Official Title:	A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Efficacy and Safety of Tocilizumab Versus Placebo in Patients With Systemic Sclerosis
NCT Number:	**NCT02453256**
Document Dates:	Protocol Amendment/Version 6: 05-May-17

PROTOCOL

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO ASSESS THE EFFICACY AND SAFETY OF TOCILIZUMAB VERSUS PLACEBO IN PATIENTS WITH SYSTEMIC SCLEROSIS**
PROTOCOL NUMBER:	WA29767
VERSION NUMBER:	6
EUDRACT NUMBER:	2015-000424-28
IND NUMBER:	112406
TEST PRODUCT:	Tocilizumab (RO4877533)
MEDICAL MONITOR:	[redacted]
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 28 February 2015
DATE AMENDED:	Version 2: 02 April 2015 Version 3: 12 July 2015 Version 4: 17 December 2015 Version 5: 06 September 2016 Version 6: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory (Clinical)	05-May-2017 23:47:30

PROTOCOL AMENDMENT, VERSION 6:
RATIONALE

Protocol WA29767 has been amended to address the following changes. These changes to the protocol, along with a rationale for each change, are summarized below:

- The scheduling of treatment discontinuation and follow-up visits has been clarified in Section 3.1.1 and Appendices 1–3.
- Language has been added to Section 3.1.2 to indicate that patients receiving escape therapy may continue to do so during the open-label period at the discretion of the investigator.
- The criterion regarding washout times has been removed from Section 4.3.4 to allow patients who discontinue study drug during the double-blind period (prior to Week 48) to participate in the open label period without having to first undergo washout of other systemic sclerosis treatments.
- Language has been added to clarify that patients who discontinue study drug prior to Week 48 and are eligible to receive open-label study drug at Week 48 must complete all Week 48 assessments per the Appendix 1 schedule of assessments (Section 4.3.4 and Appendix 3).
- Section 4.3.4 has been modified to indicate that patients who start other medications for systemic sclerosis between treatment discontinuation and Week 48 may remain on these medications during the open-label period at the discretion of the investigator.
- Language has been added to Section 4.3.4 to clarify that patients who discontinue study drug prior to Week 48 and do not participate in the open-label period should complete only the Appendix 3 reduced schedule of assessments (Section 4.3.4 and Appendix 3)
- Language regarding options for escape therapy during the open-label period has been added to Section 4.4.1.1.
- Language has been added to Section 4.5.2 to emphasize that the same assessor should conduct the modified Rodnan Skin Score evaluations for a given patient at all study visits.
- Section 4.5.12 has been updated to include information regarding repetition of pulmonary function tests in the event of over-reader rejection.
- Language has been added regarding tuberculosis testing (Sections 4.5.14 and 4.5.15 and Appendices 1– 2).
- Section 4.5.14 has been updated to clarify the testing requirements for C-Reactive Protein.
- The protocol has been revised to indicate that pregnancies will no longer be reported using the Pregnancy Report eCRF, but will be reported on the paper Clinical Trial Pregnancy Reporting Form and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form (Section 5.4.3.1).

- The protocol has been modified to reflect updates to the protocol template in the following sections:
  - The protocol has been modified to prohibit use of the term "sudden death" on the Adverse Event electronic Case Report Form (eCRF), unless it is combined with the presumed cause of death (e.g., "sudden cardiac death"), as use of the term "sudden death" will require the Sponsor to query the site for clarification on the cause of death (Section 5.3.5.8).
  - Section 5.3.5.11 has been modified to clarify the reporting of adverse events leading to hospitalization.
  - Language has been added to clarify that the Sponsor will review all protocol deviations, and prospective requests to deviate from the protocol are not allowed (Section 9.2).
  - The Web site URL for the "Roche Global Policy on Sharing of Clinical Trials Data" has been corrected (Section 9.5).
- The schedules of assessments for the double-blind period and the open-label period have been modified to make the assessments of vital signs, body weight, and IL-6 consistent (Appendix 1 and Appendix 2).
- ANA samples taken subsequent to the sample taken at baseline have been removed from the schedules of assessments as they are no longer deemed necessary (Appendix 1 and Appendix 2).
- Text was added to Appendix 2 to indicate that follow-up visits are not required for patients who transition to locally-provided tocilizumab at Week 96.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

PROTOCOL AMENDMENT, VERSION 6:
SUMMARY OF CHANGES

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

SECTION 3.1.1: Overview of Study

This Phase III, multicenter, randomized, double-blind, placebo-controlled, two-arm, parallel-group study is designed to assess the efficacy and safety of TCZ in patients with SSc. The study consists of two periods: a 48-week, double-blind, placebo-controlled period, followed by a 48-week open-label treatment period.…Approximately *212*~~210~~ patients with dcSSc will be enrolled at approximately *75*~~120~~ global sites. The study design is presented schematically in Figure 1.

All patients who discontinue study drug prematurely at any time during the study will undergo a treatment discontinuation (TD) visit as soon as possible after the decision to discontinue study drug. These patients *will also undergo follow-up assessments within 4 weeks of study drug discontinuation and at 8 weeks after study drug discontinuation.*

Patients who discontinue study drug during the double-blind period will be encouraged to remain in the study and undergo safety monitoring and key efficacy assessments at all remaining scheduled visits through Week 48. The schedule of assessments for patients who discontinue study drug is outlined in Appendix 3. These patients will be eligible to enter the open-label treatment period of the study at Week 48 and receive TCZ (as per Appendix 2), beginning at Week 48, if they meet specified eligibility criteria (described in Section 4.3.4). ~~All patients will undergo follow-up assessments within 4 weeks and at 8 weeks after study drug discontinