protocol
Amendment 4	MT-7117-G02 protocol	5.0	03-Nov-21	Global Master Protocol

1 PROTOCOL SYNOPSIS

Protocol number:	MT-7117-G02
Protocol title:	A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate Efficacy, Safety, and Tolerability of MT-7117 in Subjects with Diffuse Cutaneous Systemic Sclerosis.
Development phase:	2
Study Centers:	International multicenter study
Indication:	Treatment of diffuse cutaneous systemic sclerosis
Name of Active Ingredient:	MT-7117
Treatment regimen:	MT-7117 100 mg tablets Placebo to match MT-7117 100 mg tablets
Treatment duration:	52 weeks
Coordinating Investigator:	[redacted]
Objectives:	**Primary Objective** • To evaluate the efficacy of MT-7117 treatment in subjects with diffuse cutaneous systemic sclerosis (dcSSc) using the American College of Rheumatology Composite Response Index in Diffuse Systemic Sclerosis (ACR CRISS) at Week 52. **Secondary Objectives** • To evaluate the efficacy of MT-7117 treatment for up to 52 weeks using patient-reported outcomes (PROs) as measured by the Health Assessment Questionnaire Disability Index ([redacted]) and Patient Global Assessment. • To evaluate the efficacy of MT-7117 treatment for up to 52 weeks on pulmonary function as measured by percent predicted forced vital capacity (%pFVC). • To evaluate the efficacy of MT-7117 treatment for up to 52 weeks using the Physician Global Assessment. • To evaluate the efficacy of MT-7117 treatment for up to 52 weeks using the modified Rodnan Skin Score (mRSS). • To evaluate ACR CRISS at Weeks 16, 26, and 39. • To evaluate ACR CRISS Score improvement proportion up to 52 weeks. **Exploratory Objectives** • [redacted]

	
	Safety Objectives • To evaluate the safety and tolerability of MT-7117 treatment for up to 56 weeks in subjects with dcSSc.
	Pharmacokinetics Objective • To determine the pharmacokinetic (PK) profile of MT-7117 in subjects with dcSSc.
Study design:	Double Blind Treatment
Planned number of subjects:	Approximately 72 subjects (36 subjects in each treatment group).
Methodology:	This is a Phase 2, multi-center, randomized, double-bind, placebo-controlled, parallel-group study to evaluate the efficacy, safety, and tolerability of MT-7117 in subjects with dcSSc. The duration of the study is approximately 60 weeks; screening period up to 4 weeks, double-blind treatment period of 52 weeks, and a safety follow-up period of 4 weeks after last dose. Following completion of the all screening assessments, subjects will return to the clinical site for the double-blind treatment period (Visit 2, Day 1) and baseline assessments will be evaluated and confirmed the eligibility [Table 1]. Eligible subjects will be randomized in a 1:1 ratio to either MT-7117 at starting of 300 mg every day (QD) or matching placebo in a double-blind manner, stratified [redacted] performed at screening (positive or negative). Study drug will be administered once daily orally in the morning with or without food. During the double-blind treatment period, subjects will return to the clinical site and assessments will be collected as described in Table 1. The decision about dose reduction and tolerability should be made according to the pre-specified criteria and the Investigator's clinical judgment. If a subject is experiencing intolerance to study drug, they should first be conservatively managed using standard of care and maintain the starting dose of study drug (active or placebo). If the subject continues to present significant

	intolerable adverse events (AE) at the following scheduled or unscheduled visit and the Investigator deems it necessary, the daily dose of study drug can be reduced. Dose reductions will be conducted via the Interactive Web-based Response System (IWRS). Subjects who do not tolerate a minimum dose of 100 mg/day will be withdrawn from the study (Section 8.1, Section 10.1.3.1, and Section 10.1.3.2). Subjects with worsening scleroderma such as skin thickening or other scenarios will be allowed to use rescue therapy starting at or after Week 26, and those with confirmation of predicted FVC decline (after 2 separate confirmations within 4 weeks via an unscheduled visit) will be allowed to use rescue therapy starting at or after Week 16 (Section 11.3.1.2). An end of treatment (EOT) or an early termination (ET) visit will be performed for all subjects who will undergo efficacy and safety assessments. Efficacy evaluations will include change in the composite score of ACR CRISS Components, PGIC, PGIS, UCLA SCTC GIT 2.0 questionnaire, PROMIS-29 test questionnaire, and certain biomarkers. Subjects who discontinue from study treatment before EOT (Week 52) should be encouraged to continue in the study and complete all the required study assessments through Week 52. If a subject decides to permanently withdraw consent from the study, every attempt should be made to have the subject complete the ET visit and complete the study assessments listed at Week 52 (Table 1). A safety follow-up visit will occur at Week 56 (Visit 9) for subjects who complete the double-blind treatment period (Week 52) and 4 weeks after the last dose of study drug for subjects who early terminated from the study (Table 1). Further details can be found in the Study Design Schema.
Study Design Scheme:	 a) Starting daily dose will be MT-7117 300 mg QD or matching placebo, with possibility to reduce the dose in a stepwise manner from 300 mg QD to 200 mg QD and possibly from 200 mg QD to 100 mg QD to manage subjects' tolerability to study drug. b) At the discretion of the Investigator, rescue therapy may start as early as Week 16 with confirmation of predicted FVC decline, and as early as Week 26 with worsening scleroderma such as skin thickening or other scenarios.

Inclusion criteria:	Subjects who meet all the following criteria will be considered eligible to participate in the study: 1. Must provide signed and dated informed consent form (ICF) to participate in the study. Subjects must be able to (in the judgment of the Investigator) understand the nature of the study and all risks involved with participation in the study. Subjects must be willing to cooperate and comply with all protocol restrictions and procedures including study visits. 2. Male or female age ≥ 18 years at screening with documented diagnosis of systemic sclerosis (SSc), as defined using the 2013 ACR/European League Against Rheumatism (EULAR) criteria (Appendix 1). 3. Has diffuse cutaneous form of SSc according to Leroy and Medsger's criteria (Appendix 1). 4. Disease duration ≤ 5 years from the first non-Raynaud's phenomenon manifestation. 5. Has an mRSS of 15 to 45 units at screening and have clinical skin involvement proximal and distal to the elbows, knees, or both or any truncal involvement, with or without face involvement. 6. If disease duration is > 24 months defined as time from the first non-Raynaud phenomenon manifestation, subject must fulfill at least 1 of the criteria listed below that are indicatives of active disease at screening: a. A documentation of new skin involvement that occurred within the past 9 months, or b. Increase in mRSS ≥ 3 units within the past 9 months, or c. Presence of tendon friction rubs (TFRs) or, d. C- reactive protein (CRP) ≥ 6 mg/L, or e. Erythrocyte sedimentation rate ≥ 28 mm/hr, or f. Platelet count ≥ 330 x 10^9/L (330,000/microliter). **NOTE:** Investigator should exclude all other acute intercurrent illness if subjects fulfilling laboratory criteria (d, e, f) only. 7. Willing to follow restrictions regarding concomitant medications that are described in Appendix 2. 8. Female subjects who are non-lactating and have a negative urine pregnancy test at baseline visit prior to receiving the first dose of study drug. 9. Female subjects of childbearing potential and male subjects with partner of child-bearing potential currently using/willing to use 2 effective methods of contraception including barrier method as described in Appendix 3.
Exclusion criteria:	Subjects will be excluded from the study if any of the following criteria apply: 1. Has a history or presence of rheumatic autoimmune diseases other than dcSSc unless the dominant features of the current disease are from dcSSc, as determined by the Investigator after the discussion with the Medical Monitor. 2. Has a pulmonary disease with FVC ≤ 50% of predicted at time of screening (Section 11.5). 3. Has a diagnosis of clinically significant resting pulmonary hypertension (if exceeding estimated right ventricular systolic pressure of > 40 mmHg estimated by transthoracic echocardiography [unless the right heart catheterization is normal within the last 6 months] or mean pulmonary artery pressure > 30 mmHg as measured by right heart catheterization) and requires treatment with more than one oral medication. 4. Has a cardiac abnormality such as left ventricular failure with ejection fraction < 45%, significant arrhythmia, congestive heart failure (New

	York Heart Association Class II-IV), unstable angina, uncontrolled hypertension, or symptomatic pericardial effusion at screening. 5. Has a history of myocardial infarction in the last 26 weeks prior to screening. 6. Has a history of renal crisis within the past 52 weeks prior to screening (See Appendix 16 for definition). 7. Has a documented history of chronic kidney disease (stage 4-5, an estimated glomerular filtration rate [eGFR] < 30 mL/min at screening). 8. Presence or history of hepatobiliary disease at screening, determined as clinically significant by the Investigator after the discussion with the Sponsor Medical Monitor. 9. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) ≥ 2.0 × upper limit of normal (ULN), or total bilirubin > 1.5 × ULN at screening. 10. Has a history or presence of clinically significant disease not related to SSc [neurologic, renal, endocrine, gastrointestinal cardiovascular, hepatic, dermatologic, hematological, musculoskeletal, genitourinary, thromboembolic, advanced arteriosclerosis, hyperthyroidism, moderate to severe hypertension, immunologic disease, pulmonary (e.g., uncontrolled asthma, emphysema, chronic obstructive pulmonary disease) or any other disorder] as determined by the Investigator at screening. Conditions deemed not-clinically significant according to the Investigator's discretion are acceptable. 11. Has a history or presence of serious or clinically significant (as judged by the Investigator) psychiatric disorders including but not limited to, anxiety disorder, depression, and bipolar disorder, that may make a subject unlikely or unable to complete the study or comply with study procedures and requirements, impact the subject's ability to participate in the study and/or interfere with the study evaluation and/or safety of the subject. 12. Has any clinically significant disease or laboratory abnormality judged to be clinically significant by the Investigator and which may interfere with the study evaluation and/or safety of the subject at screening. Laboratory abnormalities include but not limited to any of the followings: Hemoglobin < 9 g/dL; WBC < 3,000/mm^3 (< 3 x 10^9/L); platelets < 100,000/mm^3 (<100 x 10^9/L). 13. Has a history of positive hepatitis B surface antigen, hepatitis C antibody, except for documented cure for the hepatitis B virus (HBV), defined as sustained, undetectable HBsAg and HBV DNA in serum and adequately treated hepatitis C virus (HCV) with documentation of sustained virologic response defined as undetectable HCV RNA at least 12 weeks after the end of treatment. 14. Has a history of positive human immunodeficiency virus (HIV). 15. Has a history of melanoma, familial melanoma (defined as having 2 or more first-degree relatives, such as parent, sibling, and/or child), or presence of melanoma and/or lesions suspicious for melanoma at screening. 16. Presence of squamous cell carcinoma, basal cell carcinoma, or other malignant skin lesions. Any suspicious lesions or nevi (Melanocytic Lesions) will be evaluated. If the suspicious lesion or nevi (Melanocytic Lesions) cannot be resolved through biopsy or excision, the subject will be excluded from the study. 17. Has history of any other malignancy(ies) in the last 5 years with the exception of cervical carcinoma in situ. 18. Has a history or planning to receive cell-depleting therapy or bone marrow transplantation during study treatment period.

	19. Has a history of ultraviolet (UV) phototherapy within 6 weeks prior to screening or planning to receive UV phototherapy during study treatment period. 20. Treatment of SSc disease with: a. Cyclophosphamide, rituximab, or cyclosporine received within 26 weeks prior to screening. b. Small molecules such as JAK inhibitors (e.g., tofacitinib) received within 12 weeks prior to screening. c. Pirfenidone received within 12 weeks prior to screening. d. Infliximab, certolizumab, golimumab, adalimumab, abatacept, tocilizumab within 10 weeks prior to screening. e. Etanercept within 4 weeks prior to screening. f. Oral, intravenous, or intramuscular corticosteroids (prednisone > 10 mg/day or equivalent) received within 30 days prior to screening g. Nintedanib within 12 weeks prior to screening. h. More than 1 of the immunosuppressant therapy listed below as concomitant therapy with study drug, has changed one of the medications below within 12 weeks prior to screening, or not on a stable dose of the same medication for at least 12 weeks prior to screening. i. Mycophenolate (up to 3 g/day), or ii. Mycophenolic acid (up to 2.14 g/day), or iii. Methotrexate (up to 25 mg/Week), or iv. Leflunomide (up to 20 mg/day), or v. Azathioprine (up to 3 mg/kg/day). 21. Treatment with afamelanotide or other MC1R agonist within 12 weeks before screening (Visit 1). 22. Treatment with any drugs or supplements which, in the opinion of the Investigator, may interfere with the objectives of the study or safety of the subject. 23. Has previously exposed to MT-7117 (this does not include placebo treated subjects). 24. Has previously treated with any investigational agent within 12 weeks prior to screening OR 5 half-lives of the investigational product (whichever is longer). 25. Female subjects who are pregnant, lactating, or intending to become pregnant during the study. 26. Using the following drugs (including but not limited to) within 1 week of screening (Visit 1) [Specific drugs are listed in Appendix 2 for reference]: a. Drugs known to be predominantly metabolized by cytochrome P450 (CYP) 3A4 with a narrow therapeutic index for which elevated plasma concentrations are associated with clinical safety concern or significant medical events. b. Drugs that are known substrates of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP)1B1, or OATP1B3 for which elevated plasma concentrations are associated with significant medical events. 27. Has a positive autoantibody status of anti-centromere antibody.
Endpoints:	**Primary Endpoint** • The ACR CRISS composite score (0-1) at Week 52. **Secondary Endpoint(s)**

- Change in HAQ-DI from baseline at Weeks 16, 26, 39, and 52.
- Change in Patient Global Assessment from baseline at Weeks 16, 26, 39, and 52.
- Change in percent predicted forced vital capacity (%pFVC) from baseline at Weeks 16, 26, 39, and 52.
- Change in Physician Global Assessment from baseline at Weeks 16, 26, 39, and 52.
- Change in mRSS from baseline at Weeks 16, 26, 39, and 52.
- ACR CRISS Score at Weeks 16, 26, and 39.
- ACR CRISS Score improvement at Weeks 16, 26, 39 and 52: Proportion of subjects with ≥ 25% improvement in mRSS, HAQ-DI, Patient Global Assessment, Physician Global Assessment, or ≥ 5% improvement in FVC for at least 3 of the 5 ACR CRISS measures.
- ACR CRISS score responder (CRISS ≥ 0.6) at Weeks 16, 26, 39, and 52.

Exploratory Endpoint(s)

- [redacted]

	• [redacted]
	Safety Endpoint(s) • Treatment-emergent adverse events ([TEAEs] including serious adverse events [SAEs], AEs leading to withdrawal, and adverse events of special interest [AESIs]). • Physical examination. • Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature). • Clinical laboratory examinations (hematology, coagulation, biochemistry, and urinalysis), including liver function markers (ALT, AST, gamma glutamyl transpeptidase [GGT], ALP, direct and total bilirubin). • 12-lead electrocardiogram (ECG). • Nevi (Melanocytic Lesions) appearance (assessed by a dermatologist or other qualified site staff). Any nevi (Melanocytic Lesions) undergoing change of clinical concern during active treatment will be biopsied for follow-up and evaluated by a central pathology laboratory.
	Pharmacokinetic Endpoint • Assessment of plasma PK concentrations of MT-7117 measured at scheduled visits
Statistical methods:	A Statistical Analysis Plan (SAP) containing details of all the analyses and outputs will be prepared and approved prior to the study database lock. The Intent-to-treat (ITT) population will be used for all efficacy analyses. All safety analysis will be performed on the Safety population and PK assessments will be performed on the PK population. Unless otherwise specified, the baseline values will be the last non-missing value prior to receiving the first dose of study drug. Continuous variables will be summarized descriptively using the number of observations, mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages. All statistical tests will be performed at the 5% 2-sided significance level. Point estimates of treatment differences will be provided with 2-sided 95% confidence intervals (CIs) where applicable.

Determination of Sample Size:

The planned sample size of 72 is expected to provide power for the comparison between MT-7117 treatment group and placebo group for ACR CRISS score at Week 52. The calculation of sample size assumes a 2-sided alpha level of 0.05 and uses EAST (Version 6.5) for Wilcoxon Mann Whitney test. The randomized 72 subjects (36 subjects for MT-7117 and 36 subjects for placebo) with a 1:1 allocation ratio would provide 80% power to detect treatment difference of 0.35 (35% improvement on MT-7117 treatment group compared to placebo group) in ACR CRISS score at Week 52 with an associated SD of 0.5.

Analysis Populations:

- Safety population: includes all randomized subjects who received at least 1 dose of study drug.
- ITT Population: includes all randomized subjects who receive at least 1 dose of study drug.
- Per-protocol Population: includes all ITT subjects who do not have any major protocol deviations and complete Week 52 (the end of double-blind treatment period).
- PK Population: includes all randomized subjects who receive at least 1 dose of study drug and who have at least 1 postdose value of plasma concentration to be included in the PK analysis without important protocol deviations which may affect the PK of study drug.

Efficacy Analysis:
Analysis of Primary Efficacy Endpoints:

The primary treatment comparisons of interest are the ACR CRISS score for MT-7117 treatment group compared with placebo group at Week 52.

ACR CRISS score is a composite endpoint assessed in a 2-step process that calculates the probability of improvement for each subject ranging from 0.0 (no improvement) to 1.0 (marked improvement) refer to Appendix 4 for further details.

The primary endpoint will be summarized using descriptive statistics with interquartile range. The distribution of ACR CRISS score may not be normal distribution. For ACR CRISS score at Weeks 16, 26, 39, and 52, the comparison between MT-7117 treatment group and placebo group will be performed using this non-parametric analysis method. The point estimates and 2-sided 95% CIs and associated P-values for the difference between the treatment groups will be obtained using the Hodges-Lehman estimator corresponding to Wilcoxon's rank sum test. The non-parametric analysis will be performed with multiple imputation method, assuming missing at random. A supportive analysis will be performed the same way for the primary endpoints using the per-protocol set (PPS). As a secondary analysis for the primary endpoint, the same analysis method will be applied to the ITT but the patients' data after taking rescue therapy will not be included. This approach will be performed to investigate a sensitivity for the primary analysis.

Analysis of Secondary Efficacy Endpoints:

Change from baseline to Week 52 in mRSS, %pFVC, HAQ-DI, Patient Global Assessment, and Physician Global Assessment will be analyzed using mixed-effect model for repeated measures (MMRM). The model will include fixed categorical terms for the treatment group, visit, the randomization factor [redacted] and the treatment group by visit interaction together with continuous covariate terms for baseline value and baseline value by visit interaction. An unstructured

correlation structure will be used to model the within-subject variance covariance errors. Should convergence of the model fail (due to the small numbers of subjects in this study), other variance covariance matrices such as autoregressive [AR(1)] correlation matrix will be used if appropriate. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. From the model described above, p-values will be produced. All available data from all subjects will be used without any imputation.

ACR CRISS Score improvement proportion at Week 52 will be analyzed using logistic regression model. The model will include the treatment group and the randomization factor [redacted] as fixed factors together with continuous covariate terms for baseline mRSS. The treatment odds ratio at Week 52 will be estimated using a contrast.

Proportion of subjects with ACR CRISS score responder (CRISS $\geq$ 0.6) at Weeks 16, 26, 39, and 52 will be analyzed using generalized linear mixed effect model with logit rink function. This analysis will use the observed values from Weeks 16 to 52 as the response. The model will include the treatment group, visit and the interaction between the treatment group, the randomization factor [redacted] and visit as fixed factors together with continuous covariate terms for baseline mRSS and baseline mRSS by visit interaction. The treatment odds ratio at Week 52 will be estimated using a contrast.

Analysis of Exploratory Endpoints:

[redacted]

	[redacted] **Safety Analysis:** TEAEs are defined as AEs that newly occurred or increased in severity on or after the first dose of study drug. The frequency and incidence of TEAEs will be summarized by System Organ Class (SOC) and Preferred Term (PT) by treatment group. The AE summaries will be presented by treatment group for the following: • TEAEs by SOC and PT • TEAEs by SOC, PT and severity • TEAEs by SOC, PT and relationship • Treatment-emergent adverse reactions by SOC and PT • Treatment-emergent adverse reactions by SOC, PT and severity • Serious TEAEs by SOC and PT • Serious treatment-emergent adverse reactions by SOC and PT • TEAEs leading to drug withdrawn by SOC and PT • TEAEs by SOC and PT for TEAEs with frequency ≥ 5 % in MT-7117 treatment group Death, serious TEAEs, and TEAEs leading to withdrawal will be listed. Other routine safety assessments such as physical examination, vital signs, 12-lead ECG, laboratory examinations, and nevi (Melanocytic Lesions) evaluation will be summarized descriptively and/or listed by treatment group. **Pharmacokinetic Analysis:** Plasma MT-7117 concentrations will be listed for each subject, scheduled visit, and treatment period.

Table 1: Schedule of Activities

	Screening Period	Double-blind Treatment Period									Safety Follow-up Period
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**6A Telephone Visit**	**7**	**7A Telephone Visit**	**8 (EOT/ET)**	**9[a] (EOS)**
Study Week	**-4**	**1**	**2**	**6**	**16**	**26**	**32**	**39**	**45**	**52**	**56**
Study Day ± Window	**–28 to -1**	**1 (Baseline)**	**15 (± 3 days)**	**43 (± 5 days)**	**113 (± 7 days)**	**183 (± 7 days)**	**225 (± 7 days)**	**274 (± 7 days)**	**316 (± 7 days)**	**365 (± 7 days)**	**393 (± 7 days)**
Informed consent	X										
Inclusion/exclusion criteria	X	X									
Prior medications	X										
Demographics	X										
Medical history	X										
Randomization		X									
Dispensing of study drug		X	X	X	X	X		X			
Drug accountability			X	X	X	X		X		X	
Body weight	X	X	X	X	X	X		X		X	
Height	X										
Physical examination[b]	X	X	X	X	X	X		X		X	X
Vital signs[c]	X	X	X	X	X	X		X		X	X
12-lead ECG	X					X				X	
[redacted]	X										
	X									X	
[redacted]	X					X		X		X	
[redacted]		X				X		X		X	

	Screening Period	Double-blind Treatment Period									Safety Follow-up Period
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**6A[a] Telephone Visit**	**7**	**7A[a] Telephone Visit**	**8 (EOT/ET)**	**9[a] (EOS)**
Study Week	**-4**	**1**	**2**	**6**	**16**	**26**	**32**	**39**	**45**	**52**	**56**
Study Day ± Window	**–28 to -1**	**1 (Baseline)**	**15 (± 3 days)**	**43 (± 5 days)**	**113 (± 7 days)**	**183 (± 7 days)**	**225 (± 7 days)**	**274 (± 7 days)**	**316 (± 7 days)**	**365 (± 7 days)**	**393 (± 7 days)**
[redacted]t	X			X	X	X		X		X	
Pregnancy test[e]	X	X	X	X	X	X	X	X	X	X	X
Hematology/coagulation, biochemistry, and urinalysis[f]	X	X	X	X	X	X		X		X	X
ESR[g]	X										
PK sampling (blood)[h]		X	X	X	X	X		X		X	
[redacted]		X									
[redacted]		X			X					X	
[redacted]		X			X	X				X	
[redacted]		X			X	X				X	
[redacted]		X			X	X				X	
SP-D, KL-6		X			X	X				X	
ACR CRISS					X	X		X		X	
[redacted]					X	X		X		X	

	Screening Period	Double-blind Treatment Period									Safety Follow-up Period
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**6A Telephone Visit**	**7**	**7A Telephone Visit**	**8 (EOT/ET)**	**9[a] (EOS)**
Study Week	**-4**	**1**	**2**	**6**	**16**	**26**	**32**	**39**	**45**	**52**	**56**
Study Day ± Window	**–28 to -1**	**1 (Baseline)**	**15 (± 3 days)**	**43 (± 5 days)**	**113 (± 7 days)**	**183 (± 7 days)**	**225 (± 7 days)**	**274 (± 7 days)**	**316 (± 7 days)**	**365 (± 7 days)**	**393 (± 7 days)**
mRSS	X	X			X	X		X		X	
%pFVC	X	X			X	X		X		X	
SHAQ[m]		X			X	X		X		X	
PtGA		X			X	X		X		X	
PhGA		X			X	X		X		X	
[redacted]				X	X	X		X		X	
[redacted]		X		X	X	X		X		X	
[redacted]		X				X				X	
[redacted]		X				X				X	
[redacted]		X				X				X	
[redacted]		X	X	X	X	X		X		X	X
Nevi (Melanocytic Lesions) evaluation[o]	X		X	X		X				X	X
Subject Question for study drug[p]										X	
Concomitant medications[q]	X	X	X	X	X	X		X		X	X
Record Adverse events	X	X	X	X	X	X		X		X	X

Abbreviations: ACR CRISS = American College of Rheumatology Composite Response Index for Systemic Sclerosis; ECG = electrocardiogram; EOS = End of Study; EOT = End of treatment; [redacted]; KL-6 = Krebs von den Lungen-6; [redacted]; HIV = human immunodeficiency virus; mRSS = modified Rodnan Skin Score; [redacted]; %pFVC = percent predicted forced vital capacity; [redacted]; PK = pharmacokinetic; [redacted]; SP-D =

Surfactant protein-D; [redacted]. SSc=Systemic Sclerosis; MC1R= melanocortin-1 receptor; SNPs= single-nucleotide polymorphisms, PhGA=Physician Global Assessment; PtGA=Patient Global Assessment; ET=Early Termination; AE=Adverse Event; eCRF= electronic Case Report Form; HAQ-DI= Health Assessment Questionnaire Disability Index; VAS= Visual Analog Scale

a. All subjects (completers and those who ET) will return to the clinical site 4 weeks after their last dose for a safety follow-up visit. For subjects who ET and will not revisit the clinical site, the site will perform a scheduled phone call for the collection of safety assessments (e.g., AEs, concomitant medication, and date of last dose of study drug).
b. A complete physical examination will be performed at Visit 1 and an abbreviated physical examination will be performed at all other specified time points.
c. Vital signs will include blood pressure, pulse rate, respiratory rate, and body temperature (e.g., oral, axillary or tympanic body temperature).
d. [redacted].
e. For female subjects of child-bearing potential, a serum pregnancy test will be performed at Visit 1, a urine pregnancy test (on-site) will be performed at all other site visits, and a urine dipstick pregnancy test at home or other home testing arrangements will be performed at Telephone Visits (Visit 6A and 7A).
f. Refer to Table 3 for laboratory evaluations.
g. ESR will be analyzed locally at the site level and at Screening only.
h. PK blood samples for MT-7117 will be collected at Visit 2 predose, Visits 3, 4, 5, 6, 7, and Visit 8 at any time during each visit. Date and time of study drug dose and date and time of PK sample collection will be recorded.
i. Blood sampling will be collected for optional PGx analysis for those subjects who have provided informed consent.
j. [redacted]
m. SHAQ is composed of HAQ-DI and VAS.
n. [redacted]
o. Nevi (Melanocytic Lesions) evaluation will be performed by a local dermatologist or qualified site staff. Baseline nevi (Melanocytic Lesions) evaluation will be performed at any time during the screening period before randomization at Visit 2 (Day 1). The nevi (Melanocytic Lesions) evaluation at Visit 9 is to assess for the reversibility if any suspicious nevi (Melanocytic Lesions) changes that were observed during treatment as per the Investigator's (and/or dermatologist's or other qualified site staff) judgment. Any follow-up will be recorded in the eCRF. Nevi (Melanocytic Lesions) assessment will be described in a separate document.
p. Subjects will be asked whether they believe they received active or placebo treatment.
q. Concomitant medications at screening, baseline and used during study treatment will be reviewed, recorded and discussed with the Sponsor and medical Monitor (as needed).
r. [redacted]

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3 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations are used in this study protocol.

Abbreviation	Definition
ACR CRISS	American College of Rheumatology Composite Response Index in Diffuse Systemic Sclerosis
AEs	Adverse events
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AR	Autoregressive
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
ATS/ERS	American Thoracic Society/European Respiratory Society
BCRP	Breast cancer resistance protein
BID	Two times a day
BLM	Bleomycin
cAMP	Cyclic adenosine 3',5'-monophosphate
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence intervals
COVID-19	Coronavirus Disease 2019
[redacted]	[redacted]
CRF	Case Report Form
CRISS	Composite response index in diffuse systemic sclerosis
[redacted]	[redacted]
CSR	Clinical study report
CYP	Cytochrome P450
dcSSc	diffuse cutaneous systemic sclerosis
[redacted]	[redacted]
DMARDs	Disease-modifying anti-rheumatic drugs
DNA	Deoxyribonucleic acid
ECG	electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOS	End of study
EOT	End of treatment
EPP	erythropoietic protoporphyria

Abbreviation	Definition
[redacted]	[redacted]
ET	Early termination
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
EUSTAR	European League Scleroderma Trials and Research
FDA	Food and Drug Administration
FVC	Forced vital capacity
GCP	Good Clinical Practice
GGT	Gamma glutamyl transpeptidase
GMP	Good Manufacturing Practice
HAQ-DI	Health Assessment Questionnaire Disability Index
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HRCT	High resolution chest tomography
IB	Investigator's Brochure
ICF	Informed consent form
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
iDMC	Independent data monitoring committee
IEC	Independent ethics committee
ILD	Interstitial lung disease
IRB	Institutional Review Board
ITT	Intent-to-treat
IWRS	Interactive Web-based Response System
KL-6	Krebs von den Lungen-6
LFT	Liver function test
MAD	Maximum Ascending Dose
MC1R	Melanocortin-1 receptor
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect model for repeated measures
mRSS	modified Rodnan Skin Score
MTDA	Mitsubishi Tanabe Pharma Development America
OATP	Organic anion transporting polypeptide
PAH	Pulmonary arterial hypertension
PD	Pharmacodynamic
PFT	Pulmonary function test
%pFVC	Percent predicted forced vital capacity

Abbreviation	Definition
[redacted]	[redacted]
[redacted]	[redacted]
P-gp	p-Glycoprotein
PGx	Pharmacogenomics
PhGA	Physician Global Assessment
PtGA	Patient Global Assessment
PK	Pharmacokinetic(s)
p.o.	Oral administration
PPS	Per-protocol set
[redacted]	[redacted]
PROs	patient-reported outcomes
PT	Preferred term
QD	Every day
QTc	Corrected QT interval
QTcB	Corrected QT interval using Bazett's formula
QTcF	Corrected QT interval using Frederica's formula
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SHAQ	Scleroderma Health Assessment Questionnaire
SNP	single-nucleotide polymorphisms
SOC	system organ class
SP-D	Surfactant protein-D
SSc	Systemic sclerosis
SSc-ILD	Systemic sclerosis- interstitial lung disease
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
[redacted]	[redacted]
[redacted]	[redacted]
ULN	Upper limit of normal
US	United States
UV	Ultraviolet
VAS	Visual Analog Scale
WHO	World Health Organization
WMA	World Medical Association
α-SMA	α smooth muscle actin

Abbreviation	Definition
XLP	X-linked protoporphyria

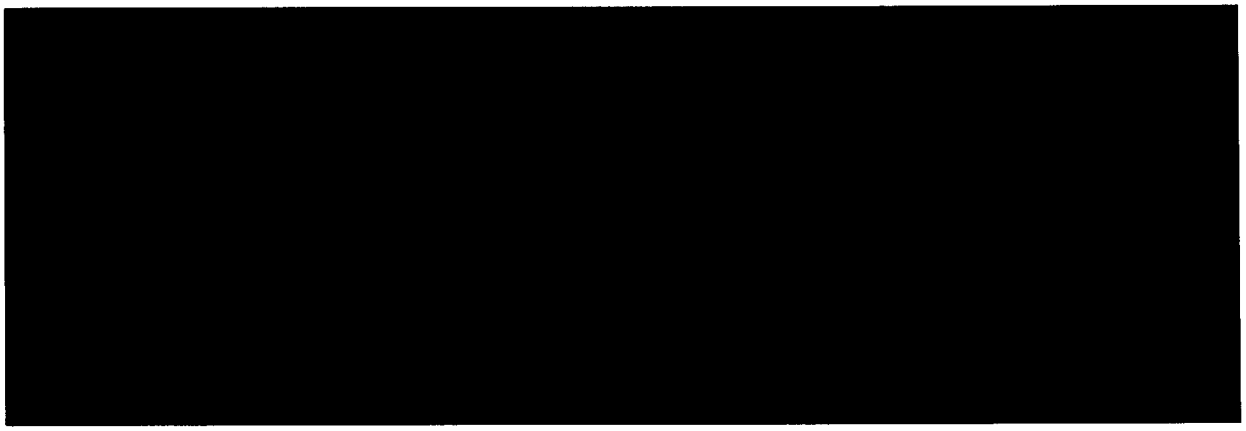
4 SIGNATURES

SPONSOR'S RESPONSIBLE SIGNATORY

Protocol Number: MT-7117-G02

A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate Efficacy, Safety, and Tolerability of MT-7117 in Subjects with Diffuse Cutaneous Systemic Sclerosis

The Protocol has been designed according to the ICH Harmonized Tripartite Guideline for Good Clinical Practice, the Declaration of Helsinki (Fortaleza, Brazil, 2013) and the Code of Federal Regulations. It has undergone both medical and scientific review by competent Sponsor personnel. The study will be initiated at the site(s) only after Institutional Review Board/ Independent Ethics Committee, regulatory, and local approvals of the necessary essential documents and study procedures will not be initiated until the subject has signed the approved Subject Information and Informed Consent Form(s).

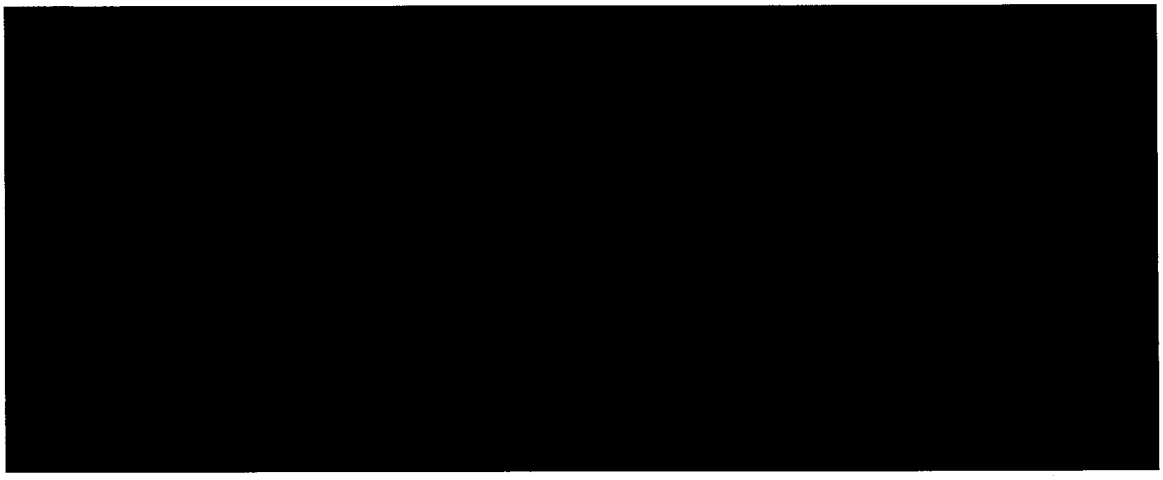


SIGNATURE PAGE (STATISTICAN)

Protocol Number: MT-7117-G02

A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate Efficacy, Safety, and Tolerability of MT-7117 in Subjects with Diffuse Cutaneous Systemic Sclerosis

The Protocol has been designed according to the ICH Harmonized Tripartite Guideline for Good Clinical Practice and has undergone statistical review.



SIGNATURE PAGE COORDINATING (PRINCIPAL) INVESTIGATOR

Protocol Number: MT-7117-G02

A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate Efficacy, Safety, and Tolerability of MT-7117 in Subjects with Diffuse Cutaneous Systemic Sclerosis

I confirm that I have read this Protocol and understand its contents. I agree to fully comply with its requirements. I understand it and will conduct the study in accordance with the procedures described in this protocol and:

_____ (initial here) The principles of GCP as described in 21 CFR, Parts, 50, 56, and 312, as well as any applicable local requirements

or

_____ (initial here) The principles of GCP as described in ICH E6 as well as any applicable local requirements.

I agree to make no changes to the conduct of the study as defined by the Protocol without the prior authorization of Mitsubishi Tanabe Pharma Development America, Inc. in the form of a Protocol Modification and without the appropriate Regulatory Authorities and Institutional Review Board/Independent Ethics Committee.

Address of Institution: _____

_____

_____

_____

_____

Signed: _____

Print Name: _____

Title: _____

Date: _____

5 SPONSOR AND ADMINISTRATION STRUCTURE

Table 2: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

6 INTRODUCTION

MT-7117 (dersimelagon) is a novel orally-administered, small molecule, which acts as an agonist of melanocortin-1 receptor (MC1R) and is being developed by Mitsubishi Tanabe Pharma to reduce active inflammatory and fibrotic processes in adults with diffuse cutaneous systemic sclerosis (dcSSc).

MC1R is a member of the G-protein-coupled receptors superfamily. It is the predominant melanocortin receptor expressed in cutaneous and hair follicle melanocytes. MC1R is activated by α-melanocyte-stimulating hormone which can be locally synthesized in response to sunlight exposure. MC1R regulates the amount and type of pigment production and is a major determinant of skin phenotype and sensitivity to ultraviolet light induced damage.[1] MC1R has also been reported to be expressed by a variety of cell types, including fibroblasts, endothelial cells, and immune cells.[2] Activation of MC1R enhances deoxyribonucleic acid (DNA) repair, upregulates antioxidant enzymes, and reduces production of proinflammatory cytokines,[3] suggesting that MC1R is important for the resolution of inflammation.[4] Therefore, agonism of MC1R is associated not only with increased skin pigmentation, but also with regulation of inflammatory responses.[1,4,5]

Systemic sclerosis (SSc) is a complex polygenetic, autoimmune, and chronic medical condition characterized by excessive production of collagen (fibrosis), microvascular damage in the skin, joints, lung, esophagus, gastrointestinal tract, kidneys, heart, and other internal organs[6], with an estimated prevalence in the United States (US) of 276-300 cases per million with an incidence of about 20 cases per million per year.[7,8] The 10-year survival has reportedly improved from the 1970s (54%–60%) to the1990s (66%–78%).[8]

The patient population is highly heterogeneous, with each patient presenting with unique combinations of organ involvement, symptoms, and progression. There are 2 major recognized patterns that the illness can take: diffuse or limited disease. In diffuse scleroderma, skin thickening occurs more rapidly and involves more skin areas than in limited disease. In addition, subjects with diffuse sclerosis have a higher risk of developing "sclerosis" (fibrous hardening) of the internal organs.[6]

The process of skin fibrosis in dcSSc is highly variable; for most subjects it includes an inflammatory phase eliciting fibrosis followed by a plateau (and slight reversal), representing established fibrosis without the presence of inflammatory signals.[9] Skin fibrosis is measured clinically by the modified Rodnan skin score (mRSS) score,[10,11] a subjective measure of skin thickness done by pinching/palpating the skin of the patient.

Systemic sclerosis-interstitial lung disease (SSc-ILD), the major systemic morbidity of the disease, is seen in about 30% to 40% of SSc subjects and lung fibrosis is the leading cause of death among SSc subjects, particularly in dcSSc.[12,13] Forced vital capacity (FVC) is a clinical correlate of lung fibrosis and has the greatest decrease during the early years of disease, although it continues to decrease over the course of disease as fibrosis increases.[12] FVC decline is greater in subjects exhibiting more severe fibrosis by high resolution chest tomography (HRCT).

SSc is an extremely difficult disorder to diagnose and manage, with unknown origin or genetic predisposition. Apart from nintedanib, there are currently no treatments indicated for SSc.

Despite some recent sets of general treatment guidelines there is,[25,41] as yet, not a defined treatment paradigm. Treatment is dependent on subtype (diffuse or limited), stage, and organ systems involved. It is believed from experts and from the literature that the reversal of established fibrosis is a difficult. Therefore, current therapeutic efforts are focused on limiting inflammation or oxidative stress in the early phase of dcSSc in order to modulate collagen overproduction and thereby prevent progression of fibrosis and controlling related symptoms. Patients receive different regimens of steroids, immunosuppressants, and anti-fibrotics. Many current treatments are minimally effective, along with carrying potentially significant safety issues, such as immune suppression.

There are numerous products in the development pipeline which target symptomatic and disease improvement in lung, skin, or both. Many of these products were initially launched for treatment of other indications (such as asthma or idiopathic pulmonary fibrosis) and are now pursued for a label extension in dcSSc. Multiple drugs in the pipeline have been discontinued due to safety and efficacy issues as well as inability to recruit clinical studies.

Mitsubishi Tanabe Pharma Development America (MTDA) is developing MT-7117 for the treatment of dcSSc. Since MT-7117 is an investigational medication, and its safety profile in humans has not yet been fully investigated, all subjects receiving MT-7117 will be closely monitored. Further information can be found in the MT-7117 Investigator's Brochure (IB).[14,40]

6.1 Nonclinical Studies

Results of the completed nonclinical studies conducted with MT-7117, including pharmacology, pharmacokinetics (PKs), and toxicology studies, can be found in the IB.[14,40]

6.2 Clinical Studies

Results of the completed clinical studies conducted with MT-7117 so far, and the information of ongoing or planned studies with MT-7117 can be found in the IB.[14,40]

7 STUDY OBJECTIVES AND ENDPOINTS

7.1 Study Objectives

7.1.1. Primary Objective

To evaluate the efficacy of MT-7117 treatment in subjects with dcSSc using the American College of Rheumatology Composite Response Index in Diffuse Systemic Sclerosis (ACR CRISS) at Week 52.

7.1.2. Secondary Objectives

- To evaluate the efficacy of MT-7117 treatment for up to 52 weeks using patient-reported outcomes (PROs) as measured by the Health Assessment Questionnaire Disability Index (HAQ-DI) and Patient Global Assessment.
- To evaluate the efficacy of MT-7117 treatment for up to 52 weeks on pulmonary function as measured by percent predicted forced vital capacity (%pFVC).
- To evaluate the efficacy of MT-7117 treatment for up to 52 weeks using the Physician Global Assessment.
- To evaluate the efficacy of MT-7117 treatment for up to 52 weeks using the mRSS.
- To evaluate ACR CRISS at Weeks 16, 26, and 39.
- To evaluate ACR CRISS Score improvement proportion up to 52 weeks.

7.1.3. Exploratory Objectives

7.1.4. Safety Objectives

- To evaluate the safety and tolerability of MT-7117 treatment for up to 56 weeks in subjects with dcSSc.

7.1.5. Pharmacokinetics Objective

- To determine the pharmacokinetic (PK) profile of MT-7117 in subjects with dcSSc.

7.2 Study Endpoints

7.2.1 Primary Endpoint

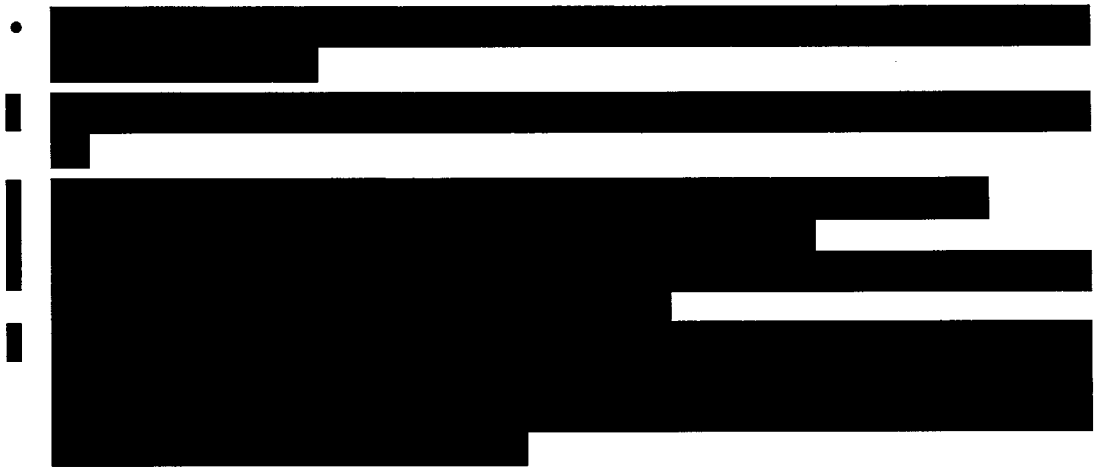
- The ACR CRISS composite score (0-1) at Week 52.

7.2.2 Secondary Endpoint(s)

- Change in HAQ-DI from baseline at Weeks 16, 26, 39, and 52.
- Change in Patient Global Assessment from baseline at Weeks 16, 26, 39, and 52.
- Change in %pFVC from baseline at Weeks 16, 26, 39, and 52.
- Change in Physician Global Assessment from baseline at Weeks 16, 26, 39, and 52.
- Change in mRSS from baseline at Weeks 16, 26, 39, and 52.
- ACR CRISS Score at Weeks 16, 26, and 39.
- ACR CRISS Score improvement at Weeks 16, 26, 39 and 52: Proportion of subjects with ≥ 25% improvement in mRSS, HAQ-DI, Patient Global Assessment, Physician Global Assessment, or ≥ 5% improvement in FVC for at least 3 of the 5 ACR CRISS measures.
- ACR CRISS score responder (CRISS ≥ 0.6) at Weeks 16, 26, 39, and 52.

7.2.3 Exploratory Endpoint(s)

- [redacted]



7.2.4 Safety Endpoint(s)

- Treatment-emergent adverse events ([TEAEs] including serious adverse events [SAEs], adverse events (AEs) leading to withdrawal, and adverse events of special interest [AESIs]).
- Physical examination.
- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature).
- Clinical laboratory examinations (hematology, coagulation, biochemistry, and urinalysis), including liver function markers (ALT, AST, gamma glutamyl transpeptidase [GGT], ALP, direct and total bilirubin).
- 12-lead electrocardiogram (ECG).
- Nevi (Melanocytic Lesions) appearance (assessed by a dermatologist or other qualified site staff). Any Nevi (Melanocytic Lesions) undergoing change of clinical concern during active treatment will be biopsied for follow-up and evaluated by a central pathology laboratory.

7.2.5 Pharmacokinetics Endpoint

- Assessment of plasma PK concentrations of MT-7117 measured at scheduled visits

8 STUDY DESIGN

8.1 Overall Study Design

This is a Phase 2, multicenter, randomized, double-bind, placebo-controlled, parallel-group study to evaluate efficacy, safety, and tolerability of MT-7117 in subjects with dcSSc.

The duration of the study is approximately 60 weeks; screening period up to 4 weeks, double-blind treatment period of 52 weeks, and a safety follow-up period of 4 weeks after last dose.

Following completion of the all screening assessments, subjects will return to the clinical site for start of the double-blind treatment period (Visit 2, Day 1) and baseline assessments will be evaluated and confirmed the eligibility (e.g., safety assessments, ACR CRISS components, and nevi (Melanocytic Lesions) evaluation, if nevi (Melanocytic Lesions) are present (Table 1)

Eligible subjects will be randomized in a 1:1 ratio to either MT-7117 at starting of 300 mg every day (QD) or matching placebo in a double-blind manner, [redacted]

Study drug will be administered once daily orally in the morning with or without food.

During the double-blind treatment period, subjects will return to the clinical site and assessments will be collected as described in Table 1.

The decision about dose reduction and tolerability should be made according to the pre-specified criteria and the Investigator's clinical judgment.

If a subject is experiencing intolerance to study drug, they should first be conservatively managed using standard of care and maintain the starting dose of study drug (active or placebo).

If the subject continues to present significant intolerable AEs at the following scheduled or unscheduled visit and the Investigator deems it necessary, the daily dose of study drug can be reduced from 300 mg QD to 200 mg QD while tolerability is managed with standard of care.

If the subject continues to present significant intolerable AEs at the following scheduled or unscheduled visit and the Investigator deems it necessary, the dose of study drug can be reduced from 200 mg QD to 100 mg QD.

If the subject continues to present significant intolerable AEs at the decreased dose of 100 mg QD and the Investigator deems it necessary, the subject may discontinue study treatment.

All dose reductions during the Treatment Period will be done in 100 mg decrements. Dose reductions will be conducted via the Interactive Web-based Response System (IWRS).

Subjects who do not tolerate a minimum dose of 100 mg/day will be withdrawn from the study (Section 10.1.3.1 and Section 10.1.3.2).

Subjects with worsening scleroderma such as skin thickening or other scenarios will be allowed to use rescue therapy starting at or after Week 26, and those with confirmation of predicted FVC decline (after 2 separate confirmations within 4 weeks via an unscheduled visit) will be allowed to use rescue therapy starting at or after Week 16 (Section 11.3.1.2).

End of treatment (EOT) or early termination (ET) assessments will be performed for all subjects, who will undergo efficacy and safety evaluations. Efficacy evaluations will include change in

the composite score of ACR CRISS Components, [redacted], [redacted], and certain biomarkers.

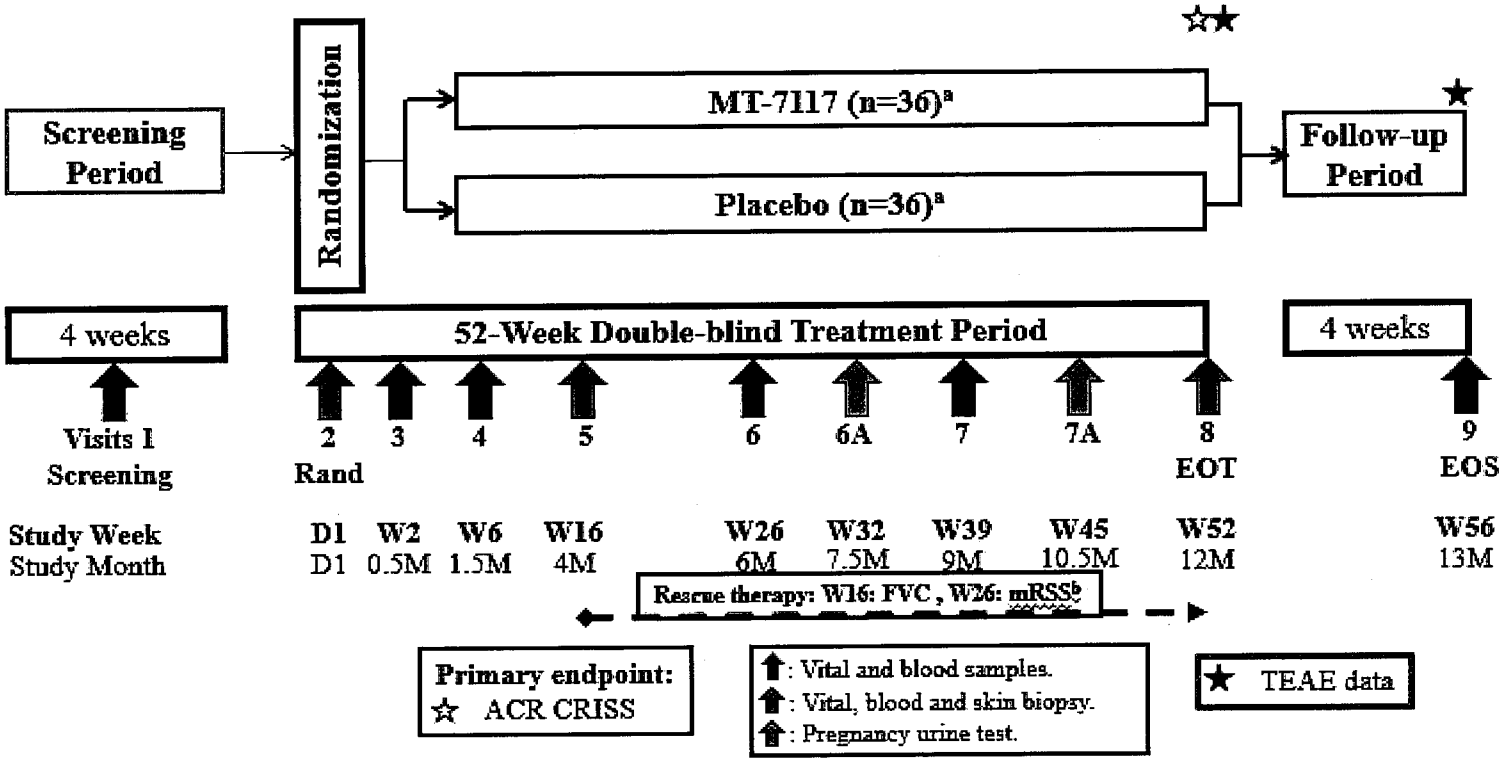
Subjects who discontinue study treatment before EOT (Week 52) should be encouraged to continue in the study and complete all the required study assessments through Week 52.

If a subject decides to permanently withdraw consent from the study, every attempt should be made to have the subject complete the ET visit and complete the study assessments listed at Week 52 (Table 1).

In the event a subject does not return to the clinical site for the ET and/or safety follow-up visit, the Investigator must make every effort to contact the subject by telephone to for the collection and source documentation of safety information such as AEs, dosing compliance, and review of concomitant medications and date of last dose of study drug. Return of unused medication will be performed by courier where allowed.

A safety follow-up visit will occur at Week 56 (Visit 9) for subjects who complete the double-blind treatment period (Week 52) and 4 weeks after the last dose of study drug for subjects who ET from the study.

Further details can be found in the Study Schema (Figure 1).



D: Day; M: Month; W: Week, EOT: End Of Treatment, EOS: End Of Study, TEAE: Treatment Emergent Adverse Event
FVC: forced vital capacity, mRSS: modified Rodnan Skin Score, ACR CRISS: American College of Rheumatology Composite Response Index in Diffuse Systemic Sclerosis

a Starting daily dose will be MT-7117 300 mg QD or matching placebo, with possibility to reduce the dose in a stepwise manner from 300 mg QD to 200 mg QD and possibly from 200 mg QD to 100 mg QD to manage subjects' tolerability to study drug.
b At the discretion of the Investigator, rescue therapy may start as early as Week 16 with confirmation of predicted FVC decline, and as early as Week 26 with worsening scleroderma such as skin thickening or other scenarios.

Figure 1: Study Design Schema

8.2 Rationale for Study Design

The objectives of this study are to obtain efficacy, safety, and tolerability for the selected dose (300 mg) of MT-7117 and placebo when administered to subjects with dcSSc over a 52-week double-blind treatment period. A standard randomized, placebo-controlled, double-blind treatment allocation is considered appropriate in order to obtain unbiased results in this study. Safety and PK/pharmacodynamic (PD), will be evaluated based upon the comparable data from the Phase 1 studies (MT-7117-E01, MT-7117-E02, and MT-7117-E03) and Phase 2 study (MT-7117-A01) in Erythropoietic Protoporphyria (EPP) or X-Linked Protoporphyria (XLP) population.

Abnormal changes in biochemical parameters related to the hepatic function were observed in rats and monkeys. In MT-7117-E01 human study, in subjects receiving 14 days of study drug, treatment-emergent transaminase elevations were reported in 6/36 (17%) subjects receiving MT-7117 and 2/12 (17%) subject receiving placebo. Of the 6 subjects who received MT-7117 for 14 days and reported treatment-emergent transaminase elevations, 4 had elevated baseline transaminase values. In this study, frequent assessments of LFTs will be performed.

The 52-week double-blind treatment period is considered a sufficient duration for evaluation of the efficacy, safety, and tolerability of MT-7117 in this study. Subjects will attend a follow-up visit 4 weeks after the EOT (or ET), which is considered a sufficient duration to evaluate safety of subjects. The primary endpoint will be measured using the composite response index in dcSSc (ACR CRISS) score. The ACR CRISS was developed with the goal of summarizing changes in clinical and PROs in a single composite score that conveys the likelihood (or probability) that the overall disease condition of a subject with dcSSc has improved, and it was developed using data from 12 months of treatment.[12]

The secondary endpoints will be measured using several assessments including the HAQ-DI, FVC, and mRSS which are individual components of the ACR CRISS. [redacted]. The effect of MT-7117 on quality of life will be assessed using validated questionnaires.

8.2.1 Risk/Benefit Assessment

8.2.1.1 Overall

MT-7117 is an investigational drug and its safety profile in humans has not yet been fully investigated. Therefore, all subjects will be closely monitored based on the completed clinical study safety observations/data. Results of the completed clinical studies conducted with MT-7117 so far, and the information of ongoing or planned studies with MT-7117 can be found in the IB.[14,40]

In embryo-fetal development study in mice, the total incidence of fetuses with skeletal anomalies was increased at 500 mg/kg/day, the lethal dose for adult female mice, with increased incidence of fused rib and fused sternebrae.

In the rat pre- and postnatal development study (ongoing study), 2 dams died on lactation day (LD) 11 and LD 18 at 300 mg/kg/day. The causal relationship of these deaths to MT-7117-

treatment has not been established. In the F1 offspring, MT-7117 related toxicities were observed in the 300 mg/kg/day group: a total litter loss of 2 dams, a significant increase or tendency towards an increase in deaths and cannibalism, and lower body weights.

Female subjects of child-bearing potential and male subjects with partners of child-bearing potential participating in this study will be required to use effective contraception as defined in Appendix 3, and female subjects who are pregnant, lactating, or intending to become pregnant during the study are excluded from the study.

The Sponsor will undertake all reasonable measures, including thorough screening and safety monitoring procedures, to minimize the risk to subjects. Due to the potential of MT-7117 to increase liver function markers, LFTs will be monitored at all planned study visits and assessment of adverse events (AEs) related to elevation of liver function markers and liver injury will be conducted. Additionally, subjects will be instructed to immediately stop study treatment if they meet any of the withdrawal criteria listed in Section 9.5.

The risk-benefit relationship was carefully considered in the planning of the study. Based on the nonclinical and clinical data obtained so far, the conduct of this study is considered justifiable using the dose and dosage regimen of MT-7117 as specified in this clinical study protocol.

8.2.1.2 Impact of COVID-19

Systemic sclerosis (SSc) is a rare life threatening autoimmune and chronic connective tissue disease, which affects skin, blood vessels, lungs, heart, kidneys, gastrointestinal (GI) tract and musculoskeletal system.[15] SSc is also characterized by immune dysfunction, vasculopathy, cellular inflammation and fibrosis of the skin and multiple internal organs.

The lungs are frequently involved in SSc, with interstitial lung disease (ILD) a common and chronic manifestation. SSc-ILD is a progressive lung disease in which lung function declines over time, and it can be debilitating and life-threatening. SSc-ILD is the leading cause of death among people with SSc, typically resulting from loss of pulmonary function that occurs when the lungs cannot supply enough oxygen to the heart leading to end stage chronic heart failure.[16]

Infections, specifically septic shock, a life-threatening organ dysfunction caused by a dysregulated host-response to infection,[17] may also play a significant role for the increased morbidity and mortality of patients with SSc. Septic shock was shown to contribute to the morbidity and mortality of these patients infected with Coronavirus Disease 2019 (COVID-19) by causing major organ failure involving the liver, kidney and gastrointestinal system. In a retrospective study with the patients infected with COVID-19, led by Zhou *et al* (2020) has shown that sepsis was the most frequently observed complication, followed by respiratory failure, ARDS, heart failure, and septic shock.[18] Predisposition of SSc patients to infections such as sepsis is derived from both poor functional status and immunosuppressive treatment.

COVID-19 is a viral influenza-like illness caused by a novel strain of coronavirus named "SARS-CoV-2." It is primarily a respiratory (lung) infection. It appears that COVID-19 is a more deadly pathogen on a case-by-case basis and can be spread very rapidly during the asymptomatic phase. The higher burden and mortality may be attributed to the fact that COVID-19 is a "newly emerged" disease, and consequently, there is very little innate immunity among humans, unlike the "seasonal" variety of influenza where both prior infection and annual

vaccination can provide protection.[18,19] In most severe cases, COVID-19 has emerged over the past few months as a clinical syndrome caused by COVID-19 and named Severe Acute Respiratory Syndrome (SARS) when the patient's pulmonary function rapidly deteriorates requiring mechanically assisted ventilation.

The pulmonary life-threatening complications in human COVID-19 patients are due to an exuberant local inflammatory response with diffuse alveolar damage. Patients dying because of SARS have lung consolidation ("ground glass" appearance at the base of the lungs seen on chest x-ray or CT scan), edema and mucopurulent material in the bronchial tree.[20,21] In systemic sclerosis pathogenesis, endothelial damage favors vascular leak of complement factors fostering varying degrees of inflammation and fibrosis in the lungs, heart and other viscera.[22,23] A particular concern with COVID-19 is that it tends to affect the lungs, which may already be injured in some patients with SSc. Therefore, patients with chronic diseases including lung disease such as SSc patients, if infected, are at higher risk for the most severe form of the disease course either due to underlying ILD and/or immunosuppression.[24]

The COVID-19 pandemic may have life-threatening implications for patients with SSc, particularly those undergoing a variety of immunosuppressive therapies. As it seems obvious that immunosuppressive therapy increases their risk of severe disease if infected with COVID-19, many patients have the tendency to stop their immunosuppressive treatments, especially in highly impacted areas.[20] Therefore, SSc patients taking immunosuppressive drugs should be recommended to maintain the chronic therapy, prevent infection by avoiding social contacts and pausing immunosuppressants in case of infection.[20] To do so, might run the risk of exacerbating the underlying autoimmune disease (e.g., SSC) while being infected with COVID-19. However, Matucci-Cerinic *et al* (2020), recommended if SSc patients develop COVID-19 symptoms or if someone else in the household develops COVID-19, immunosuppression should be put on hold.[24] The new ACR guidance for Management for Rheumatic Disease in Adult Patients During the COVID-19 Pandemic also includes some guidance on treatment including in those taking immunosuppressants, in various situations related to COVID-19.[42] While following these general guidances is recommended, each case should be managed on a case-by-case basis, in discussion with the medical monitor, as this guidance is not intended for research settings.

MT-7117 is not known to compromise the human immune system. In non-clinical repeated dose toxicity studies, there were no changes suggestive of immunosuppression. Completed Phase 1 and Phase 2 studies did not show increased risk of infection. Based on the evidence available so far, it is unlikely that MT-7117 exposure will increase the risk of COVID-19 infection; however, it is unknown if MT-7117 exposure will increase this risk. There may be additional risk to subjects due to exposure to COVID-19 during study related visits (depending on the country/region conditions).

Although there are risks in participating in Clinical Trials at these times with an experimental drug such as MT-7117, certain benefits must be acknowledged. SSc is a debilitating disease where there are unmet medical needs. The investigational product, MT-7117 has been shown to have acceptable safety profile in the many pre-clinical and early phase Clinical Trials. It is this acceptable safety profile that has led to further clinical investigation in safety and efficacy of MT-7117 in a challenging disease such as SSc. This benefit is also supported by the anti-inflammatory and antifibrotic effects of MT-7117 seen in animal studies where the human data

obtained from this clinical trial is expected to further support this drug's purported mechanism of action in establishing its role as an effective treatment for SSC. The Sponsor believes that these benefits outweigh any of the procedural or other risks associated with participation in the trial.

Because the scientific community still does not have knowledge about the infection rate and course of COVID-19 in SSc patients undergoing immunosuppressive therapies, a set of practical recommendations to improve the management of COVID-19 patients and to decrease the risk of acquiring this infection are:

1. Because there are no approved treatments for COVID-19 the Health Community emphasizes strongly for strict adherence to the basic protective measures recommended by the WHO: handwashing, maintaining social distancing, avoiding touching one's face, practicing proper respiratory hygiene, staying at home if feeling unwell, and obtaining prompt medical care if fever, cough, and breathing difficulty develop together.
2. Other recommendations may include wearing face masks/coverings and avoid social gatherings during the conduct of the clinical trial and site visits, as long as COVID-19 is prevalent. Additionally, the Sponsor will monitor country specific conditions and prepare contingency plans for COVID-19 related restrictions that may prevent site visits. All the above measures will eventually help reduce the transmission of coronavirus (COVID-19).

In COVID-19 environment SSc patients are a great challenge for the physician to achieve an effective protective strategy or, when infected, to optimize a real-time treatment as suggested by the rapidly evolving guidelines however the clinical need for relief from the symptoms of SSc remains high. Taking into consideration the mitigation strategies currently in place for the study it has been determined by the Sponsor that the potential benefits of MT-7117 to the subjects outweigh any of the potential risks of being infected with COVID-19.

8.2.2 Rationale for Dose Selection

The current Phase 2 proof of concept study will investigate efficacy, safety, and tolerability of MT-7117 in subjects with dcSSc.

In the MT-7117-E01 human healthy volunteer study, single doses up to 600 mg and multiple doses of up to 450 mg administered over 14 days in healthy male subjects, and single doses of 100 mg in healthy female subjects, have been shown to be safe. Some reversible increases in skin pigmentation, consistent with the expected pharmacology, were noted following repeated dosing and appeared to show a dose-dependent trend. No SAEs occurred during Study MT-7117-E01. In the Phase 1 Maximum Ascending Dose (MAD) study, daily dosing with 450 mg of MT-7117 was very well tolerated with an AE profile not different from 300 mg QD. The majority of AEs reported were mild, with only 2 severe cases (both receiving 300 mg MT-7117). Both cases were with melanocytic nevus with pre-existing moles which increased in size and became darker and were excised as a precautionary measure for histopathological diagnosis. The results of the excised moles [nevi (Melanocytic Lesions)] revealed lentiginous compound nevus (benign).

In Study MT-7117-E02, a single dose of 100 mg [^{14}C]-MT-7117 was well-tolerated. No deaths, SAEs, or TEAEs leading to withdrawal occurred during the study.

In Study MT-7117-E03, a 300 mg single dose was well tolerated under the gastric conditions studied. No new safety issues were identified during this study, and there were no deaths, SAEs, or discontinuations due to AEs.

In the MT-7117-A01 Phase 2 study of MT-7117 in 102 subjects with EPP or XLP, there were no major safety concerns, and well tolerated with the doses of 100 and 300 mg MT-7117 during the 16 weeks dosing and 6 weeks follow-up period. It was noted MT-7117 300 mg group had a higher incidence of TEAEs, severe TEAEs, TEAEs causing discontinuations compared to MT-7117 100 mg or placebo, which were primarily driven due to hyperpigmentation events, headache, nausea, vomiting, and diarrhea.

In a nonclinical study, prophylactic treatment with MT-7117 [≥0.3 mg/kg/day oral administration(p.o.)] inhibited the increase of collagen content of the skin, the serum level of surfactant protein-D (SP-D), and the weight of the lung in a mouse model of bleomycin (BLM)-induced skin fibrosis and interstitial lung disease (ILD). Therapeutic treatment with MT-7117 (≥3 mg/kg/day p.o.) significantly suppressed skin thickening, lung inflammation and the numbers of α smooth muscle actin (α-SMA)-positive myofibroblasts in a mouse model of pre-established BLM-induced skin fibrosis. The dose of 3 mg/kg/day p.o. in mouse therapeutic treatment model corresponds to approximately 200 mg QD in human.

Higher doses of MT-7117 (beyond 300 mg daily) may translate in a meaningful efficacy, but may increase the risk of tolerability, which will be associated with an increase in undesirable AEs, and consequently increase the rate of discontinuations.

Based on the non-clinical data and data from clinical studies, a dose of 300 mg QD is likely to provide anti-inflammatory, anti-vasculopathy, and anti-fibrosis effects while providing acceptable tolerability. As previously indicated, in subjects with EPP or XLP, a daily 300 mg dose was found to be safe and well tolerated for up to 16 weeks. Should tolerability become unacceptable for an individual subject, the Investigator may choose to reduce the dose to 200 mg or 100 mg per day, on a case by case basis.

9 SELECTION AND WITHDRAWAL OF SUBJECTS

The Sponsor does not operate a protocol waiver system for eligibility criteria.

9.1 Number of Subjects

Approximately 72 subjects are planned to be randomized in this study (36 subjects in each treatment group).

9.2 Recruitment Methods

A sufficient number of subjects will be screened to ensure the planned sample size will be achieved. Each subject will be screened according to the criteria described in Section 9.2 and Section 9.4. Only subjects who are eligible for the study will be randomized.

9.3 Inclusion Criteria

Subjects who meet all the following criteria will be considered eligible to participate in the study:

1. Must provide signed and dated informed consent form (ICF) to participate in the study. Subjects must be able to (in the judgment of the Investigator) understand the nature of the study and all risks involved with participation in the study. Subjects must be willing to cooperate and comply with all protocol restrictions and procedures including study visits.
2. Male or female age ≥ 18 years at screening with documented diagnosis of SSc, as defined using the 2013 ACR/European League Against Rheumatism (EULAR) criteria (Appendix 1).
3. Has diffuse cutaneous form of SSc according to Leroy and Medsger's criteria (Appendix 1).
4. Disease duration ≤ 5years from the first non-Raynaud's phenomenon manifestation.
5. Has an mRSS of 15 to 45 units at screening and have clinical skin involvement proximal and distal to the elbows, knees, or both or any truncal involvement, with or without face involvement.
6. If disease duration is > 24 months defined as time from the first non-Raynaud phenomenon manifestation, subject must fulfil at least 1 of the criteria listed below that are indicatives of active disease at screening:
    a. A documentation of new skin involvement that occurred within the past 9 months, or
    b. Increase in mRSS ≥ 3 units within the past 9 months, or
    c. Presence of tendon friction rubs (TFRs) or,
    d. C- reactive protein ≥ 6 mg/L, or
    e. Erythrocyte sedimentation rate ≥ 28 mm/hr, or
    f. Platelet count ≥ 330 x 10^9/L (330,000/microliter).

NOTE: Investigator should exclude all other acute intercurrent illness if subjects fulfilling laboratory criteria (d, e, f) only.

7. Willing to follow restrictions regarding concomitant medications that are described in Appendix 2.

8. Female subjects who are non-lactating and have a negative urine pregnancy test at baseline visit prior to receiving the first dose of study drug.
9. Female subjects of childbearing potential and male subjects with partner of child-bearing potential currently using/willing to use 2 effective methods of contraception including barrier method as described in Appendix 3.

9.4 Exclusion Criteria

Subjects will be excluded from the study if any of the following criteria apply:

1. Has a history or presence of rheumatic autoimmune diseases other than dcSSc unless the dominant features of the current disease are from dcSSc, as determined by the Investigator after the discussion with the Medical Monitor.
2. Has a pulmonary disease with FVC $\leq$ 50% of predicted at time of screening (Section 11.5).
3. Has a diagnosis of clinically significant resting pulmonary hypertension (if exceeding estimated right ventricular systolic pressure of > 40 mmHg estimated by transthoracic echocardiography [unless the right heart catheterization is normal within the last 6 months] or mean pulmonary artery pressure > 30 mmHg as measured by right heart catheterization) and requires treatment with more than one oral medication.
4. Has a cardiac abnormality such as left ventricular failure with ejection fraction < 45%, significant arrhythmia, congestive heart failure (New York Heart Association Class II-IV), unstable angina, uncontrolled hypertension, or symptomatic pericardial effusion at screening.
5. Has a history of myocardial infarction in the last 26 weeks prior to screening.
6. Has a history of renal crisis within the past 52 weeks prior to screening (See Appendix 16 for definition).
7. Has a documented history of chronic kidney disease [stage 4-5, an estimated glomerular filtration rate (eGFR) < 30 mL/min at screening].
8. Has a presence or history of any hepatobiliary disease at screening, determined as clinically significant by the Investigator after the discussion with the Sponsor Medical Monitor.
9. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) $\geq$ 2.0 × upper limit of normal (ULN), or total bilirubin > 1.5 × ULN at screening.
10. Has a history or presence of clinically significant disease not related to SSc [neurologic, renal, endocrine, gastrointestinal cardiovascular, hepatic, dermatologic, hematological, musculoskeletal, genitourinary, thromboembolic, advanced arteriosclerosis, hyperthyroidism, moderate to severe hypertension, immunologic disease, pulmonary (e.g., uncontrolled asthma, emphysema, chronic obstructive pulmonary disease) or any other disorder] as determined by the Investigator at screening. Conditions deemed not-clinically significant according to the Investigator's discretion are acceptable.
11. Has a history or presence of serious or clinically significant (as judged by the Investigator) psychiatric disorders including but not limited to, anxiety disorder, depression, and bipolar disorder, that may make a subject unlikely or unable to complete the study or comply with study procedures and requirements, impact the subject's ability

to participate in the study and/or interfere with the study evaluation and/or safety of the subject.

12. Has any clinically significant disease or laboratory abnormality judged to be clinically significant by the Investigator and which may interfere with the study evaluation and/or safety of the subject at screening. Laboratory abnormalities include but not limited to any of the followings: Hemoglobin < 9 g/dL; WBC_< 3,000/mm^3 (< 3 x 10^9/L); platelets < 100,000/mm^3 (<100 x 10^9/L).
13. Has a history of positive hepatitis B surface antigen, hepatitis C antibody, except for documented cure for the hepatitis B virus (HBV), defined as sustained, undetectable HBsAg and HBV DNA in serum and adequately treated hepatitis C virus (HCV) with documentation of sustained virologic response defined as undetectable HCV RNA at least 12 weeks after the EOT.
14. Has a history of positive human immunodeficiency virus (HIV).
15. Has a history of melanoma, familial melanoma (defined as having 2 or more first-degree relatives, such as parent, sibling, and/or child), or presence of melanoma and/or lesions suspicious for melanoma at screening.
16. Presence of squamous cell carcinoma, basal cell carcinoma, or other malignant skin lesions. Any suspicious lesions or nevi (Melanocytic Lesions) will be evaluated. If the suspicious lesion or nevi (Melanocytic Lesions) cannot be resolved through biopsy or excision, the subject will be excluded from the study.
17. Has history of any other malignancy(ies) in the last 5 years with the exception of cervical carcinoma in situ.
18. Has a history or planning to receive cell-depleting therapy or bone marrow transplantation during study treatment period.
19. Has a history of ultraviolet (UV) phototherapy within 6 weeks prior to screening or planning to receive UV phototherapy during study treatment period.
20. Treatment of SSc disease with:
    a. Cyclophosphamide, rituximab, or cyclosporine received within 26 weeks prior to screening.
    b. Small molecules such as JAK inhibitors (e.g., tofacitinib) received within 12 weeks prior to screening.
    c. Pirfenidone received within 12 weeks prior to screening.
    d. Infliximab, certolizumab, golimumab, adalimumab, abatacept, tocilizumab within 10 weeks prior to screening.
    e. Etanercept within 4 weeks prior to screening.
    f. Oral, intravenous, or intramuscular corticosteroids (prednisone > 10 mg/day or equivalent) received within 30 days prior to screening.
    g. Nintedanib within 12 weeks prior to screening.
    h. More than 1 of the immunosuppressant therapy listed below as concomitant therapy with study drug, has changed one of the medications below within 12 weeks prior to screening, or not on a stable dose of the same medication for at least 12 weeks prior to screening.
        i. Mycophenolate (up to 3 g/day), or
        ii. Mycophenolic acid (up to 2.14 g/day), or
        iii. Methotrexate (up to 25 mg/Week), or

iv. Leflunomide (up to 20 mg/day), or
v. Azathioprine (up to 3 mg/kg/day).

21. Treatment with afamelanotide or other MC1R agonist within 12 weeks before screening (Visit 1).
22. Treatment with any drugs or supplements which, in the opinion of the Investigator, may interfere with the objectives of the study or safety of the subject.
23. Has previously exposed to MT-7117 (this does not include placebo treated subjects).
24. Has previously treated with any investigational agent within 12 weeks prior to screening OR 5 half-lives of the investigational product (whichever is longer).
25. Female subjects who are pregnant, lactating, or intending to become pregnant during the study.
26. [redacted]
27. Has a positive autoantibody status of anti-centromere antibody.

9.5 Withdrawal from the Study and/or Treatment

A subject will be withdrawn from the study if ANY of the following criteria are met:

1. The subject requests to voluntarily withdraw from further participation in study.
2. The subject is significantly noncompliant with the protocol.
3. A female subject becomes pregnant while on the study.
4. Continuing in the study would be detrimental to the subject's safety in the opinion of the Investigator, for example:

    a. The subject experiences intolerable AEs, SAEs, or adverse events of special interest (AESIs).
    b. The subject has clinically significant changes in safety parameters at any of the postdose time points, as confirmed with a repeat assessment performed as soon as possible after the initial out-of-range result.
    c. The subject experiences any clinically significant adverse findings from postbaseline nevi (Melanocytic Lesions) evaluation and adverse change is demonstrated histologically and confirmed by central pathologist. Visual evaluation of change will not be acceptable criteria for permanent discharge from treatment (Section 12.4).
    d. Development of any clinically significant liver abnormalities defined as follows:

- ALT or AST > 8 x ULN.
- ALT or AST > 5 x ULN for more than 2 weeks.
- Elevated total bilirubin > 2 × ULN and ALT or AST > 3 x ULN or
- Symptoms consistent with liver dysfunction (e.g., fatigue, nausea, vomiting, abdominal pain or tenderness, fever, rash, eosinophilia > 5%) with concomitant ALT or AST values > 3 × ULN.

Subjects meeting the laboratory criteria of ALT/AST and total bilirubin defined above (with or without alternative etiology), regardless of whether clinically significant or not, should be reported as a hepatic AESI (Section 14.3). The Investigator should discuss with the Sponsor Medical Monitor about the determination of etiology and the potential of interruption or withdrawal from study drug.

In the case of an increase of ALT or AST > 3 × ULN, it is preferable to be followed by repeat testing within 48 to 72 hours of at least four of the usual serum measures (ALT, AST, ALP, and total bilirubin) at local or central laboratory to confirm the abnormalities and to determine if they are increasing or decreasing. In addition, repeat laboratory testing can include albumin, CK, direct and indirect bilirubin, GGT, and PT/INR. There also should be inquiry made about symptoms. A detailed history including but not limited to the following formations, such as symptoms, prior or concurrent disease, concomitant drugs (including nonprescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, exposure to environmental chemical agents, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection, autoimmune biomarkers and liver imaging (e.g., biliary tract) may be warranted.

Any other laboratory or clinical abnormality that the Sponsor Medical Monitor and/or Investigator considered as clinically significant should be considered as a potential reason for interruption (see Section 10.1.3.3) or withdrawal from study drug. Subjects who have withdrawn from study drug may remain in the study and be followed per protocol (Section 14.6). In addition, a subject may be withdrawn from study drug at any time for reason(s) other than those listed here. Subjects who have withdrawn from study drug cannot resume study drug.

Subjects who prematurely discontinue study treatment (withdraw from study drug) before the EOT should be encouraged to remain in the study and complete all the required study assessments and procedures through Week 52 based on the Investigator's discretion.

If a subject decides to permanently withdraw consent from the study, every attempt should be made to have the subject complete the ET visit and perform the assessments listed at Week 52 for the collection and source documentation of safety information such as AEs, dosing compliance, and review concomitant medications and date of last dose of study drug. Return of unused medication will be performed by courier where allowed.

PK blood samples are not required for subjects who have withdrawn from study drug and their last dose is ≥ 7 days before the next time point of a PK blood sample collection.

If a subject is discontinued prematurely from either study treatment or permanently from the study, the date and the reason of the subject's discontinuation will be recorded on the site source documents and in the electronic Case Report Form (eCRF).

In the event a subject does not return to the clinical site for the ET and/or safety follow-up visit, the Investigator must make every effort to contact the subject by telephone to discuss AEs, dosing compliance, and review concomitant medications. In these cases, the collected information (AEs, concomitant medications, date of last dose of medication, etc.) via telephone will be documented in the site source documents and eCRF. Return of unused study drug and any other materials will be performed by courier where allowed.

Unresolved AEs/SAEs will be followed according to Section 14.9.

Subjects who become pregnant during the study should be withdrawn from the study treatment. Also see Section 14.10 for necessary documentation and procedures for following up with the subject.

Subjects withdrawn from the study following randomization into the double-blind treatment period and prior to dosing may not re-enter the study.

9.6 Study-Stopping Criteria

The study may be terminated by the Sponsor at any time upon becoming aware of data that could compromise the safety and/or well-being of subjects, or for any other reason it deems appropriate.

10 STUDY PLAN

10.1 Description of Study Periods

Refer to (Table 1) for an outline of procedures required at each study period and/or visit.

Prior to performing any study procedures, the Investigator (or designated personnel) will ensure that the subject is provided full and adequate oral and written information about the study and the subject must sign the Informed Consent Form (ICF), as described in Section 17.2.1.

10.1.1 Screening Period

Screening assessments will be performed up to 28 days prior to Day 1 of the double-blind treatment period. All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria.

10.1.2 Rescreening

At the end of the screening period, if a subject has not met all eligibility criteria at the end of the screening period, the subject will be registered as a screen failure. Screen failures may be eligible for rescreening 1-time following consultation with the Sponsor and Medical Monitor.

Note: If the rescreening occurs more than 30 days after the first screening and signing of the original ICF, all screening procedures, including ICF, must be repeated. If within 30 days, repeat assessments should be discussed with the Medical Monitor.

If a subject does not meet eligibility criteria for laboratory and pulmonary function tests (PFTs), the subject may undergo repeat laboratory and PFTs up to 2 additional times during the 4-week screening period. Repeat of laboratory or PFTs is not considered rescreening.

10.1.3 Double-blind Treatment Period

Subjects who successfully complete the screening period will return to the clinical site on Day 1 of the double-blind treatment period to reconfirm his/her eligibility by reviewing the inclusion and exclusion criteria (Table 1) and evaluate other baseline criteria prior to randomization. To be randomized into the double-blind treatment period, the subject must meet the required criteria at screening and at baseline. Eligible subjects will be randomized, and study drug administration will begin on Day 1 (Visit 2) after confirmation of all baseline criteria.

Study visits will occur at the study site per the Schedule of Activities (Table 1).

10.1.3.1 Dose Reduction Visit

If a subject experience any intolerable AEs, the dose can be reduced as described below in Section 10.1.3.2. Subjects with intolerable AEs, will have to come back to the clinical site for an unscheduled visit where the following procedures will be performed:

- Physical examination including vital signs.
- Adverse events and concomitant medications, if any, will be assessed since from the previous visit.
- Local urine pregnancy test (if applicable).
- Safety blood and urine samples will be collected and submitted to the central laboratory for analysis.

- Study drug will be collected, IWRS will allocate new study drug, and treatment compliance will be reviewed.

If a dose reduction is deemed necessary by the Principal Investigator, the IWRS will be used for assignment of the new blister packs to be provided to the subject for dose reduction and study drug dispensation. The date of dose reduction visit and the reason will be recorded in the eCRF.

10.1.3.2 Dose Reduction Criteria

Subjects will be informed regarding potential side effects. If the side effects experienced by subjects are not manageable through nonpharmacologic and pharmacologic treatment (using standard of care), dose reduction (from 300 mg QD to 200 mg QD, or from 200 mg QD to 100 mg QD) should be considered to manage the incidence and/or intensity of the subject-reported AEs (including but not limited to vomiting, diarrhea, headache, hyperpigmentation).

For safety reasons, the Investigator may also decide to implement a dose reduction for a subject. The following are criteria for Investigator initiated dose reduction:

- AEs which are classified as serious and/or moderate/severe (in severity), which did not improve with clinical management according to standard of care per Investigator's judgement, AND
- AEs assessed as having reasonable possibility of relationship to MT-7117 per Investigator's judgement (Section 14.5).

Examples of severe AEs include AE which limit self-care activities of daily living (independently eat, dress, walk/transfer from 1 position to another, bathe, toilet, maintaining bowel/bladder continence).

Note: Dose up-titration after dose reduction is not allowed.

10.1.3.3 Dose Interruption

Dose interruption can be considered after the discussion with the Sponsor Medical Monitor in the case, such as

1) in subjects with suspicious lesions or change in nevi (Melanocytic Lesions) that had their dose temporarily interrupted can resume study treatment at the same dose they were interrupted at after the evaluations are complete and nevi (Melanocytic Lesions) and/or other lesions are determined to be benign; or

2) in a subject with an initial positive urine pregnancy test, awaiting a confirmatory test. If the confirmatory test is definitively negative, dosing may resume at the same dose they were interrupted; or

3) in a subject with any laboratory or clinical abnormality such as meeting the criteria of AESI (see Section 14.3 and 14.3.1), awaiting a confirmatory test and/or a judgement whether it is clinically significant. Resumption of dosing at the same dose they were interrupted will be considered based on the discussion with the Sponsor Medical Monitor and Investigator and should be closely followed up.

At any time during the study, subjects may be withdrawn from study treatment if continuing study treatment would be detrimental to the subject's safety in the opinion of the Investigator.

10.1.4 End of Treatment/Early Termination

The EOT/ET visit will occur at Week 52.

If a subject is permanently discontinued from the study, every attempt should be made to have the subject complete the ET assessments as described in Table 1. In the event a subject does not return to the clinical site for the ET visit, the Investigator must make every effort to contact the subject by telephone to discuss AEs, dosing compliance, and review concomitant medications, and the date of the last dose of study drug. In these cases, the collected information (AEs, concomitant medications, date of last dose of medication, etc.) via telephone will be documented in the site source documents and eCRF. Return of unused study drug and any other materials will be performed by courier where allowed.

10.1.5 Safety Follow-up Period/End of Study

For all subjects who complete the double-blind treatment period, a safety follow-up visit will occur at Week 56 (Visit 9), 4 Weeks (±7 days) after the last dose of study drug.

Any unresolved AE or SAE will be followed according to Section 14.9.

10.1.6 Unscheduled Visits

An unscheduled visit is defined as any visit to the clinical site outside of the protocol specified time visits due to safety reasons or when a repeated measurement is required (e.g., obvious measurement errors, measuring device failure, confirmation of out-of-range results), where the subject is seen by study personnel.

At the discretion of the Investigator, if deemed necessary, additional unscheduled safety assessments such as routine blood sampling, dose reductions may be performed. All unscheduled visits and assessments performed during the unscheduled visits will be recorded in the source documents and eCRF.

11 STUDY PROCEDURES

All subjects must sign and date the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved ICF before any study-specific procedures are performed. Refer to Section 17.2.1 for further details.

All study procedures will be performed per the Schedule of Activities in Table 1.

11.1 Demographics and Other Baseline Characteristics

Demographic data will include year of birth, age, sex, body weight, body mass index, height, ethnicity*, and race*.

*where local law permits

11.2 Medical and Surgical History

Medical/surgical history before the screening period will include but not limited to medication, smoking, alcohol, psychiatric disease, and surgical history. In addition, history of hepatic injury (e.g., viral hepatitis, autoimmune hepatitis, nonalcoholic steatohepatitis, hypoxic/ischemic hepatopathy, biliary tract disease) will be recorded.

11.3 Prior and Concomitant Medication

Any prior medication, including prescription and over-the-counter medications, taken within 30 days before screening and all SSc-related medications used since diagnosis will be recorded on the eCRF and source documents. The following information will be collected: name of medication, dose, duration, and reason for use.

Concomitant medication(s) is defined as any medication, other than study drug, which is taken during the study, including prescription, over-the-counter medications, herbals, dietary supplements, and recreational drugs. All concomitant medication(s) taken while the subject is participating in the study will be recorded.

Concomitant medication(s) will be provided only if deemed necessary by the Investigator or the subject's personal physician.

Follow restrictions regarding concomitant medications are described in Appendix 2.

11.3.1 Treatments for Systemic Sclerosis

Apart from nintedanib that was recently approved for the treatment of SSc-ILD, no other drugs are approved for the treatment of SSc, and no adequate and well-controlled studies have demonstrated substantial evidence of a treatment effect in this disease. In the absence of approved drugs, evidence-based, consensus-derived recommendations to help guide treatment for subjects with SSc have been developed by the EULAR and European League Scleroderma Trials and Research (EUSTAR) group, a group of experts from the US and the European Union.[25] The EUSTAR consensus statement includes 16 recommendations for the treatment of organ-specific complications. The actual recommendations are aimed to guide pharmacological treatment of SSc-specific organ involvement. These recommendations are not meant to replace the physician's clinical judgement or the patient-physician shared decision. With respect to skin involvement, EUSTAR recommends that methotrexate may be considered for treatment of skin manifestations of early dcSSc but notes that no positive effects on other organ manifestations have been established for methotrexate. Despite its known toxicity, EULAR recommends

treatment of SSc-ILD using cyclophosphamide. Other recommended treatments include autologous stem cell transplant.[25]

Treatment with investigational agents, cell-depleting therapy or bone marrow transplantation, ultraviolet (UV) phototherapy, cyclophosphamide, rituximab, or cyclosporine, Small molecules such as JAK inhibitors (e.g., tofacitinib), pirfenidone, tocilizumab, TNF Inhibitors (etanercept, infliximab, certolizumab, golimumab, adalimumab) and abatacept are prohibited during the study (Section 9.4).

Patients will be allowed to receive rescue therapy for worsening of skin thickening and/or deterioration of FVC and/or other scenarios, as described below (Section 11.3.1.2).

Concomitant therapies for treatment of other SSc complications and disease manifestations are permitted as described in Sections 11.3.1.1and 11.3.1.3. It is important that dose regimens of medications taken by patients during the double-blind treatment period (through Week 52) remain stable if intended for chronic use. However, dose adjustments for such medications will be allowed as required for patient safety, after discussion with the Medical Monitor.

Concomitant treatments other than those described below (Sections 11.3.1.1 and 11.3.1.3) may be initiated for management of SSc complications after discussion with the Medical Monitor.

11.3.1.1 Medications Commonly Used in Systemic Sclerosis

NSAIDs and Analgesics

Patients may be treated with NSAIDs, including cyclooxygenase-2 (COX-2) inhibitors during the study. The dose of NSAIDs should remain stable through Week 52, unless dose reduction is required for patient safety. The choice and doses of NSAIDs are at the discretion of the Investigator. For patients who receive corticosteroids and/or NSAIDs, prophylactic treatment with proton-pump inhibitors or H2-receptor blockers may be added at the Investigator's discretion, according to local standard of care. Analgesics up to the maximum recommended dose may be used as required to treat pain. However, patients should be discouraged from using analgesics, including NSAIDs, within 12 hours prior to performance of efficacy assessments at every clinic visit.

Oral, Intravenous, or Intramuscular Corticosteroids

Subjects may receive corticosteroids at a stable dose of $\leq$ 10 mg/day of prednisone or equivalent during the study. Increases in corticosteroid doses for chronic treatment of SSc are not allowed during the study. To treat non-SSc-related conditions, doses of oral corticosteroids up to $\leq$ 40 mg/day of prednisone (or equivalent) are permitted for 2 weeks. The dose of the corticosteroid should be tapered down to the previous level as rapidly as medically possible. Decreases in corticosteroid doses for safety reasons are permitted.

DMARDs/Immunosuppressive Agents

All conventional Disease-modifying anti-rheumatic drugs (DMARDs)/Immunosuppressive agents, except for the permitted Immunosuppressant Therapy listed below, must be discontinued with appropriate washout prior to the initiation of study drug as described in the Exclusion criteria (Section 9.4) and are prohibited during the study, except when given as rescue therapy as described in Section 11.3.1.2 or for other significant systemic sclerosis complications as described in Section 11.3.1.3.

Permitted Immunosuppressant Therapy

Only one of the following immunosuppressant therapy is allowed during the study. Switching and addition of an immunosuppressant therapy is not allowed during study treatment (see Section 9.4) except when given as rescue therapy as described in Section 11.3.1.2.

- Mycophenolate (up to 3 g/day)
- Mycophenolic acid (up to 2.14 g/day)
- Methotrexate (up to 25 mg/Week)
- Leflunomide (up to 20 mg/day)
- Azathioprine (up to 3 mg/kg/day)

Vaccine

During study treatment, subject is allowed to receive non-live (inactivated) vaccines, such as some of the seasonal flu vaccines (Influenza) and Pneumovax vaccines. Subjects on any immunosuppressant therapy will need to hold their therapy per local guidelines, if they plan to receive any live or live-attenuated vaccines such as Covid-19 vaccine once it becomes available.

11.3.1.2 Rescue Therapy

Subjects with worsening scleroderma such as skin thickening with worsening in mRSS of a minimum of 5 points and at least 25% increase relative to baseline will be allowed to use rescue therapy starting at or after Week 26.

At or after Week 16, rescue therapy will also be allowed with a decrease of > 10 relative percentage points in %pFVC compared with baseline, such a decline from baseline confirmed on two separate occasions within a 4-week period (after 2 separate confirmations within 4 weeks via an unscheduled visit).

Initiation of rescue therapy will be based on Investigator's clinical judgment and should be discussed with the Medical Monitor(s).

For worsening of skin thickening at or after Week 26, immunosuppressive therapies (methotrexate, mycophenolate mofetil and others) may be used as rescue therapy after discussion with the Medical Monitor.

For worsening FVC at or after Week 16, treatment of SSc-related ILD should be initiated as indicated by local treatment guidelines. The choice of rescue therapy for worsening FVC should be discussed with the Medical Monitor prior to initiation of treatment.

For other scenarios related to worsening scleroderma such as involving organ impairment or life-threatening or debilitating disease manifestations, the Investigator should contact the Medical Monitor(s).

Start date, reason and use of rescue therapy during the double-bind treatment period will be documented in the eCRF.

The subjects who initiate rescue therapy will be allowed to continue taking study drug in order to complete study treatment to Week 52. Only one rescue therapy can be added during the study treatment. A change in rescue therapy is permitted after discussion with the Medical Monitor

and Sponsor. The analysis using the subject's data after taking rescue therapy is described in the Section 16.3.4.1.

11.3.1.3 Treatments for Other Systemic Sclerosis Complications

Initiation of treatments for SSc complications (except prohibited therapies, per Section 11.3.1) should be discussed with the Medical Monitor unless an urgent intervention is necessary as a result of the patient's medical condition.

11.3.2 Drug-Drug Interaction

In vitro studies of CYP and UGT inhibitions by MT-7117 were conducted in human liver microsomes, and the results are described in the IB. MT-7117 showed a direct inhibition of CYP2C9, with lower inhibition seen for CYP2C19 and CYP2C8 and exhibited a potential for a time-dependent inhibition of CYP3A. MT-7117 showed no notable inhibitory effect on the other CYPs. MT-7117 showed a potent inhibition of UGT1A1, with lower inhibition seen for UGT1A3.

An in vitro study of P-gp and BCRP inhibition by MT-7117 was conducted in Caco-2 cell monolayers, and an *in vitro* study of OATP1B1, OATP1B3, OAT1, OAT3, organic cation transporter (OCT) 2, multidrug and toxin extrusion (MATE) 1, and MATE2-K inhibitions by MT-7117 was conducted in HEK293 cells, expressed with human OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, and MATE2-K, respectively. The results are summarized in the IB. MT-7117 has the potential to inhibit P-gp, BCRP, OATP1B1, OATP1B3, and OAT3.

In vitro experiments have revealed that MT-7117 has inhibitory potential to several CYP enzymes and transporters with the IC50 values less than 50 μmol/L. Among the CYP enzymes and transporters, risk of in vivo DDI cannot be excluded for CYP3A, P-gp, OATP1B1/1B3, BCRP and OAT3 inhibition based on the PK profile of MT-7117 at the intended clinical dose range (100 mg QD to 300 mg QD) and the inhibition parameters, IC50 or Ki values, with reference to the FDA's guidance for industry entitled "In Vitro Drug Interaction Studies - Enzyme- and Transporter-Mediated Drug Interactions (2020, January)." [39]

The risk of in vivo inhibition can be excluded for CYP2C isoforms and UGT1A3 because the ratio of expected maximum exposure at steady state after MT-7117 dosing (300 mg) compared to in vitro inhibition potential were less than cut-off value having no effect on the level of CYP2Cs and UGT1A3 enzymes with the basic model. In terms of UGT1A1 inhibition, the risk of in vivo inhibition by MT-7117 was less likely to occur on the assessment using mechanistic static model (AUCR at MT-7117 300 mg: less than 1.25).

Based on the above results, the following drugs (including but not limited to) within 1 week of screening (Visit 1) is prohibited:

a. Drugs known to be predominantly metabolized by cytochrome P450 (CYP) 3A4 with a narrow therapeutic index for which elevated plasma concentrations are associated with clinical safety concern or significant medical events.
b. Drugs that are known substrates of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP)1B1 or OATP1B3 for which elevated plasma concentrations are associated with significant medical events.

The list of Prohibited or Precautionary Concomitant Medications due to drug-drug interactions is described in Appendix 2.

11.4 Composite Response Index for Diffuse Cutaneous Systemic Sclerosis

The ACR CRISS score[12] is a composite endpoint that calculates the probability of improvement for each subject ranging from 0.0 (no improvement) to 1.0 (marked improvement). Its use involves a 2-step process of identifying any significant disease worsening or new end-organ damage of renal or cardiopulmonary involvement, and then calculating the probability of subject improvement after 1 year of treatment on a 0- to 1-point scale based on changes from baseline in 5 variables: the mRSS, %pFVC, Patient Global Assessment and Physician Global Assessments, and HAQ-DI. Refer to Appendix 4 for further details.

An ACR CRISS score of 0.60 or greater indicates that a subject improved on treatment and a score of less than 0.6 suggests that a subject has not improved.

At the Investigator's discretion, if a subject's medical conditions are worsening such as %pFVC decline, an HRCT scan may be performed as a part of standard of care based on a local guidance to confirm worsening.

11.5 Pulmonary Function Test

Pulmonary function tests (PFTs) are a group of tests that measure how well the lungs are performing. The test includes how well the subject is able to breathe and how effective the lungs are able to bring oxygen to the rest of the body. PFTs will include [redacted] and FVC.

Details of PFTs are described in full in a separate document (provided by the central PFT vendor) and will be in accordance with the American Thoracic Society/European Respiratory Society (ATS/ERS) Consensus Statement. Sites will receive centralized systems to perform spirometry tests (provided by a central PFT vendor) that will be in accordance with the study requirements and with ATS/ERS guidelines. Sites will perform [redacted] using their own equipment but will be required to enter the data into the system provided by the central PFT vendor.

PFT evaluators need to be trained and appropriately qualified to perform both Spirometry and [redacted] FVC measurements will be conducted in the clinical site at around the same time of day where possible with the subject in a sitting upright position. Subjects should undertake at least 3 attempts to generate acceptable and reproducible FVC data per ATS/ERS guidelines. The highest acceptable value will be selected following quality review by a centralized over read specialist in agreement with the site Investigator.

[redacted]. At least 2 acceptable tests that meet repeatability criteria will be performed. The best value (mean from acceptable values) will be selected following quality review by a centralized over read specialist in agreement with the site Investigator.

The acceptability of the FVC and [redacted] data will be determined by a centralized over read specialist. The centralized over read specialist will state whether a session has been accepted (passed QA) or rejected (failed QA). If rejected, the FVC measurements at screening and from Week 16 onwards should be repeated within 2 weeks. Only one repeat visit is required. The

clinical site should confirm that FVC is acceptable at screening visit before subjects are randomized.

Abnormalities of clinical significance will be reported as AEs.

[redacted]

If a subject's medical condition is worsening such as %pFVC decline, and at the Investigator's discretion, an HRCT scan may be performed as a part of standard of care based on local guidance to confirm worsening.

11.6 Dual (Safety/Efficacy) Assessor Approach

The Dual (Safety/Efficacy) Assessor Approach is described as having at least two assessors;

" Safety Assessor " and " Efficacy Assessor " at the clinical sites that will perform various clinical assessments in order to prevent potential unblinding due of observable efficacy changes.

1. **Safety Assessor**
   - Safety Assessor should be Principal Investigator, treating physician or delegate physician. Delegate physician is anyone qualified that is not the Efficacy Assessor.
   - Safety Assessor will see the patient and perform medical history, physical examination, and the remaining efficacy assessments and will have access to the efficacy assessment performed by the Efficacy Assessor in order to complete physician global assessment (PhGA). The Safety Assessor should carefully monitor the subject's safety and well-being.
2. **Efficacy Assessor**
   - Efficacy Assessor can be any physician or any trained health care professional.
   - Efficacy Assessor will only perform the following efficacy assessments: Skin thickening using mRSS (modified Rodnan Skin Score), Tendon Friction Rubs (TFRs), and tender and swollen joint counts, and will NOT perform any safety or other efficacy assessments.

To ensure consistency of assessments and limit inter-observer variability, it is essential that the same Efficacy Assessor conduct the mRSS, TFRs and Tender and Swollen joint counts evaluations for a given subject at all study visits whenever possible. Details regarding the Dual (Safety/Efficacy) Assessor Approach, the criteria of Efficacy Assessor, and the training methods to be qualified as Efficacy Assessor are provided in a separate document.

11.6.1 Modified Rodnan Skin Score

The mRSS will be assessed by a qualified and trained Efficacy Assessor to limit the variability. The Efficacy Assessor will measure skin thickness on 17 different body areas on a scale from 0 (normal) to 3 (severe). Global average scoring method (The assessor scores individual sub-areas, as needed for differences within large areas and takes average of sub-areas to attain the score for that overall area) will be used as a scoring technique in this study.[43] Worsening of skin fibrosis as measured by the mRSS score was associated with a disease progression and overall mortality in subjects with dcSSc, indicating that the mRSS is a good surrogate marker for disease progression.[13]

The same Efficacy Assessor should conduct the mRSS evaluations for a given subject at the times described in Table 1. An example of the mRSS is presented in Appendix 5.

11.6.2 [redacted]

[redacted]

A sample form is shown in Appendix 15.

11.7 [redacted]

[redacted]

11.8 [redacted]

[redacted]

11.9 Physician Global Assessment

The Physician Global Assessment is used to assess the physician's rating of overall health of the subject. Physicians rate the perceived health of the subject on an 11-point scale from 0 (excellent) to 10 (extremely poor).

An example of the Physician Global Assessment is presented in Appendix 8.

11.10 Patient Reported Outcomes

To minimize bias, subjects will be assured that all data will be treated confidentially, and the answers will not have any influence on study drug treatment. Unless otherwise noted (e.g., Investigator or designee to complete questionnaire), subjects will complete the questionnaires on their own, or with the help of relatives, friends or study staff if restricted by digital lesions, and it is also desirable that subjects complete those before being seen by the clinician at the respective visit. Subsequently, a member of the site Investigator's team will enter the responses into the eCRF.

All PROs will be completed at the times described in Table 1.

11.10.1 Scleroderma Health Assessment Questionnaire

The SHAQ is composed of the HAQ-DI scale (Section 11.10.2) and the VAS (Section 11.10.3). HAQ-DI[2628] was developed and has been used extensively in SSc. The VAS was added to the HAQ-DI to create the SHAQ.[34] The SHAQ consists not only the 8 domains of the HAQ-DI but also includes the VAS scales: Each VAS item is rated separately, with higher scores indicating more severe disease. The 5 VAS scales are: 1) intestinal disease, 2) breathing problems, 3) Raynaud syndrome, 4) digital ulcers, and 5) overall disease.

Subject will complete the SHAQ at the times described in Table 1.

An example of the SHAQ is presented in Appendix 6.

11.10.2 Health Assessment Questionnaire - Disability Index

The HAQ-DI[26,27] has been used extensively in studies of rheumatoid arthritis and has been validated in patients with scleroderma.[35,36] The HAQ-DI is a self-administered instrument that measures physical disability in 8 different domains of function: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and common activities. Subjects are asked about 2 or 3 activities associated with each category and choose whether they are able to perform the activity 'without any difficulty', 'with some difficulty', 'with much difficulty', or 'unable to do'. An additional section asks subjects to indicate if they used any aids or devices or needed assistance to perform daily activities.

11.10.3 Visual Analog Scales

The VAS is also part of the SHAQ. Subjects will complete, as part of the SHAQ, 5 VAS scales that were originally developed by Steen and Medsger 1997[34] to measure the impact of SSc on the daily activity of intestinal disease, breathing problems, Raynaud's syndrome, digital ulcers, and overall disease during the previous week.

11.10.4 Patient Global Assessment

The Patient Global Assessment is used to assess the subject's rating of their overall disease activity. Subjects rate their perceived health on an 11-point scale from 0 (excellent) to 10 (extremely poor).

An example of the Patient Global Assessment is presented in Appendix 7.

11.10.5 [redacted]

11.11 Subject Question for Study Drug

At Week 52 or early termination (Visit 8), subjects will be asked whether they believe they received active or placebo treatment. The results will be recorded in the source documents and the eCRF.

11.12 [redacted]

[redacted]

12 SAFETY ASSESSMENTS

The following safety assessments will be assessed at the times described in Table 1.

12.1 Physical Examination

A full complete physical examination will consist of major body systems: abdominal, respiratory, cardiovascular, general appearance, head, eyes, ears/nose/throat, lymph nodes, musculoskeletal, neck, neurological, dermatological, and 'other'.

An abbreviated physical examination will consist of an assessment of the following body systems: abdominal, respiratory, cardiovascular, general appearance, and 'other'.

12.2 Vital Signs

The following vital sign measurements will include systolic and diastolic blood pressure, heart rate (e.g., beats per minute), respiratory rate, and body temperature (e.g., oral, axillary or tympanic body temperature) and the same method is to be used throughout the study. The position and arm selected for a subject to assess blood pressure should be the same that is used throughout the study and documented on the eCRF.

The Investigator will perform an overall evaluation for safety purposes and the recording will be reported as 'normal', 'abnormal clinically significant', or 'abnormal not clinically significant'.

Abnormalities of clinical significance will be reported as AEs. Repeat measurements will be performed if needed.

12.3 Electrocardiogram

A 12-lead ECG will be performed after the subject has rested for at least 5 minutes. in the supine position. The Investigator will perform an overall evaluation of the ECG for safety purposes and the recording will be reported as 'normal', 'abnormal clinically significant', or 'abnormal not clinically significant'. Abnormalities of clinical significance will be reported as AEs. Repeat measurements will be performed if needed. Any ECG, which demonstrates a clinically significant abnormality at the screening Visit, is exclusionary and the subject should not be enrolled in the study.

12.4 Nevi (Melanocytic Lesions) Evaluation

Nevi (Melanocytic lesions) will be assessed at the specified timepoints listed in the Schedule of Activities (Table 1). Baseline nevi (Melanocytic Lesions) evaluation will be conducted at any time (Visits 1 or 2) before randomization.

Nevi (Melanocytic Lesions) will be assessed locally by a visual full body examination performed by a local dermatologist or the qualified site staff. Any subject with suspicious nevi (Melanocytic Lesions) of clinical concern will have treatment temporarily discontinued and be referred for further nevi (Melanocytic Lesions) evaluation (e.g., biopsy), as deemed necessary by the dermatologist or the qualified site staff.

Any biopsy samples collected during the study will be sent for evaluation to the central pathology laboratory and also to the local pathologist if needed by local standard of care. If there are any clinically significant adverse findings from the biopsy, subjects will not be

allowed to resume study drug and will be discontinued from study treatment Adverse change must be demonstrated histologically and confirmed by central pathologist. Visual evaluation of change will not be acceptable criteria for complete discharge from treatment. If central assessment determines that lesion or nevi (Melanocytic Lesions) is benign, and the findings are not clinically significant, subject will be allowed to resume study treatment at the same dose when study drug was interrupted. Clinical sites will have access to a centralized dermatology/dermatopathology specialist with experience on nevi (Melanocytic Lesions). The centralized dermatology/dermatopathology specialist will be available to communicate with the Investigator, dermatologist and/or qualified staff on the changes of any expected potential changes in nevi (Melanocytic Lesions) and advice on the process management prior and after biopsy.

The results will be recorded in the source documents and the eCRF. Nevi (Melanocytic Lesions) of clinical concern must be recorded as AE.

Nevi (Melanocytic Lesions) assessment details will be fully described in a separate document.

12.5 Clinical Laboratory Tests

Blood and urine samples will be collected for routine clinical laboratory safety evaluations.

The laboratory parameters that will be evaluated during the study are presented in Table 3.

12.5.1 Additional Laboratory Assessments

Additional laboratory safety evaluations will be performed at other times, if judged to be clinically appropriate, or if the ongoing review of the data suggests a more detailed assessment of laboratory safety evaluations is required. Any changes to the scheduled times of laboratory safety tests will be agreed with the Sponsor and documented in the Trial Master File.

The Investigator will perform a clinical assessment of all laboratory safety data. The Investigator will record the assessment as 'normal', 'abnormal clinically significant', or 'abnormal not clinically significant'. Laboratory test abnormalities of clinical significance will be reported as AEs. Repeat laboratory tests or measurements will be performed if needed.

Subjects who meet treatment withdrawal criteria for elevated liver function tests, the subjects should be treated using standard of care as directed by the Investigator and followed until resolution (Section 9.5).

Table 3: Laboratory Evaluations

Hematology:	
Hemoglobin	Mean corpuscular hemoglobin
Hematocrit	Mean corpuscular hemoglobin concentration
Platelet count	Mean corpuscular volume
Red blood cell (RBC) count	White blood cell count and differential
	Erythrocyte sedimentation rate (ESR)[c]
Biochemistry:	
Alkaline phosphatase (ALP)	Cholesterol
Aspartate aminotransferase (AST)	Triglycerides
Alanine aminotransferase (ALT)	High density lipoprotein-cholesterol (HDL)
γ-glutamyl transpeptidase (GGT)	Low density lipoprotein-cholesterol (LDL)

Potassium Sodium Chloride Inorganic phosphate Glucose Bilirubin (direct and total) C-reactive protein (CRP)	Protein (total) Albumin Creatine phosphokinase (CPK) Creatinine Ferritin Calcium Blood urea nitrogen (BUN) hCG[b]
Coagulation: Prothrombin time International normalized ratio	Activated partial thromboplastin time
Urinalysis: Specific gravity, pH, protein, glucose, ketones, urobilinogen, blood Microscopic examination[a]	
Serology: Screening only: Anti-nuclear antibodies, SSc-specific [redacted] Baseline (day 1 of Week 1 prior to randomization) and Weeks 16, 26, and 52: Surfactant protein-D (SP-D), and Krebs von den Lungen-6 (KL-6)	

[a] Performed only if required, based on urinalysis results
[b] Female subjects of child-bearing potential only; serum pregnancy test will be performed at Visit 1 and a urine pregnancy test at all other site visits and a urine dipstick pregnancy test at home or other home testing arrangements will be performed at Telephone Visits (Visit 6A and 7A).
[c] ESR will be analyzed locally at the site level and at Screening only.

Blood and urine samples will be analyzed by the Central Laboratory and/or specialized laboratory where applicable using standard methods. Procedures for the handling of samples will be described in full in a separate document.

12.5.2 [redacted]

12.5.3 [redacted]

12.5.4 [redacted]

[redacted]

12.5.5 Pharmacokinetic Assessments

Blood samples will be collected by direct venipuncture in a suitable vein. The date and time of each blood sample and the most recent dose date and time will be recorded in the source document and eCRF.

For each PK assessment, 1 blood sample of approximately 4 mL will be collected to ensure there is sufficient plasma for primary and backup samples.

Sample handling details will be described fully in a separate document.

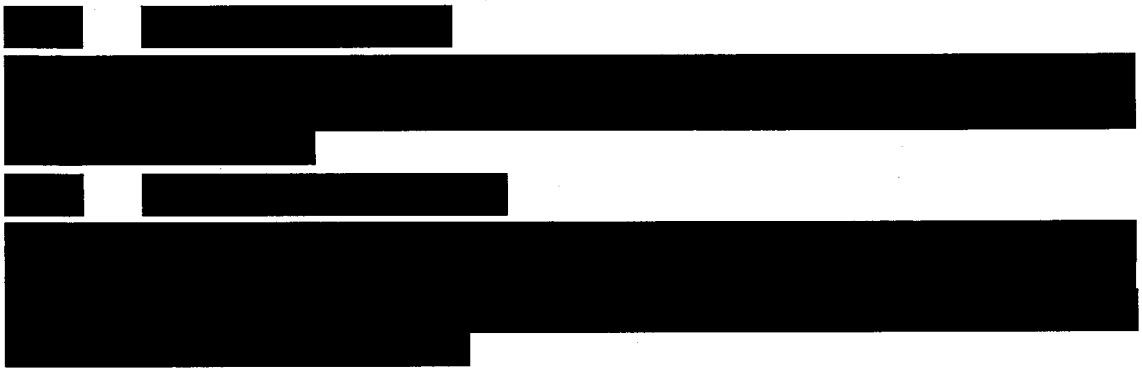
12.5.6 Pharmacogenomics Sampling

Blood samples will be collected for pharmacogenomic analysis for those subjects who provided informed consent for optional PGx analysis at Visit 2.

[redacted] Samples may be retained for future research genetic analysis for SSc and/or any efficacy/safety concern occur.

Sample handling details of pharmacogenomic samples will be described fully in a separate laboratory manual.

12.6 [redacted]



12.7 Pregnancy Test

Pregnancy test is to be performed at all visits for female subjects of child-bearing potential. A serum pregnancy test will be performed at Visit 1, a urine pregnancy test (on-site) will be performed at all other site visits, and a urine dipstick pregnancy test will be performed at Telephone Visit 6A and 7A (Table 1).

- A serum pregnancy test on site: Visit 1 (Screening visit)
- A urine pregnancy test on site: Visit 2, 3, 4, 5, 6, 7 and 8 (Day 1, Week 2, 6, 16, 26, 39, and 52) and follow-up visit (Week 56)
- A urine dipstick pregnancy test: Telephone Visit 6A and 7A (Week 32 and 45)

Subject will have Telephone Visits (Visits 6A and 7A, Week 32 and 45, respectively), and a urine dipstick pregnancy test at home or other home testing arrangements will be performed.

The result of every urine dipstick pregnancy test should be actively requested by the site at Telephone Visits as soon as the test is due. The subject must report the result to the site without delay.

A urine dipstick pregnancy test may also be performed using alternatives such as that the subject may come to the clinic or go to a local laboratory for administration of the test. Such arrangements must be approved by the Sponsor.

If the result of the pregnancy test is positive via urine test, it must be confirmed with a serum pregnancy test, and the dose should be temporarily interrupted until it confirmed that subject is not pregnant. In the event of a pregnancy, a referral to an obstetrician/gynecologist for confirmation of pregnancy must be organized as soon as possible. In addition, the pregnancy must be reported to the Sponsor as described in Section 14.10. In the event that a pregnancy test result is uncertain, the patient should contact the site immediately to discuss further steps (e.g., exclusion of pregnancy by serum pregnancy test).

The study treatment can be resumed at the same dose prior to the interruption if confirmatory test is definitely negative.
Importantly, any subject who becomes pregnant while on the study treatment must be withdrawn from the treatment.

13 STUDY DRUG TREATMENT

13.1 Investigational Medicinal Product

13.1.1 Drug Product

MT-7117 and matching placebo tablets are dark-orange, film-coated tablets with no identifying marks. MT-7117 100 mg tablets contain 100 mg of active drug product (its free-base form). TT). The matching placebo tablets will be manufactured to be physically identical to the MT-7117 100 mg tablets. All MT-7117 100 mg tablets and the matching placebo tablets will be manufactured, tested, and released according to Good Manufacturing Practice (GMP).

A bulk supply of MT-7117 100 mg and matching placebo tablets will be packed into double-polyethylene bags with a desiccant and placed into stainless steel drums with desiccant (silica gel) and shipped to PCI USA, Rockford, IL for packaging into finished study drug.

Individual subject doses will be packed in blister wallets using cold form aluminum/aluminum, then labeled and released from PCI USA according to GMP. PCI USA will provide the finished study drug for use in USA and Canada. Finished study drug will be shipped from PCI USA to PCI Bridgend (UK) /PCI Millmount (Ireland) for qualified person certification and for distribution to the sites in Europe. All labeling will comply with applicable regulatory requirements.

13.1.2 Study Drug Supply

The Sponsor will provide MT-7117 and placebo tablets in aluminum/aluminum blister wallets to each site, for each subject, for the duration of their participation in the study. The IWRS will allocate sufficient uniquely numbered, blinded blister wallets, to be dispensed by the Investigator, study nurse or hospital pharmacist, according to the subject's randomized treatment group (MT-7117 300 mg or placebo) and study visits. Where down titration is required the IWRS will allocate the dose accordingly.

Subjects will be instructed to bring their study drug with them to each visit. Subjects will return all study drug that may remain in their possession to the study staff at the EOT visit. In cases where subjects forget to return to the clinical site with their blister wallets suitable for all treatment groups (placebo, 300 mg, 200 mg, and 100 mg), sites will be instructed to inquire as to the subjects daily dosing compliance, capturing total number of days missed. Subjects will be instructed to return study drug packaging at the follow up visit.

13.1.3 Formulation, Packaging, Site Storage, and Labeling (MT-7117)

Study drug tablets will be provided in 2 strengths: 0 mg (placebo) and 100 mg (MT-7117) tablets. Study drug will be provided to the study sites in labeled blister wallets. All study drug should be stored according to the study drug clinical label.

Required study site documentation for MT-7117 tablets will include, but may not be limited to, the following information:

- Receipt date
- Description of study drug package, and study drug product
- Lot number or code/Batch number or code
- Expiration and manufacturing dates

- Dispensing information
- IND number
- Certificate of Compliance

13.1.4 Certificate of Compliance Shipping, Receipt, Handling and Storage

On receiving a shipment of finished study drug at the Investigator site, the Investigator or designee will conduct an inventory check and complete a supplies-receipt document, the original of which will be retained at the Investigator site. In addition, a copy must be returned to the Sponsor or designee. The Investigator or designee will maintain a record of all study drug received and returned.

Study drug at the Investigator site will be stored according to the conditions stated on the study drug clinical label in a locked, restricted-access area. A temperature log recording the daily continuous temperature of the storage area will be maintained (including weekends). Any study drug storage temperature deviations will be reported to the Sponsor as soon as possible.

13.1.5 Dispensing

At each visit, the Investigator or designee will provide the subject with the allocated dose. A record of the study drug dispensed to each subject will be maintained by the Investigator or designee in an Investigational Product Accountability Log. Dispensed study drug will not be re-allocated to a subject.

In the cases where a subject encounters a missed visit that renders a subject without sufficient study drug to maintain daily dosing (e.g., a subject resides out of state relative to the Investigator's location and experiences a travel conflict), the site may ship additional wallet to the subject upon written Sponsor approval, the site may ship additional study drug until the subject can make the next scheduled visit to the clinical site to the subject. In these instances, the Sponsor (and/or the Clinical Research Organization designee) will assist the site to ensure the process is documented appropriately. Shipments made in these rare instances will require that study drug be maintained within the required temperature range along with confirmation of receipt by the study subject. This process will not be allowed where site policies prohibit it. Subjects should return to the clinical site to complete the scheduled visit and carry out the required assessment and dispensation of study drug.

13.1.6 Study Drug Accountability

The Investigator or designee must maintain an accurate record of the shipment and dispensing of study drug in an Investigational Product Accountability Log. Study drug accountability will be noted by the field monitor during site visits and at the completion of the study. Subjects will be asked to return all unused study drug and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

13.1.7 Disposal and Destruction

At study close-out, and as appropriate during the course of the study and only once full accountability has taken place, the Investigator will return all used and unused study drug, packaging, study drug labels, and a copy of the completed Investigational Product Accountability Log to the Sponsor's designated monitor or to the address provided in the Investigator Binder at each site.

The study drug supply may be destroyed at the designated Sponsor facility or third party, only once authorization to destroy has been provided by the Sponsor. Site with documented drug destruction procedures and facilities may destroy drug on site only once authorization to destroy has been given by the Sponsor.

13.2 Dosing of MT-7117 or Placebo

Subjects are to self-administer the study drug 3 tablets once daily in the morning with or without food.

MT-7117 and/or placebo tablets should be swallowed whole with approximately 240 mL of water (subjects may drink an additional 240 mL of water if they have difficulty swallowing the tablets). The tablets are not to be chewed, crushed, or divided.

13.3 Treatment Compliance

The prescribed dosage, timing, and mode of administration of study drug will not be changed. Subjects will be asked questions regarding the compliance, any departures from the intended regimen will be recorded in the eCRF.

Study drug accountability and subject compliance will be documented throughout the double-blind treatment period using study-specific study drug dispensing and return record forms. For subjects who do not return their blister wallets, the site will question each to determine compliance (e.g. number of doses missed since the last visit).

Subjects will be asked to return all unused medication including empty and partially used wallets. Study drug dispensed at the previous visit will be retrieved by the Investigator or designee and compliance assessed by returned medication count.

Non-compliance will be defined as taking $\leq$ 80% or $\geq$ 120% of study drug during any evaluation period (from any visit to the following visit).

13.4 Subject Identification

Each subject will be assigned a unique subject number at the screening visit. At randomization, each subject will receive a unique randomization number. Both the subject number and the randomization number will be documented in the subject's source documents. The subject number will be used to identify subjects in the study.

A list identifying the subjects by their subject number will be kept at the Investigator site. The randomization numbers will be stored in the IWRS database until the database lock.

13.5 Procedures for Assigning Subjects to Treatment Groups

Randomization will take place after reconfirmation of inclusion/exclusion criteria before the first administration of study drug on Day 1 of the double-blind treatment period. Subjects will be randomly allocated on a 1:1 basis to 1 of 2 treatments (active or placebo) (Section 8.1). Subjects will be randomized via IWRS. [redacted]

13.6 Maintenance of the Study Blind and Unblinding

All study treatments will be double-blinded during the 52 weeks study; neither the subject nor the study site personnel will know which treatment is being taken. Each subject's treatment will

be provided a unique code number, traceable to the identity, dose, and batch number of the study drug. The IWRS will be used to hold treatment codes for each subject. The codes will only be accessible to authorized IWRS users.

Subjects down-titration will be processed via IWRS. Subjects in the MT-7117 300 mg treatment group will be assigned to the MT-7117 200 mg treatment by IWRS. Subjects in the MT-7117 200 mg treatment group will be assigned to the MT-7117 100 mg treatment group for the second time for down-titration. Subjects in the placebo treatment group will remain in the placebo group by IWRS.

The IWRS should not normally be accessed with a request to break the treatment code for reasons other than safety or in an emergency. Should the Investigator wish to break the code for such reasons, he/she are advised to consult the Sponsor (or designee) in advance where feasible. If this is not possible, the Investigator may access the IWRS to obtain the treatment code and provide the system with the reason for breaking the blind. The Sponsor should be notified as soon as possible thereafter. If the blind is broken for any individual subject, the subject must be withdrawn from the study, and any procedures accompanying withdrawal will be performed (Section 9.5).

The Sponsor and study team will remain blinded throughout the entire duration of the study.

An electronic list of randomization codes will be retrieved from IWRS and transferred to the Sponsor at the end of the study.

As PK analysis will only be performed on samples from subjects receiving active study drug, unblinded randomization codes will be provided to the PK laboratory.

Since melanin density values could potentially be unblinding, adequate measures will be taken to protect the spectrophotometry data from disclosure to the Sponsor and the study team until the end of the study. Melanin density component data will be measured by the dedicated site staff who is not involved in routine blinded assessment of the subject, securely uploaded to and processed by the dedicated independent data management team member. The data handling procedure for melanin density will be described in the study specific procedure for melanin density endpoint posting process and data management plan.

MT-7117 and placebo tablets will be physically identical in appearance and will be packaged identically and suitably labeled to maintain the blind for the 52-week double-blind treatment period.

14 ADVERSE EVENT MANAGEMENT

All AEs and SAEs will be recorded in the source documents. All AEs and SAEs that occur from the time written informed consent is obtained until the end of the Safety Follow-up Period (4 weeks after the last treatment visit, for safety monitoring) will be recorded in the eCRF. Even if the AE is assessed by the Investigator as not related to study drug, its occurrence must be recorded in the source documents and eCRF. AEs will be classified as occurring at 'baseline' if they occur before the administration of study drug. AEs will be classified as 'treatment-emergent' if they arise following the first administration of study drug in the double-blind treatment period (after randomization) or if a predose AE increases in severity following dosing in the double-blind treatment period (after randomization).

At each study visit, after the subject has had an opportunity to spontaneously mention any problems, the Investigator or designee should inquire about the occurrence of AEs. The questioning should be open-ended and non-leading to avoid notifying either the subject or study site personnel of the actual treatment being administered.

14.1 Definition of an Adverse Event

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of study drugs, whether or not considered related to the study drugs.

14.2 Definition of a Serious Adverse Event

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening.
- Requires hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event.

Medical and scientific judgment should be exercised in deciding whether an AE is serious and whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of medication dependency or medication abuse. These should also usually be considered serious.

The term 'life threatening' refers to an event/reaction in which the subject was at risk of death at the time of the event/reaction; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe.

Admission to a hospital as a new subject is deemed as meeting this criterion, even when the length of hospital stay was less than 24 hours. Transfer to other departments of the same hospital due to a newly emerged event during the hospitalization (e.g., transfer from the psychiatry ward to the internal medicine ward, from the internal medicine ward to the coronary intensive care unit, or from the neurology ward to the TB ward) is also counted as hospitalization.

SAEs will be recorded and reported as described in Section 14.8.

14.3 Adverse Events of Special Interest

One AESI that will be considered during this study includes hepatic AESIs, defined as

- Develop liver dysfunction defined as any one of the following:
  - ALT or AST > 8 × ULN
  - ALT or AST > 5 × ULN for more than 2 weeks
  - Elevated total bilirubin > 2 × ULN and ALT or AST > 3 x ULN, or
  - Symptoms consistent with liver dysfunction (e.g., fatigue, nausea, vomiting, abdominal pain or tenderness, fever, rash, eosinophilia > 5%) with concomitant ALT or AST values > 3 × ULN.
- Hepatic AEs or hepatic laboratory abnormalities that lead to study drug interruption or discontinuation (Section 9.5).
- Any other laboratory or clinical abnormality that Sponsor Medical Monitor and/or Investigator considered as significant.

14.3.1 Management and Evaluation of Hepatic Adverse Events of Special Interest

Hepatic AESIs should be treated per the Investigator's approved standard of care and assessed for possible alternative etiology(ies). Hepatic AESIs will be followed clinically until resolution.

Subjects meeting the laboratory criteria of ALT/AST and total bilirubin defined in Section 14.3 (with or without alternative etiology), regardless of whether clinically significant or not, should be reported as a hepatic AE of special interest (AESI).

In the case of an increase of ALT or AST > 3 × ULN, it is preferable to be followed by repeat testing within 48 to 72 hours of at least four of the usual serum measures (ALT, AST, ALP, and total bilirubin) at local or central laboratory to confirm the abnormalities and to determine if they are increasing or decreasing. In addition, repeat laboratory testing can include albumin, CK, direct and indirect bilirubin, GGT, and PT/INR. There also should be inquiry made about symptoms. A detailed history including but not limited to the following formations, such as symptoms, prior or concurrent disease, concomitant drugs (including nonprescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, exposure to environmental chemical agents, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection, autoimmune biomarkers and liver imaging (e.g., biliary tract) may be warranted.

Regarding any subject who meets the AESI criteria, the Investigator should discuss with the Sponsor Medical Monitor about the determination of etiology and the possibility for

interruption (see Section 10.1.3.3) or withdrawal from study drug. Resumption of dosing will be considered based on the discussion with the Sponsor Medical Monitor and Investigator and should be closely followed up.

14.4 All hepatic AESIs (including event management and evaluation) will be recorded and reported similar to SAEs as described in Section 14.8.Severity of Adverse Events

The severity of AEs will be classified according to the following criteria:

- Mild: The event is transient and easily tolerated by the subject.
- Moderate: The event causes discomfort and interferes with the subject's general condition.
- Severe: The event causes considerable interference with the subject's general condition and may be incapacitating.

To ensure no confusion or misunderstanding of the difference between the terms 'serious' and 'severe', which are not synonymous, the following note of clarification is provided:

The term 'severe' is often used to describe the severity of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This will not be the same as 'serious', which will be based on subject/event outcome or action criteria usually associated with events that would pose a threat to a subject's life or functioning. Seriousness (not severity) will serve as a guide for defining regulatory reporting obligations.

14.5 Relationship of Adverse Events to Investigational Medicinal Product

The causal relationship of the AE to study drug will be determined as either 'a reasonable possibility' or 'no reasonable possibility,' and will be defined as having either 1 of the following:

- **Reasonable Possibility:** The relationship of the clinical event to the study drug makes a causal relationship possible, and other drugs, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.
- **No Reasonable Possibility:** The relationship of the clinical event to the study drug makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

14.6 Clinical Laboratory Abnormalities, and Other Abnormal Assessments

The Investigator will exercise medical judgment in deciding whether abnormal laboratory test results are clinically significant. Laboratory abnormalities which are clinically significant will be recorded as AEs or SAEs.

If an abnormal laboratory value or assessment is clearly related to a medically defined diagnosis or syndrome, the diagnosis or syndrome will be recorded on the AE form, not the individual laboratory values.

All 'abnormal, clinically significant' laboratory results or assessments will be followed until they resolve (return to normal or baseline values) or stabilize, or until they are judged by the Investigator to be no longer clinically significant. Repeat laboratory tests or measurements will be performed if needed.

The criteria for determining whether an abnormal objective test finding should be reported as an AE and include:

1. Test result is associated with accompanying symptoms, and/or
2. Test result requires additional diagnostic testing or medical/surgical intervention, and/or
3. Test result leads to a change in dosing (outside of protocol-stipulated dose adjustments), discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
4. Test result is considered to be an AE by the Investigator or Sponsor.

14.7 Recording and Reporting of Adverse Events

All AEs, regardless of the relationship to study drug, occurring from the time written informed consent is obtained from a subject until the end of the safety follow-up period or the withdrawal of the subject from the study, and any AEs or SAEs reported spontaneously through the end of the safety follow-up period, should be reported to the Sponsor or designee.

NOTE: Elective hospitalization or procedure/surgery planned before subject enrollment for a preexisting medical condition does not constitute an AE unless the underlying disease or condition worsens after signing informed consent.

At each study visit, after the subject has had an opportunity to spontaneously mention any problems, the Investigator should inquire about the occurrence of AEs. The questioning will be open-ended and non-leading.

All AEs will be recorded in the source documents and AE eCRF. The AE eCRF will contain a description of the event, date of onset, date of resolution, severity, treatment required, relationship to study drug, action taken with the study drug, outcome, and whether the event is classified as serious.

The Investigator will evaluate the severity of the AEs as defined in Section 14.4 and will assess the causality between the AEs and the study drug as defined in Section 14.5.

Pre-existing illnesses, which started before entry and is still ongoing at the start of the study, will not be considered AEs unless they worsen during the treatment period. Pre-existing conditions will be recorded as medical history.

If the Investigator becomes aware of any new safety information, or any safety information which appears to be either study or study drug related after the final follow-up period, then they must notify the Sponsor or the designee immediately.

14.8 Recording and Reporting of Serious Adverse Events or Hepatic Adverse Events of Special Interest

All SAEs and Hepatic AESI occurring from the time written informed consent is obtained from a subject until the end of the safety follow-up period or the withdrawal of the subject from the study must be reported to the Sponsor or the designee using the ***Serious Adverse Event/Adverse Event of Special Interest (SAE/AESI) in a Clinical Study Form*** within 24 hours of the Investigator becoming aware of the SAE/AESI. All SAE/AESIs must also be entered in the AE section of the eCRF as soon as possible.

The SAE/AESI report should be completed as thoroughly as possible, including an assessment of causality. All such reports will identify subjects by unique code numbers assigned to the study participants, rather than by the subjects' names, personal identification numbers, or addresses.

The reporting contact for SAE/AESIs by email is as follows:

Email: [redacted]

In case of any email problems, the SAE/AESI form will be sent to [redacted] via fax to:

Fax: [redacted]

Reports of pregnancy, although **not** classified as an SAE, will be handled and reported as in Section 14.10.

The Sponsor will comply with the applicable regulatory requirements related to the reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs) to the Regulatory Authorities and central IRB/IEC(s). The Investigator will be responsible for informing the local IRB/IEC(s) of SUSARs, as per local laws and requirements.

14.9 Follow-up of Adverse Events

The Investigator should follow up with subjects who experienced AEs/SAEs, until the event has resolved or stabilized, and any abnormal laboratory values have returned to baseline; or until there is a satisfactory explanation for the changes observed. In the case of death, if possible, a pathologist's full report should be supplied.

The reference safety information for this clinical study is the IB.

14.10 Pregnancy

If a female subject who has been exposed to the study drug becomes pregnant, the course and outcome of the pregnancy should be monitored and documented. Where possible, if a female partner of a male subject who has been exposed to the study drug becomes pregnant and the subject provides this information, then the pregnancy will be documented based on information provided by the subject.

A pregnancy that occurs in a subject who has been exposed to the study drug must be reported using the same timelines and contact details as an SAE (Section 14.8) by a paper ***Pregnancy in a Clinical Study Notification Form***, although pregnancy alone will not be classified as an SAE. If the outcome of the pregnancy or an event occurs during the course of pregnancy that involves an SAE (e.g., a congenital anomaly), then the ***Serious Adverse Event (SAE) in a Clinical Study Form*** will also be completed.

Subjects who become pregnant while on study must be withdrawn from treatment, as described in Section 9.5.

14.11 Overdose

There is no known antidote for MT-7117. Any signs or symptoms of a possible overdose will be treated supportively. In the case of an emergency, standard emergency procedures and supportive medical care will be provided.

If the subject takes a dose which is greater or more frequent than that specified in the protocol (with or without associated symptoms), this overdose is an AE and must be reported to the Sponsor or the designee on the AE eCRF.

If the overdose results in AEs that meet serious criteria, the SAE must be reported to Sponsor or the designee immediately or within 24 hours of awareness using the ***Serious Adverse Event (SAE) Form in Clinical Study*** according to SAE reporting procedures (Section 14.8).

If the subject experiences any other associated symptoms as a result of the overdose, the Investigator will record this as a separate AE/SAE.

15 DATA COLLECTION AND PROCESSING

15.1 Independent Data Monitoring Committee

An external independent Data Monitoring Committee (iDMC) will be established to perform regular review of the safety data to ensure the ongoing safety of participating subjects until the last subject completes the double-blind treatment period. The frequency of data review will be described in the iDMC Charter. Analyses required for the iDMC's review will be performed by a Contract Research Organization as described in the iDMC Statistical Analysis Plan (SAP). The committee's composition and a description of its responsibilities will be provided in the iDMC Charter.

15.2 Data Collection

Subject data will be collected on individual eCRFs and will be substantiated by source documents (such as laboratory reports, medical records, or ECGs) at the Investigator site. All relevant data will be transcribed into the eCRF from source documents, entered into the study database directly from source documents, or transferred electronically to the study database. Where no printed or electronic source documents exist, data will be entered directly into the eCRF and the eCRF will be considered the source document.

Before the start of the study, the Investigator will complete a Delegation of Responsibility List. The Sponsor or designee will provide training for completion of the eCRF. The eCRF will be completed according to guidelines provided by the Sponsor or its designee in writing, electronically, and/or verbally.

Completed eCRFs will be reviewed by the Study Monitor for the study to ensure data accuracy, completeness, and consistency in accordance with the study monitoring plan and other relevant procedural documents. Any relevant discrepancies found during the eCRF review or during data validation and/or quality assurance reviews of the data by data management or other functions are to be clarified by the Investigator (or his/her designated personnel).

The Investigator or designee must record all required subject data using the previously specified data collection method defined by the Sponsor. An explanation must be documented for any missing data where required. The Investigator must sign and date a declaration on the eCRF attesting to his/her responsibility for the quality of all data recorded, and that the data represents a complete and accurate record of each subject's participation in the study. The data collected in the eCRF will be returned to the Sponsor, and an electronic copy will be retained by the Investigator.

15.3 Case Report Form Completion

The eCRF will be presented in an electronic casebook comprising a series of electronic forms. The Subject Number should always be indicated and date (and time, if applicable) of each assessment should be entered in the eCRF.

The eCRFs must be completed in timely manner so that this does not delay the ongoing data validation, review, and quality control. The final, completed eCRF for each subject must be signed and dated by the Investigator on the appropriate eCRF form to signify that he/she has reviewed the casebook and certifies it to be complete and accurate.

The eCRF will feature a special means for correcting errors in the previously entered data. A complete audit trail of the original entries, changes and deletions, session dates and times, and the credentials of the eCRF user who performed the operation will be maintained by the system.

15.4 Data Processing

The data collected on the eCRFs will be captured in a specially constructed and validated database. The data will be validated using both manual and electronic means. Clarification of data will be requested from the Investigator site as required. An audit trail of the original database entries, changes and deletions, session dates and times, and the credentials of the database user who performed the operation will be maintained by the system. The completed database will be quality assured and locked to prevent further changes. A full database extract will be made available for statistical analysis according to the methods outlined in Section 16 and the Statistical Analysis Plan (SAP).

AEs and medical history entries will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. Versions of the dictionaries used will be documented in the Data Management Plan and SAP.

15.5 The Impact of COVID-19

Since study subjects may not be able to come to the clinical site for protocol-specified visits, specific information on COVID-19 will be captured via eCRFs to explain the missed protocol-specified information due to COVID-19.

If any study procedures are deemed unsafe or in need of special precautions to safeguard the subject or others from the transmission of COVID 19, these will be documented in the TMF, and, if altered in any way relevant to data collection or interpretation, or statistical analysis, will be addressed in the final SAP.

16 STATISTICAL METHODS AND PLANNED ANALYSES

The SAP will detail the implementation of all the planned statistical analyses in accordance with the protocol. The SAPs may be revised during the study to accommodate amendments to the clinical study protocol and to make changes to adapt to unexpected issues in study execution and data that may affect the planned analyses. Any deviations from the planned analysis will be described and justified in a separate document and in the Clinical Study Report (CSR).

Database lock and statistical analysis takes place when the last subject completes the last visit occurs and includes all subject data collected at Week 56 visit or during the safety follow-up period visit (Week 56). The database lock will be associated with a designated SAP. The SAP will be approved and signed prior to the database lock.

16.1 Determination of Sample Size

The planned sample size of 72 is expected to provide power for the comparison between MT-7117 treatment group and placebo group for ACR CRISS score at Week 52. The calculation of sample size assumes a 2-sided alpha level of 0.05 and uses EAST (Version 6.5) for Wilcoxon Mann Whitney test. The randomized 72 subjects (36 subjects for MT-7117 and 36 subjects for placebo) with a 1:1 allocation ratio would provide 80% power to detect treatment difference of 0.35 (35% improvement on MT-7117 treatment group compared to placebo group) in ACR CRISS score at Week 52 with an associated standard deviation (SD) of 0.5.

16.2 Analysis Population

16.2.1 Safety Analysis Population

The safety analysis population is defined as all randomized subjects who received at least 1 dose of study drug.

16.2.2 Intent-to-Treatment Population

The Intent-to-treat (ITT) population includes all randomized subjects who receive at least 1 dose of study drug.

16.2.3 Per-protocol Population

The per-protocol population includes all ITT subjects who do not have any major protocol deviations and complete Week 52 (the end of double-blinded treatment period).

16.2.4 Pharmacokinetic Population

The PK population includes all randomized subjects who receive at least 1 dose of study drug and who have at least 1 postdose value of plasma concentration to be included in the PK analysis without important protocol deviations which may affect the PK of study drug. PK analysis will only be performed on samples with active study drug.

16.3 Statistical Analysis

16.3.1 General Considerations

An SAP containing details of all the analyses and outputs will be prepared and approved prior to the study database lock. The SAP will be performed using SAS® Version 9.4 or higher.

The ITT population will be used for all efficacy analyses. All safety analysis will be performed on the Safety population and PK assessments will be performed on the PK population.

Unless otherwise specified, the baseline values will be the last non-missing value prior to receiving the first dose of study drug.

Continuous variables will be summarized descriptively using the number of observations, mean, SD, median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages.

All statistical tests will be performed at the 5% 2-sided significance level. Point estimates of treatment differences will be provided with 2-sided 95% confidence intervals (CIs) where applicable.

16.3.2 Data Handling

16.3.2.1 Definition of baseline for Efficacy and Safety Endpoints

Unless otherwise specified, the baseline values for the endpoints will be the latest available data obtained prior to the first administration of study drug.

16.3.2.2 Handling of Time Point Data in Analyses Performed by Measurement time Point (Analysis Visit Windows)

For the analyses performed for each measurement time point, the allowable range of data handling for the analysis will be specified as analysis visit window in the SAP.

No data imputation will be performed using data from outside the allowable range. If multiple values are available within the allowable range for the endpoint in question, then the latest and closest value of the window value will be used for analysis.

16.3.2.3 Handling of Reference Values and Indeterminate Values for Clinical Laboratory Test Parameters

If a laboratory test value or its reference is indeterminate due to a problem with the test sample, then this value will be handled as a missing value.

16.3.3 Statistical Analysis Method

16.3.3.1 Subject Disposition

The following will be provided:

- The total number of screened subjects: defined as those who met the inclusion criteria regarding the target indication and signed the ICF
- The total number of randomized subjects: defined as those who received a randomization number
- The total number (%) of subjects in each analysis populations
- The total number (%) of subjects who completed Week 52
- The total number (%) of subjects who discontinued the study, and the reasons for discontinuation of study

16.3.3.2 Demographic and Other baseline Characteristics

Baseline demographic variables including year of birth, sex, body weight, body mass index, ethnicity and race, and other baseline characteristics will be summarized by treatment group using descriptive statistics on the ITT population.

16.3.3.3 Medical History

Medical history will be coded using MedDRA. The frequency and percentage of subjects will be summarized using MedDRA PT within the system organ class (SOC). The summary will be sorted by International Agreed Order for SOC and alphabetical order for PT.

16.3.3.4 Prior and Concomitant Medications

All prior and concomitant medication will be coded using the WHO DD and Anatomical Therapeutic Chemical (ATC) system. Each medication will be classified as prior medication if it is stopped prior to the first dose of study drug, or as concomitant medication if it is ongoing at the time of the first dose of study drug or is started after the first dose of study drug. Prior and concomitant medications will be summarized by treatment group by ATC level 2 categories and preferred name.

16.3.4 Efficacy Analysis

16.3.4.1 Analysis of Primary Efficacy Endpoints

The primary treatment comparisons of interest are the ACR CRISS score for MT-7117 treatment group compared with placebo group at Week 52.

ACR CRISS score is a composite endpoint assessed in a 2-step process that calculates the probability of improvement for each subject ranging from 0.0 (no improvement) to 1.0 (marked improvement) refer to Appendix 4 for further details.

The primary endpoint will be summarized using descriptive statistics with interquartile range. The distribution of ACR CRISS score may not be normal distribution. For ACR CRISS score at Weeks 16, 26, 39, and 52 the comparison between MT-7117 treatment group and placebo group will be performed using this non-parametric analysis method. The point estimates and 2-sided 95% CIs and associated P-values for the difference between the treatment groups will be obtained using the Hodges-Lehman estimator corresponding to Wilcoxon's rank sum test. This non-parametric analysis will be performed with multiple imputation method, assuming missing at random. A supportive analysis will be performed at the same way for the primary endpoints using the per-protocol set (PPS). As a secondary analysis for the primary endpoint, the same analysis method will be applied to the intent to treat (ITT) population but the patients' data after taking rescue therapy will not be included. This approach will be performed to investigate a sensitivity for the primary analysis.

16.3.4.2 Analysis of Secondary and Other Efficacy Endpoints

Change from baseline to Week 52 in mRSS, %pFVC, HAQ-DI, Patient Global Assessment, and Physician Global Assessment will be analyzed using mixed-effect model for repeated measures (MMRM). The model will include fixed categorical terms for the treatment group, visit, the randomization factor [redacted] and the treatment group by visit interaction together with continuous covariate terms

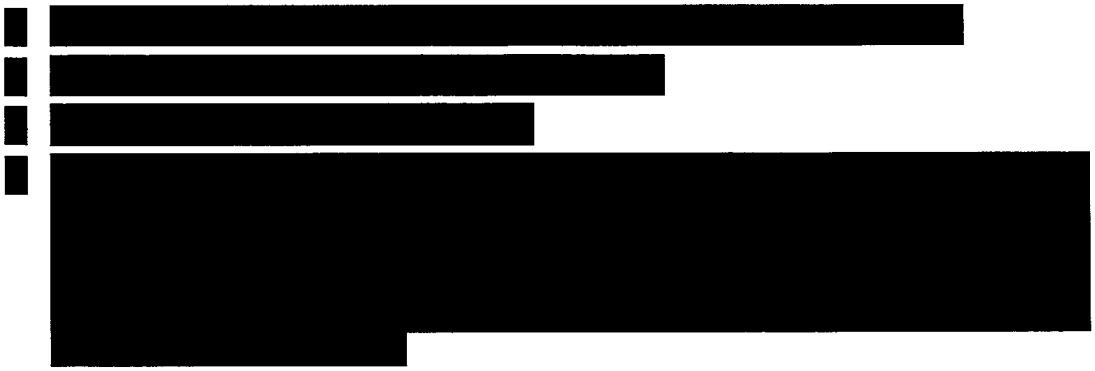
for baseline value and baseline value by visit interaction. An unstructured correlation structure will be used to model the within-subject variance covariance errors. Should convergence of the model fail (due to the small numbers of subjects in this study), other variance covariance matrices such as autoregressive [AR(1)] correlation matrix will be used if appropriate. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. From the model described above, p-values will be produced. All available data from all subjects will be used without any imputation.

ACR CRISS Score improvement proportion at Week 52 will be calculated in Step 1 as specified in Section 11.4 and will be analyzed using logistic regression model. The model will include the treatment group and the randomization factor [redacted] as fixed factors together with continuous covariate terms for baseline mRSS. The treatment odds ratio at Week 52 will be estimated using a contrast. The missing data at Week 52 due to no available core set measures will be addressed as non-improvement.

Proportion of subjects with ACR CRISS score responder (CRISS $\geq$ 0.6) at Weeks 16, 26, 39, and 52 will be analyzed using generalized linear mixed effect model with logit rink function. This analysis will use the observed values from Weeks 16 to 52 as the response. The model will include the treatment group, visit and the interaction between the treatment group, the randomization factor [redacted] and visit as fixed factors together with continuous covariate terms for baseline mRSS and baseline mRSS by visit interaction. The treatment odds ratio at Week 52 will be estimated using a contrast.

16.3.4.3 Analysis of Exploratory Endpoints

[redacted]



16.3.5 Safety Analysis

16.3.5.1 Adverse Events

TEAEs are defined as AEs that newly occurred or increased in severity on or after the first dose of study drug. The TEAEs are summarized for subjects with at least 1 TEAE, at least 1 treatment-emergent adverse reaction, at least 1 serious TEAE, at least 1 serious treatment-emergent adverse reaction, at least 1 TEAE leading to drug withdrawn, at least 1 treatment-emergent adverse reaction leading to drug withdrawn, at least 1 hepatic AE, and at least 1 AESI.

The frequency and incidence of TEAEs will be summarized by SOC and PT by treatment group. For this table, SOC is sorted by International order; then within SOC, PT is sorted by descending counts under MT-7117 Total group, then descending counts under Placebo group, then alphabetic order for PTs with the same count.

The AE summaries will be presented by treatment group for the following:

- TEAEs by SOC and PT
- TEAEs by SOC, PT and severity
- TEAEs by SOC, PT and relationship
- Treatment-emergent adverse reactions by SOC and PT
- Treatment-emergent adverse reactions by SOC, PT and severity
- Serious TEAEs by SOC and PT
- Serious treatment-emergent adverse reactions by SOC and PT
- TEAEs leading to drug withdrawn by SOC and PT
- TEAEs by SOC and PT for TEAEs with frequency ≥ 5 % in total MT-7117 treatment group

For each of the summaries, multiple occurrences of the same event within a subject will be counted once in the summaries by SOC and PT; multiple occurrences of the same event within a subject will be counted once in the maximum severity category (severe > moderate > mild) and/or maximum study drug relationship category (reasonable possibility/no reasonable

possibility). If severity or relationship is found to be missing the most severe occurrence will be imputed for that particular summary.

All AEs for each subject, including multiple occurrences of the same event, will be listed.

Death, serious TEAEs, and TEAEs leading to study withdrawal will be listed.

16.3.5.2 Safety Laboratory Assessments

Laboratory test values and changes from baseline will be summarized descriptively by treatment and visit.

The laboratory tables will be generated for each laboratory categories (hematology, coagulation, biochemistry, and urinalysis).

All laboratory data will be listed with clinically relevant values flagged (L = Lower than lower limit of normal range, H = Higher than ULN range or A = Abnormal).

The number of subjects with postbaseline assessments ≥ x 2 ULN and ≥ x 3 ULN and so on will be calculated for ALT, AST, GGT, ALP, direct and total bilirubin and summarized by treatment group for each postbaseline visit.

The figure of mean (or median) and standard error value of ALT, AST, total bilirubin, and ALP by visit will be plotted.

16.3.5.3 Vital Signs and 12-lead Electrocardiogram

Vital signs and 12-lead ECG variables and changes from baseline will be descriptively summarized at each visit by treatment group.

The baseline for the vital sign parameters and 12-lead ECG measurements will be the last valid assessment obtained on Day 1 prior to the administration of double-blind treatment period.

- For ECGs, number and percentage of subjects meeting the criteria listed below will be presented in tables:
- baseline corrected QT interval (QTc) < 450 msec and > 500 msec at EOT
- baseline QTc < 450 msec and 500 msec ≥ QTc > 480 msec at EOT
- baseline QTc < 450 msec and 480 msec ≥ QTc > 450 msec at EOT
- Increase from baseline at EOT in QTc > 30 msec
- Increase from baseline at EOT in QTc > 60 msec
- These criteria will be applied to both corrected QT interval using Bazett's formula (QTcB) and corrected QT interval using Frederica's formula (QTcF).

16.3.5.4 Physical Examination and Nevi (Melanocytic Lesions) Evaluation

Physical examination data will be summarized descriptively (number and percentage of the subjects) in tables by treatment and time point.

Nevi (Melanocytic Lesions) appearance will be summarized descriptively (number and percentage of the subjects) in tables by treatment and analysis visit for subjects' suspicious nevi (Melanocytic Lesions) found.

16.3.6 Pharmacokinetic Analysis

Plasma MT-7117 concentrations will be listed for each subject, scheduled visit, and treatment period with the same precision as provided by the bioanalytical laboratory. PK sample collection times, most recent dosing times, as well as derived actual sampling time relative to the most recent dose will be provided in a listing. The actual sampling time relative to the most recent dose will be calculated in hours and rounded to 2 decimal points. Plots of individual concentration vs actual sampling time will be presented overlaid with visits.

Population PK analysis will be performed using the plasma concentration of MT-7117 obtained in this study in combination with data obtained from other clinical studies. Population PK analysis results will be reported separately from the CSR.

17 STUDY MANAGEMENT, ETHICAL AND REGULATORY REQUIREMENTS

17.1 Good Clinical Practice

The Investigator will ensure that this study is conducted in compliance with the 2013 (Fortaleza, Brazil) revision of the 1964 Declaration of Helsinki. This study will also be conducted in accordance with Good Clinical Practice (GCP) requirements described in the current revision of The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) of Technical Requirements of Pharmaceuticals for Human Use Guidelines. This study will also be carried out in accordance with regional and local legal requirements. Before the first subject is enrolled in the study, all ethical and legal requirements will be met.

17.2 Investigator Responsibilities

17.2.1 Informed Consent

Prior to undergoing any study-specific procedure, all legally competent subjects must consent in writing to participate. An ICF will be provided to each subject, which will contain all regulatory-required elements, all ICH-required elements, and data protection information, when applicable, in a language that is understandable to the subject.

In the event that a subject is legally incompetent, the enrollment of such a subject should be in accordance with all applicable laws, and consent sought by the Investigator from the subject's legally authorized representative.

Either the Investigator or a designated person, qualified to meet any applicable local regulations, who is equally knowledgeable about the study will explain the aims, methods, anticipated benefits and potential hazards of the study and any discomfort it may entail. Procedures may include sample collection for pharmacogenomic testing obtained for the noted exploratory endpoints. Biopsy may be requested for safety if they arise via the postbaseline nevi (Melanocytic Lesions) assessments per the Investigator judgement. For pharmacogenomic testing, DNA and messenger ribonucleic acid will be measured. These procedures will be performed only on subjects who specifically provided consent to undergo these optional procedures. Separate informed consent for pharmacogenomic testing will be required. The review must be in a form understandable to the subject. A corresponding written explanation will also be provided, and the subject allowed sufficient time to consider the study information.

If the subject is willing to participate in the study, the ICF will be signed and dated by the subject, the Investigator or, if applicable, the designated person who explained the nature of the study. The subject will receive a copy (together with the information sheet) and the original ICF will be retained with the study records at the Investigator site.

The date (and time, if required) on which the ICF is signed by the subject must be recorded in the source notes.

The Investigator or his/her designee must emphasize to the subject that study participation is entirely voluntary and that consent regarding study participation may be withdrawn at anytime without penalty or loss of benefits to which the subject is otherwise entitled.

If the ICF is amended during the study, the Investigator must follow all applicable regulatory requirements pertaining to approval of the amended ICF by the IRB/IEC. The Investigator site

personnel must use the amended ICF for all new subjects and repeat the consent process with the amended ICF for any ongoing subjects.

17.2.2 Ethical and Regulatory Approval

The study will be conducted in accordance with ethical principles that have their origins in the Declaration of Helsinki and that are consistent with GCP as described in:

- Declaration of Helsinki, concerning medical research in humans (Adopted by the 18th World Medical Association [WMA] General Assembly, Helsinki, Finland, June 1964 and amended by the: 29th WMA General Assembly, Tokyo, Japan, October 1975; 35th WMA General Assembly, Venice, Italy, October 1983; 41st WMA General Assembly, Hong Kong, September 1989; 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996; 52nd WMA General Assembly, Edinburgh, Scotland, October 2000; 53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added); 55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added); 59th WMA General Assembly, Seoul, Republic of Korea, October 2008; 64th WMA General Assembly, Fortaleza, Brazil, October 2013).
- ICH Harmonized Tripartite Guidelines for GCP 1996
- Directive 91/507/European Economic Community, The Rules Governing Medicinal Products in the European Community
- The Medicines for Human Use (Clinical Studies) Regulations 2004 (Statutory Instrument 2004 No 1031) and subsequent amendments
- Association of the British Pharmaceutical Industry Guidelines for Phase I Studies (2012)
- EMEA, Committee for Medicinal Products for Human Use (CHMP). September 2007. Guideline on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Studies with study drugs. (EMEA/CHMP/Safety Working Party/28367/07).
- Code of Federal Regulations Title 21

The Investigator and Sponsor will sign this Protocol to confirm agreement to abide by it.

Before any study-related procedure is performed on a subject, all IRB/IEC, regulatory and local approvals of this Protocol will be obtained. While the study is ongoing and at study completion/discontinuation, the Sponsor or Investigator will submit information to the IRB/IEC(s) in accordance with institutional/local regulations, for example:

- Information on SUSARs.
- Periodic reports on the progress of the study.
- Notification of the end of study (EOS) or ET.
- Final study summary upon completion or closure.

The Sponsor will ensure that any SUSARs from this study and other studies with this study drug are reported promptly to the regulatory authorities.

If it is necessary to amend the Protocol during the study, proper notification will be made to the regulatory authorities and IRB/IECs in the form of a Protocol Modification. Protocol Modification requiring IRB/IEC approval may be implemented only after a copy of the IRB/IEC's approval/favorable opinion letter has been transmitted to the Sponsor and regulatory

authority approval has been obtained (if required). Protocol Modifications that are intended to eliminate an apparent immediate hazard to subjects may be implemented prior to receiving Sponsor, regulatory authority and/or IRB/IEC approval. However, in this case, approval must be obtained as soon as possible after implementation.

Any Protocol or other deviations that occur during the study will be documented and reported to the Sponsor. Depending on the nature of the deviation, this may be reported to the appropriate regulatory authority and IRB/IEC.

17.2.3 Source Document Requirements and Document Access During the Study

The Investigator must retain a comprehensive and centralized filing system of all study related documentation (including, but not limited to: essential documents, copies of Protocols, eCRFs, source data such as original reports of test results, study drug dispensing logs, correspondence, records of ICF and other documents pertaining to the conduct of the study) that is suitable for inspection by the Sponsor and representatives of regulatory authorities.

The Investigator /institution will permit study-related monitoring, audits, IRB/IEC reviews, and regulatory inspections providing direct access to source data/documents.

17.2.4 Study Records Retention

Study-related documentation must be kept for at least 25 years or until notified by the Sponsor. Documents should be stored in such a way that they can be accessed/data retrieved at a later date. Consideration should be provided to security and environmental risks.

No study document will be destroyed without prior written agreement between the Sponsor and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

17.2.5 Protocol Deviations

The Sponsor does not allow prospective deviations from the protocol. Any deviations (classified as important) affecting subject eligibility and/or safety must be reviewed or approved by the IRB/IEC and regulatory authority, as per applicable requirements. The Investigator is responsible for complying with all protocol requirements, and applicable to laws pertaining to protocol deviations. If a protocol deviation occurs (or is retrospectively identified) after a subject has been enrolled, the Investigator is responsible for notifying their IRB/IEC, regulatory authorities (as applicable), after discussion with Medical Monitor and Sponsor.

Protocol deviations will be discussed with the Medical Monitor and the Sponsor.

17.3 Study Monitoring

In accordance with applicable regulations, GCP, and the procedures of the Sponsor or its designees, the Study Monitor will periodically contact the Investigator site, and conduct on-site visits. The extent, nature, and frequency of on-site visits will be based on study complexity, enrolment rate, and data quality at the Investigator site. Through these visits and frequent communications (e.g., letter, email, and telephone), the Study Monitor will verify that the investigation is conducted according to protocol, regulatory, and Sponsor requirements.

The Investigator will allow the Study Monitor direct access to all relevant documents and allocate his/her time and the time of his/her personnel to the Study Monitor to discuss findings and any relevant issues.

In addition to contacts during the study, the Study Monitor will contact the Investigator site personnel before the start of the study to discuss the protocol and data collection procedures.

At study closure, the Study Monitor will conduct all activities as indicated in Section 17.5.

17.4 Quality Assurance and Auditing

Authorized representatives of the Sponsor, IRB/IEC and/or regulatory authorities may conduct an audit or inspection of this study either during or after completion. In such cases, the Investigator will give the auditor/inspector direct access to all relevant documents and source data and will allocate his/her time and the time of his/her personnel as may be required to discuss findings and any relevant issues.

17.5 End of Study and Site Closure

The end of the study is defined as the last visit for the last subject. Upon completion of the study, or if the study or an Investigator site is prematurely discontinued, the following activities, where applicable, must be conducted by the Study Monitor in conjunction with the Investigator:

- Return of all study data to the Sponsor.
- Completion of data clarifications and/or resolutions.
- Accounting, reconciliation, and final disposition of used and unused study drug.
- Review of Investigator site study records for completeness.

Any unresolved AEs of SAEs will be followed according to Section 14.9.

17.6 Premature Discontinuation of the Study

The Sponsor reserves the right to discontinue the study because of safety concerns, ethical issues, or serious and/or persistent non-compliance with the protocol.

If the study is suspended or terminated, the Sponsor will promptly inform the Investigator, and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. The Investigator is responsible for promptly informing the IRB/IEC and providing the reason(s) for the suspension or termination of the study.

For all subjects, the follow-up visit assessments should be performed per Table 1.

Any unresolved AE or SAE will be followed up according to Section 14.9.

The Sponsor may at any time, at its sole discretion, discontinue the study for various reasons, including, without limitation, the following:

- Failure of the Investigator to enrol subjects into the study at a reasonable rate
- Failure of the Investigator to comply with applicable laws and/or pertinent regulations
- Submission of knowingly false information from the research facility to the Sponsor, Study Monitor, or regulatory authorities
- Insufficient adherence to Protocol requirements.

The Sponsor will issue a written notice to the Investigator, which will contain the reasons for taking such action. If the Investigator site is terminated for non-compliance, appropriate regulatory authorities will also be notified by the Sponsor.

17.7 Liability and Insurance

Please refer to the written study information provided to the subject.

17.8 Coordinating Investigator

A Coordinating Investigator is nominated and is responsible to coordinating between Investigators at different centers participating in this multicenter trial. The Coordinating Investigator represents all Investigators for decisions and discussions regarding this trial, consistent with the ICH Topic E6 GCP. The Coordinating Investigator will provide expert medical input and advice relating to trial design and execution and is responsible for the review and signoff of the CSR.

18 DISCLOSURE OF DATA

18.1 Confidentiality

All information concerning MT-7117 is the sole property of the Sponsor. For the avoidance of doubt, the Sponsor has full ownership of the eCRFs completed as part of the study. The Investigator will agree to use the information only for the purposes of carrying out this study and for no other purpose unless prior written permission from the Sponsor is obtained.

Subjects will be informed that all personal information made available for inspection will be handled in confidence and in accordance with applicable laws and regulations. All personnel involved in the study will observe and work within the confines of applicable data protection regulations.

18.2 Publication

By signing the study Protocol, the Investigator agrees that the results of the study may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals by the Sponsor. If necessary, the regulatory authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement.

The Sponsor will retain ownership of all data. All proposed publications based on the study will be subject to the Sponsor's approval requirements.

The Sponsor or designee will prepare a final report on the study. The Investigator's right to publish or present any information on the study, and publication procedures to be followed, will be defined in the Investigator site agreement.

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20 APPENDICES

Appendix 1 American College of Rheumatology/European Scleroderma Trials and Research Criteria for the Classification of Systemic Sclerosis and Leroy and Medsger's Criteria for Diffuse Cutaneous Systemic Sclerosis

American College of Rheumatology/European Scleroderma Trials and Research Criteria for the Classification of Systemic Sclerosis[30,31]

Item	Sub-item(s)	Weight/score†
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints *(sufficient criterion)*	–	9
Skin thickening of the fingers *(only count the higher score)*	Puffy fingers	2
	Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints)	4
Fingertip lesions *(only count the higher score)*	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia	–	2
Abnormal nailfold capillaries	–	2
Pulmonary arterial hypertension and/or interstitial lung disease *(maximum score is 2)*	Pulmonary arterial hypertension	2
	Interstitial lung disease	2
Raynaud's phenomenon	–	3
SSc-related autoantibodies (anticentromere, anti–topoisomerase I [anti–Scl-70], anti–RNA polymerase III) *(maximum score is 3)*	Anticentromere Anti–topoisomerase I Anti–RNA polymerase III	3

* These criteria are applicable to any patient considered for inclusion in an SSc study. The criteria are not applicable to patients with skin thickening sparing the fingers or to patients who have a scleroderma-like disorder that better explains their manifestations (e.g., nephrogenic sclerosing fibrosis, generalized morphea, eosinophilic fasciitis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft-versus-host disease, diabetic cheiroarthropathy).
† The total score is determined by adding the maximum weight (score) in each category. Patients with a total score of ≥9 are classified as having definite SSc.

Leroy and Medsger's Criteria for Diffuse Cutaneous Systemic Sclerosis[32,33]

lSSc: RP (objective documentation)
plus any one: SSc-type nailford capillary pattern
or
SSc selective autoantibodies
or
RP (subjective only)
plus both: SSc-type nailfold capillary pattern
and
SSc selective antibodies (see Table 2)

lcSSc: criteria for lSSc
plus: distal cutaneous changes

dcSSc: criteria for lSSc
plus: proximal cutaneous changes

Diffuse fasciitis with eosinophilia (DFE):
proximal cutaneous changes without criteria for lSSc or lcSSc

Appendix 2 Prohibited or Precautionary Concomitant Medications

Prohibited medication may be allowed based on medical discretion and discussion with Study Medical Monitor. Allowance of prohibited medication should be based on confirmation with the Study Medical Monitor. Precautionary medications may be allowed based on medical discretion and discussion with Study Medical Monitor. Allowance of any medication should be based on confirmation, that the medication does not represent a safety issue, and will not impact study conduct adversely. Please see study procedures for restricted medication for further detail.

Drugs known to be predominantly metabolized by CYP3A4 with a narrow therapeutic index and drugs that are known major substrates of P-gp, BCRP, OATP1B1, or OATP1B3 (for which elevated plasma concentrations are associated with significant medical events), are restricted from use within 1 week before the screening (Visit 1) and during the study (Table 1).

Table 4: Prohibited Concomitant Medications

Drug Class/ Proprietary Name (US), but not limited to	**Drug Name**
CYP3A4 substrates	
Orap	Pimozide; hERG blocker, D2 receptor antagonist; Schizophrenia
Buspar	Buspirone; Antidepressant
Colcrys	Colchicine; mitotic poison; Gout
Juxtemid	Lomitapide; microsomal triglyceride transfer; Familial Hypercholesterolemia
P-gp substrates	
Pradaxa	Dabigatran; benzamidine-based thrombin inhibitor; Atrial fibrillation, Deep venous thrombosis
Lanoxin	Digoxin; Na/K/ATPase blocker; Myocardium-atrial fibrillation, flutter, PVC's
Allegra	Fexofenadine; antihistamine; H1blocker; Allergies
Samsca	Tolvaptan; vasopressin R2 antagonist; Hyponatremia, Polycystic renal disease
Zortress	Everolimus; mTORC1 antagonist; Renal carcinoma
BCRP substrates	
Azulfidine	Sulfasalazine; anti-inflammatory; Rheumatoid Arthritis, Inflammatory Bowel Disease
Hycamtin	Topotecan; Relapsed small cell lung cancer
OATP1B1, 1B3 substrates	
Allegra	Fexofenadine; antihistamine; H1blocker; Allergies
Glyburide	Glyburide; sulfonylurea receptor antagonist; Diabetes Mellitus
Starlix	Nateglinide; insulin release; Diabetes Mellitus
Prandin	Repaglinide; insulin release; Diabetes Mellitus
Tracleer	Bosentan; endothelin A/B antagonist; Pulmonary Artery Hypertension
Taxotere	Docetaxel; cytotoxin; Breast, Lung, Colon, Ovarian, Gastric, Prostate Cancers
Taxol	Paclitaxel; cytotoxin; Breast, Lung, Colon, Ovarian, Gastric, Prostate Cancers

Table 5: Precautionary Concomitant Medications

Drug Class/ Proprietary Name (US), but not limited to	**Drug Name**
Zocor	Simvastatin; HMG-COA-reductase inhibitor; Hyperlipidemia
Lipitor	Atorvastatin; HMG-COA-reductase inhibitor; Hyperlipidemia
Crestor	Rosuvastatin; HMG-COA-reductase inhibitor; Hyperlipidemia
Livalo	Pitavastatin; HMG-COA-reductase inhibitor; Hyperlipidemia
Pravachol	Pravastatin; HMG-COA-reductase inhibitor; Hyperlipidemia
Mevacor	Lovastatin; HMG-COA-reductase inhibitor; Hyperlipidemia
Stenda	Avanafil; PDE5 inhibitor; Erectile dysfunction
Halcion	Triazolam; benzodiazepine; Antianxiety
Versed	Midazolam; benzodiazepine; Antianxiety
Ambien	Zolpidem; benzodiazepine; Insomnia
Clozaril	Clozapine; Schizophrenia
Cyclosporine	Neoral, Gengraf, Sandimmune; Cogan's Syndrome, Crohn's disease, Eczema

Appendix 3 Contraception

Contraception

Female subjects of child-bearing potential* must be willing and able to practice birth control for the duration of the study, from screening until 3 months after the last dose of study drug. Male subjects must be willing and able to practice birth control for the duration of the study, from the time of the first dose of study drug until 3 months after the last dose of study drug.

- **Female subjects** must be willing to use a highly effective method of birth control (ie, contraceptive measure with a failure rate of < 1% per year), in conjunction with male barrier contraception (ie, male condom with spermicide). Highly effective methods of contraception include:
    - Placement of an intrauterine device or intrauterine system.
    - Established use of oral, injected or implanted hormonal methods of contraception associated with inhibition of ovulation.
    - Male sterilisation (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). (For female subjects on the study, the vasectomised male partner should be the sole partner for that subject.)
    - Bilateral tubal ligation.
    - True abstinence: when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.)

Female subjects must not donate ova for the duration of the study, from the time of the first dose of study drug until 3 months after the last dose of study drug.

- **Male subjects** with partners of child-bearing potential must use a barrier method of contraception (ie, male condom with spermicide) in addition to a second method of acceptable contraception used by their female partners. In addition to the list of highly effective contraception methods above, other acceptable methods of contraception include:
    - Progesterone only oral contraception, where inhibition of ovulation is not the primary mode of action.
    - Cap, diaphragm or sponge with spermicide.

Male subjects must not donate sperm for the duration of the study, from the time of the first dose of study drug until 3 months after the last dose of study drug.

*Note: Women are considered to be of child-bearing potential unless they meet 1 of the following criteria as documented by the Investigator:

- Post-menopausal (age > 55 and amenorrheic for at least 1 year)
- Hysterectomy, bilateral oophorectomy or salpingectomy.
- Congenital sterility.

Subjects must not have unprotected sexual intercourse with a female who is pregnant or breastfeeding during the study.

Appendix 4 Composite Responses Index for Diffuse Cutaneous Systemic Sclerosis[12]/ [redacted]

ACR CRISS is a 2-step process.

Step 1: Subjects who develop new or worsening of cardiopulmonary and/or renal involvement due to systemic sclerosis are considered as not improved (irrespective of improvement in other core items) and assigned a probability of improving equal to 0.0. Specifically, if a subject develops any of the following

- New scleroderma renal crisis (See Appendix 16 for definition)
- Decline in %pFVC ≥ 15% (relative), confirmed by another %pFVC within a month, high resolution computer tomography (HRCT) to confirm ILD (if previous high-resolution computer tomography of chest did not show ILD) and %pFVC below 80% predicted*
- New onset of left ventricular failure (defined as left ventricular ejection fraction ≤ 45%) requiring treatment*
- New onset of pulmonary arterial hypertension (PAH) on right heart catheterization[37] requiring treatment.* PAH is defined as mean pulmonary artery pressure ≥ 20 mm Hg at rest and an end-expiratory pulmonary artery wedge pressure ≤ 15 mm Hg and a pulmonary vascular resistance > 3 Wood units

Step 2: For the remaining subjects, Step 2 involves computing the predicted probability of improving for each subject using the following equation (equation to derive predicted probabilities from a logistic regression model):

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

where ΔMRSS indicates the change in MRSS from baseline to follow-up, ΔFVC denotes the change in FVC% predicted from baseline to Follow- up, ΔPt-glob indicates the change in subject global assessment, ΔMD-glob denotes the change in physician global assessment, and ΔHAQ-DI is the change in HAQ-DI. All changes are absolute change ($Time_2$–$Time_{baseline}$).

*= Attributable to systemic sclerosis

[redacted]

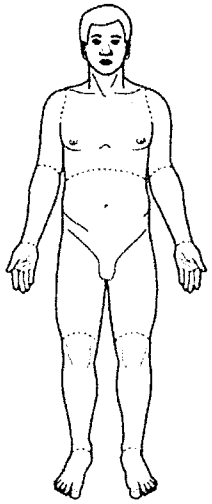
[redacted]

Appendix 5 Modified Rodnan Skin Score

Modified Rodnan Skin Score (MRSS) Document

Subject ID: _____

Date of Examination: _____



	Right				Left			
Fingers	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Hands	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Forearms	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Upper Arms	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Face			0☐	1☐	2☐	3☐		
Anterior Chest			0☐	1☐	2☐	3☐		
Abdomen			0☐	1☐	2☐	3☐		
Thighs	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Legs	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Feet	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Column Totals								
Total:								

Key: 0 – No Thickening 1 – Mild Thickening 2 – Moderate Thickening 3 – Severe Thickening

Notes:

Examiner:

Printed Name: _____

Signature: _____ Date: _____

Appendix 6 Scleroderma Health Assessment Questionnaire

HEALTH ASSESSMENT QUESTIONNAIRE

In this section we are interested in learning how your illness affects your ability to function in daily life.

Please check the response which best describes your usual abilities OVER THE PAST WEEK:

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

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

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

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

_____ Dressing and Grooming	_____ Eating
_____ Arising	_____ Walking

Please check the response which best describes your usual abilities OVER THE PAST WEEK:

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

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

_____ Raised toilet seat	_____ Bathtub bar
_____ Bathtub seat	_____ Long-handled appliances for reach
_____ Jar opener (for jars previously opened)	_____ Long-handled appliances in bathroom
	_____ Other (Specify: _____)

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

_____ Hygiene	_____ Gripping and opening things
_____ Reach	_____ Errands and chores

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

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

PLACE A VERTICAL (I) MARK ON THE LINE TO INDICATE THE SEVERITY OF THE PAIN.

NO PAIN	SEVERE PAIN

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

PLACE A VERTICAL (I) MARK ON THE LINE TO INDICATE THE LIMITATION OF ACTIVITY

INTESTINAL PROBLEMS DO NOT LIMIT ACTIVITIES — VERY SEVERE LIMITATION

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

PLACE A VERTICAL (I) MARK ON THE LINE TO INDICATE THE LIMITATION OF ACTIVITY

BREATHING PROBLEMS DO NOT LIMIT ACTIVITIES — VERY SEVERE LIMITATION

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

PLACE A VERTICAL (I) MARK ON THE LINE TO INDICATE THE LIMITATION OF ACTIVITY

RAYNAUD'S DOES NOT LIMIT ACTIVITIES — VERY SEVERE LIMITATION

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

PLACE A VERTICAL (I) MARK ON THE LINE TO INDICATE THE LIMITATION OF ACTIVITY

FINGER ULCERS DO NOT LIMIT ACTIVITIES — VERY SEVERE LIMITATION

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

PLACE A VERTICAL (I) MARK ON THE LINE TO INDICATE THE LIMITATION OF ACTIVITY

NO DISEASE — VERY SEVERE LIMITATION

Appendix 7 Patient Global Assessment

PATIENT GLOBAL ASSESSMENT

On a scale of 0-10, how was your overall health in the LAST WEEK? (Mark one box)

Excellent Extremely Poor

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

Appendix 8 Physician Global Assessment

PHYSICIAN GLOBAL ASSESSMENT

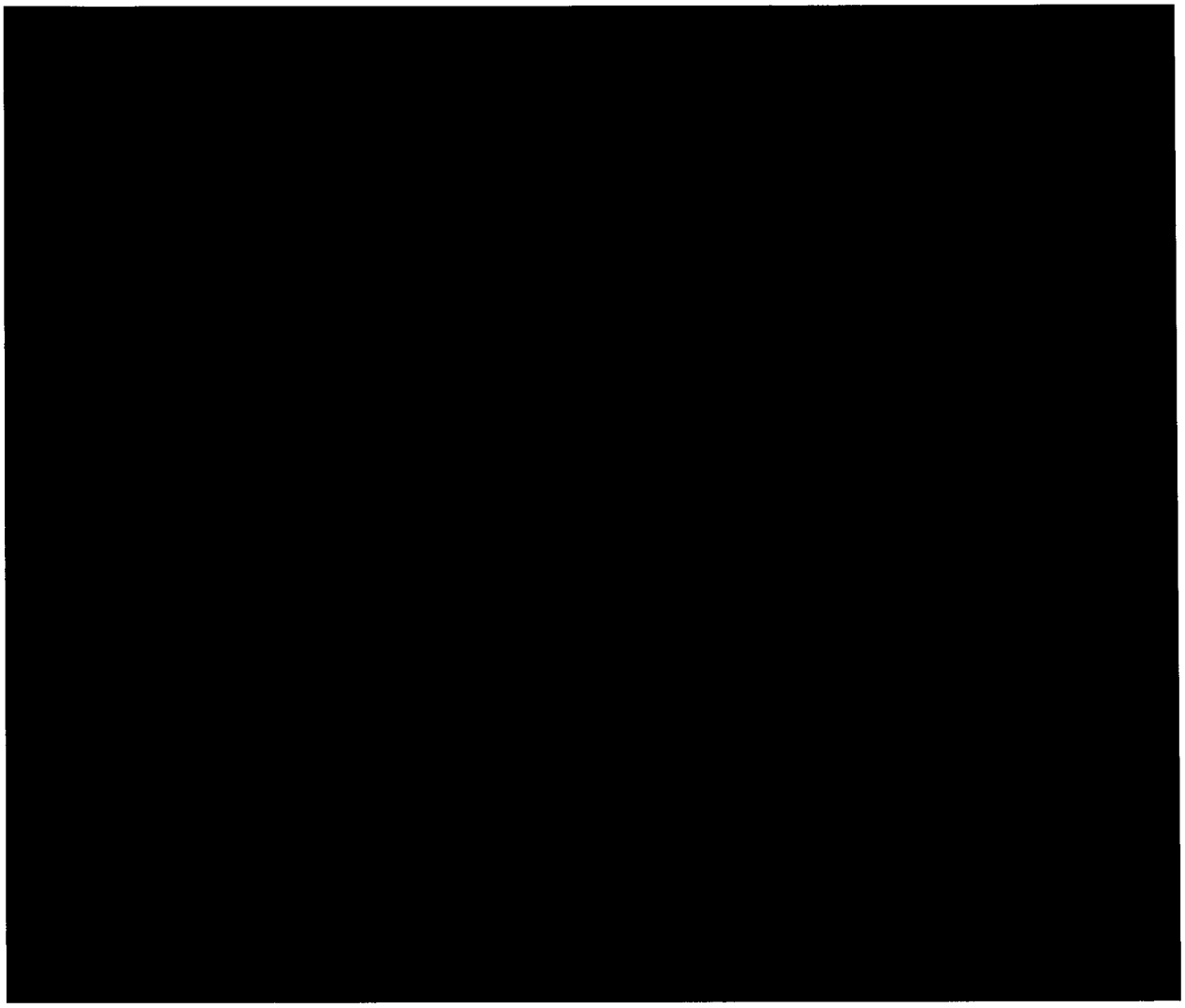
For a new patient to your clinic, please mark NOT KNOWN.
On a scale of 0-10, how was your patient's overall health in the LAST WEEK?
(Check one box)

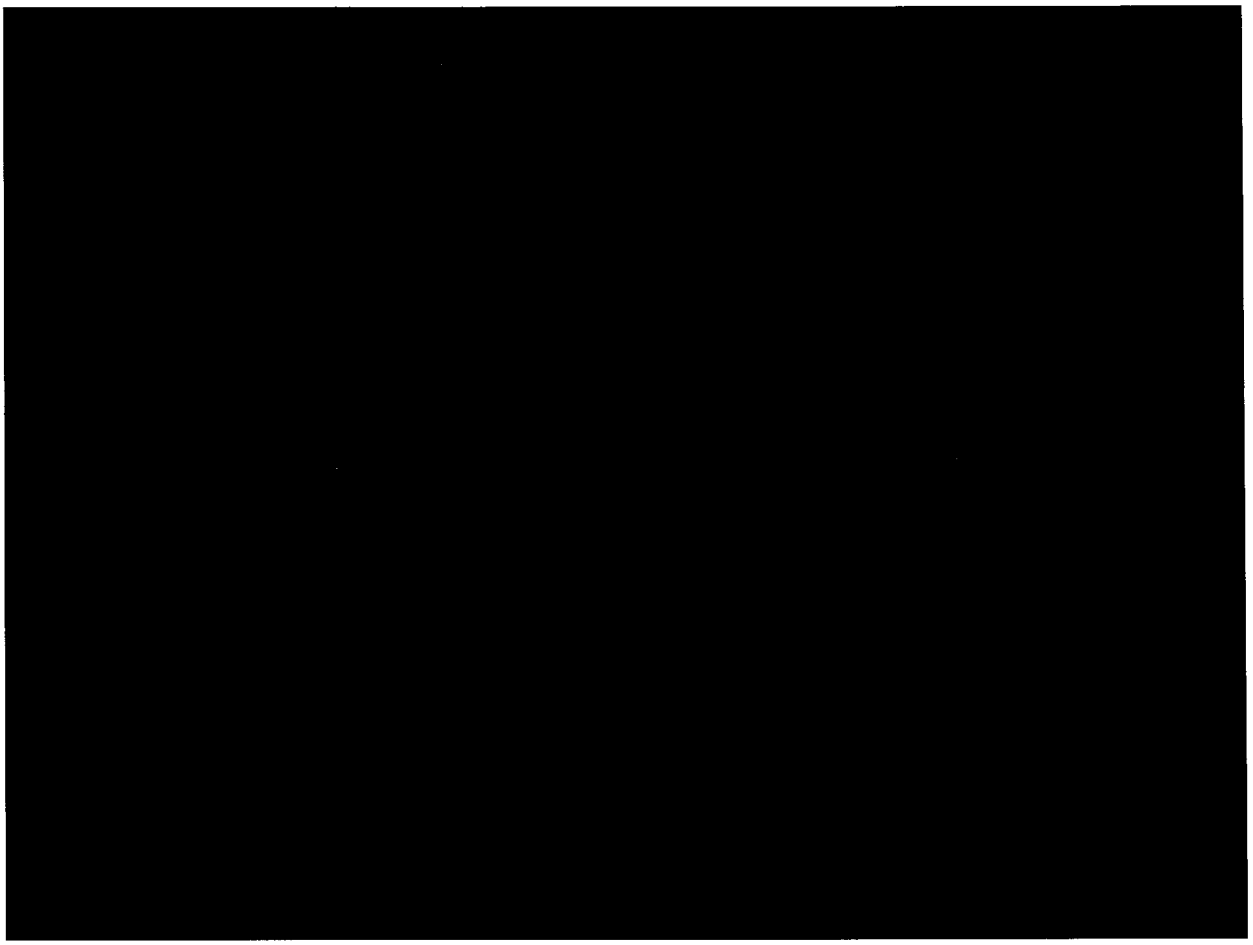
Excellent — Extremely Poor

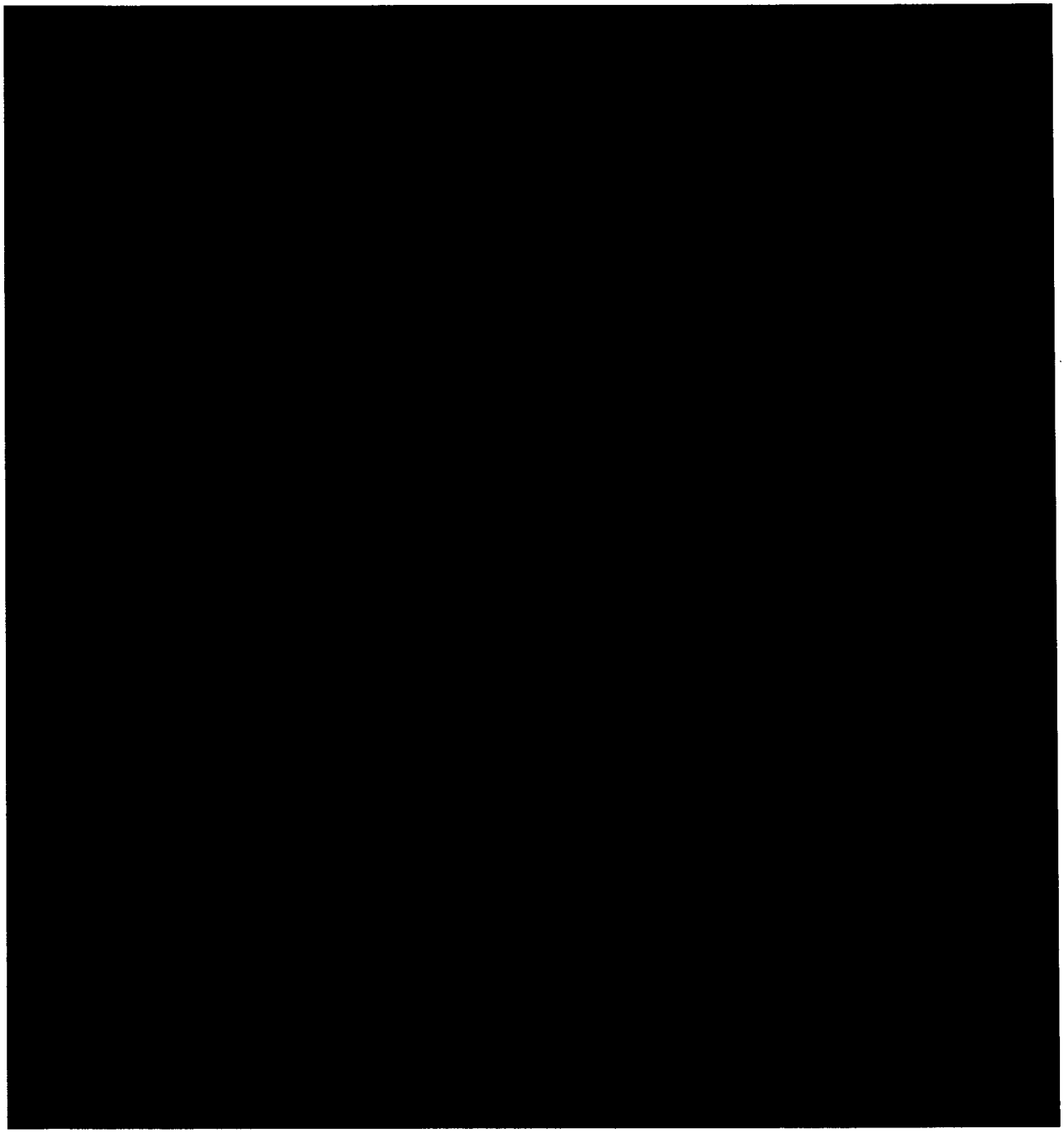
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Not Known	0	1	2	3	4	5	6	7	8	9	10

Appendix 9 [redacted]

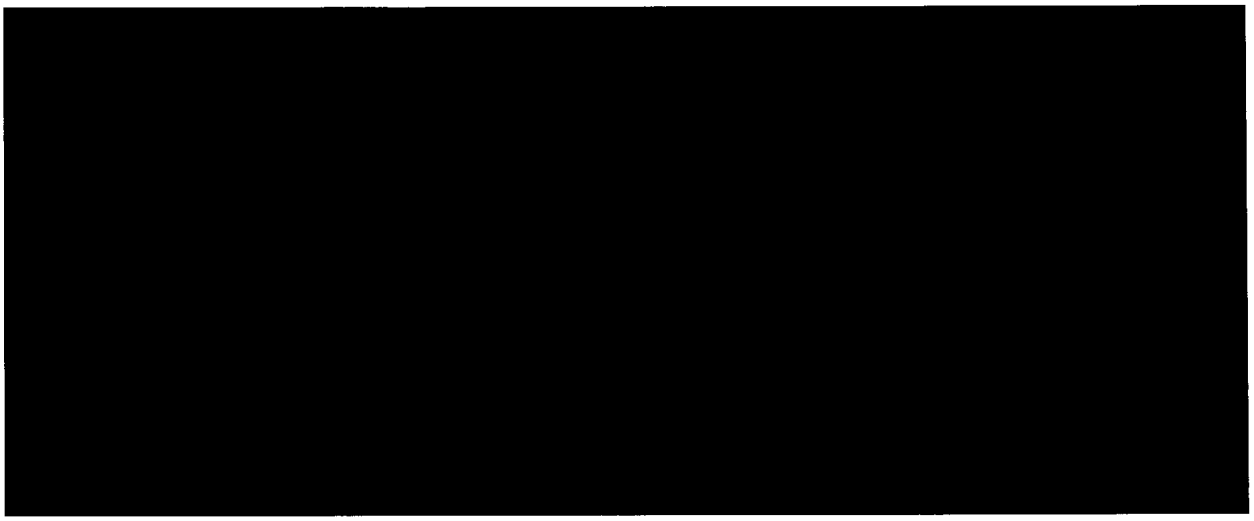
[redacted]







Appendix 10 Patient Global Impression of Change

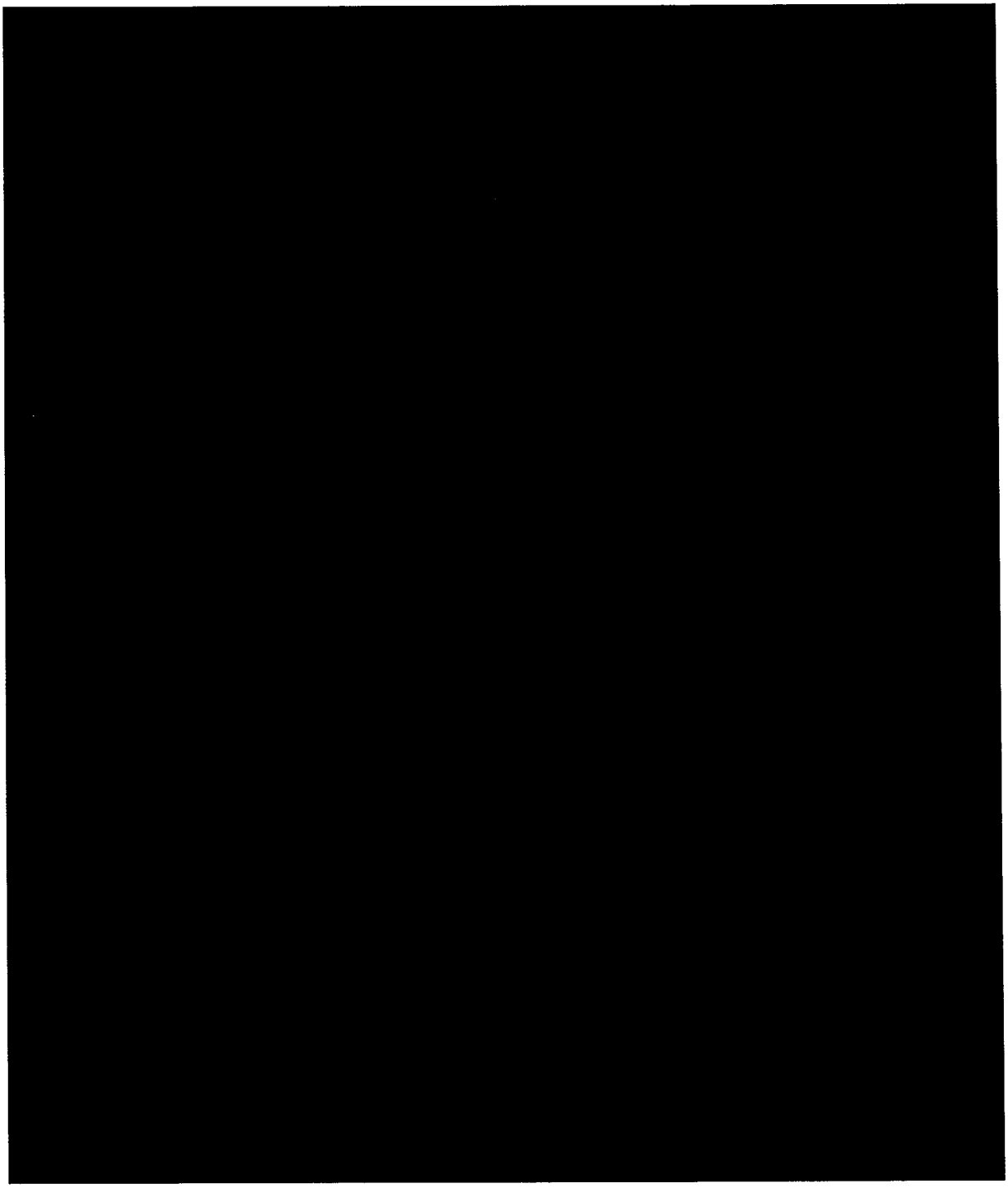


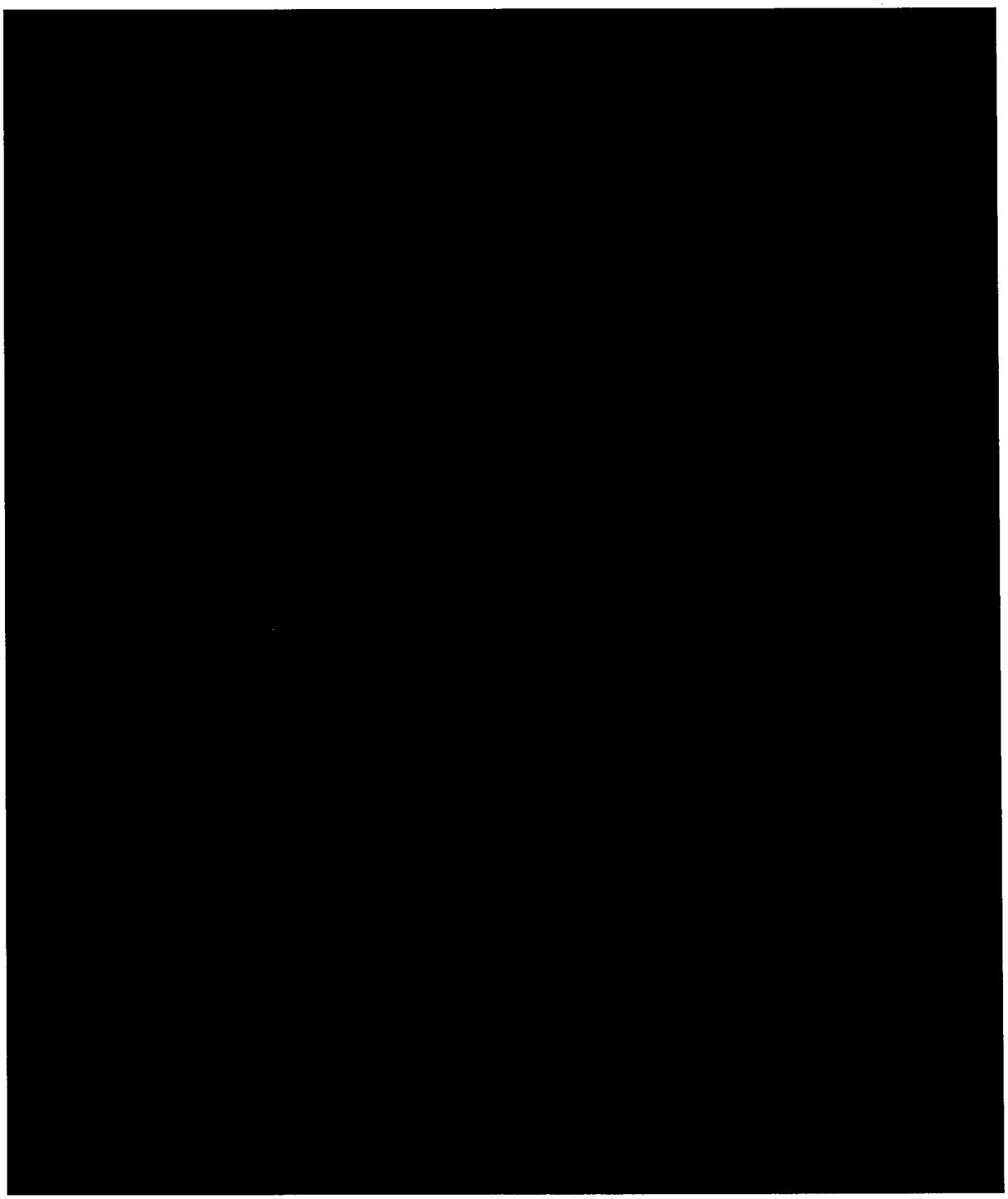
Appendix 12 [redacted]

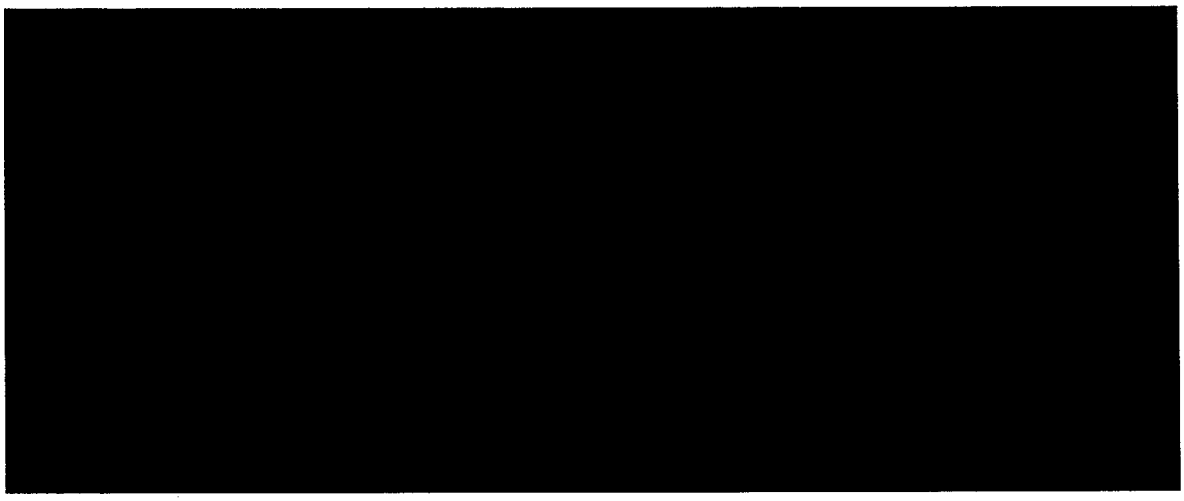
[redacted]

[redacted]

Appendix 13 [redacted]

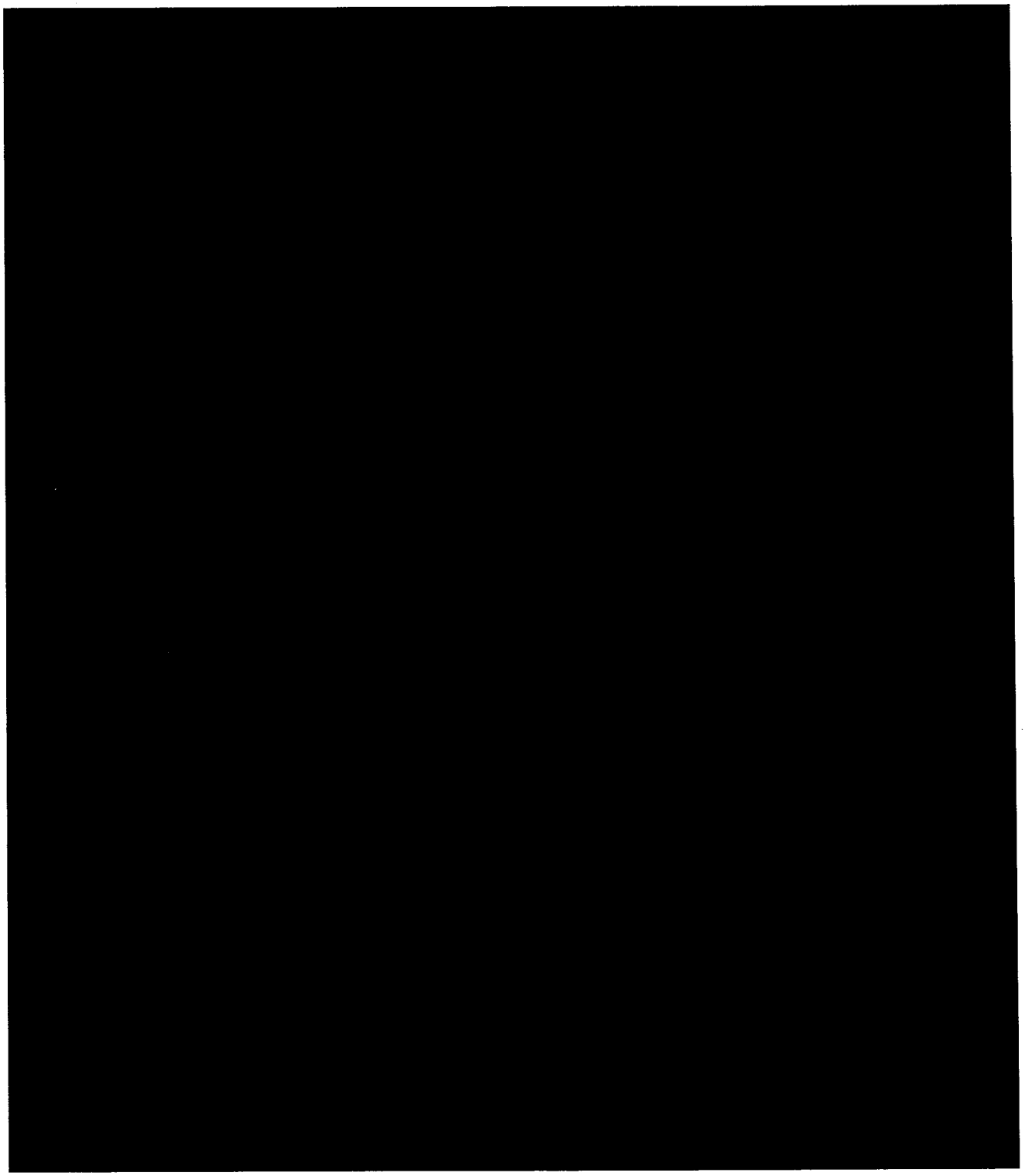




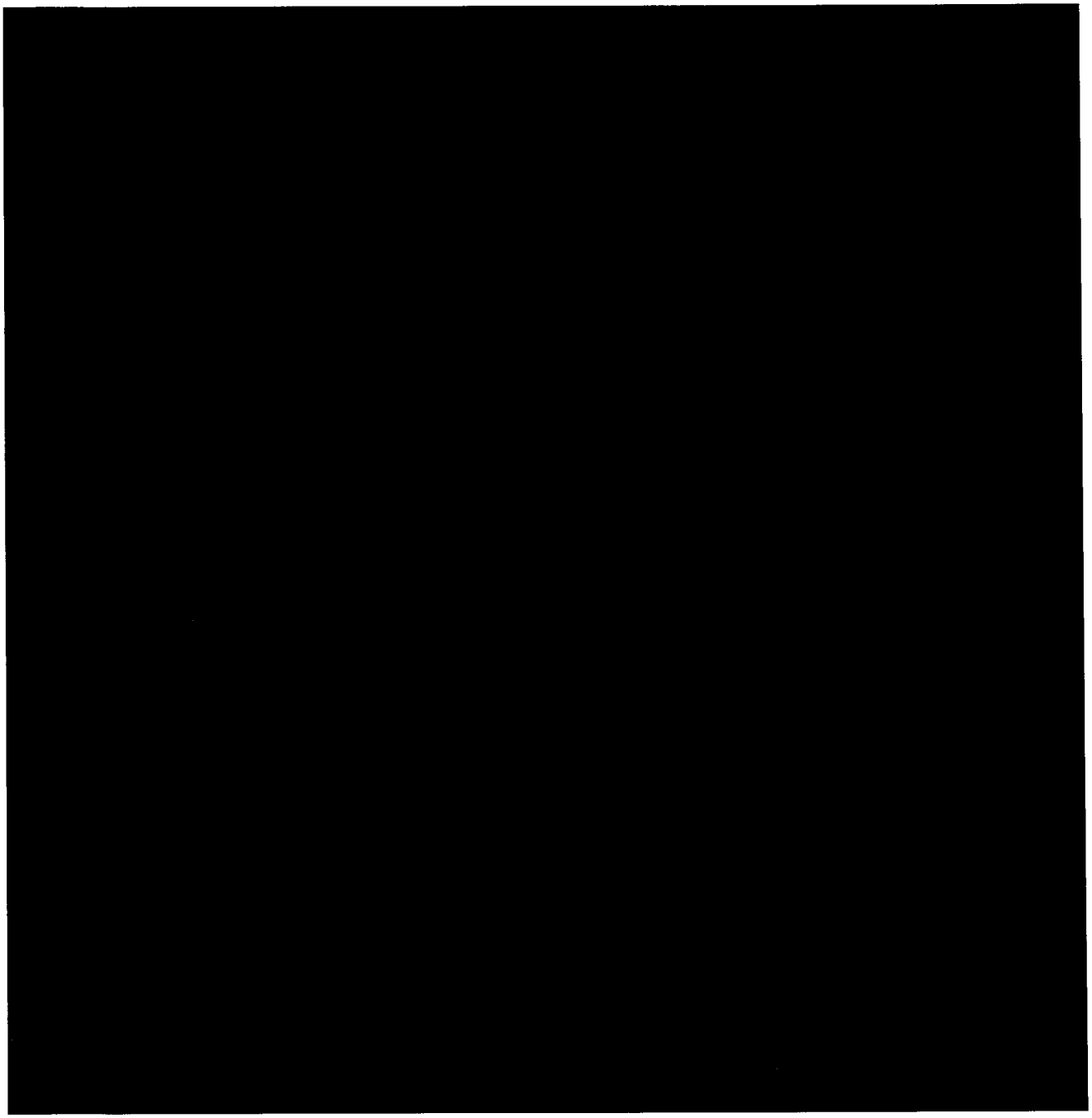


Appendix [redacted]

[redacted]



Appendix 15 [redacted]



Appendix 16 The Definition of Systemic Sclerosis Renal Crisis [38]

The criteria for scleroderma renal crisis as a renal manifestation of scleroderma.

Definitions assume findings are not explained by other medical conditions.

A. Hypertensive scleroderma renal crisis (fulfills both A1 and A2)

1. New onset hypertension; defined as any of the following:
   a) Systolic blood pressure ≥ 140 mg Hg
   b) Diastolic blood pressure ≥ 90 mg Hg
   c) Rise in systolic blood pressure ≥ 30 mm Hg
   d) Rise in diastolic blood pressure ≥ 20 mm Hg

AND

2. One (1) of the following five (5) features:
   a) Increase in serum creatinine by 50+% over baseline
   OR serum creatinine ≥ 120% of upper limit of normal for local laboratory
   b) Proteinuria ≥ 2+ by dipstick
   c) Hematuria ≥ 2+ by dipstick or ≥ 10 RBCs/HPF
   d) Thrombocytopenia: < 100,000 plts/mm^3
   e) Hemolysis defined as anemia not due to other causes and either of the following:
   (1) Schistocytes or other RBC fragments seen on blood smear
   (2) increased reticulocyte count

B. Normotensive scleroderma renal crisis (fulfills both B1 and B2)

1. Increase in serum creatinine >50% over baseline
   OR serum creatinine ≥ 120% of upper limit of normal for local laboratory

AND

2. One (1) of the following five (5) features:
   a) Proteinuria ≥ 2+ by dipstick
   b) Hematuria ≥ 2+ by dipstick or ≥ 10 RBCs/hpf
   c) Thrombocytopenia: < 100,000 /mm^3
   d) Hemolysis defined as anemia not due to other causes and either of the following:
   (1) Schistocytes or other rbc fragments seen on blood smear
   (2) Increased reticulocyte count
   e) Renal biopsy findings consistent with scleroderma renal crisis (microangiopathy)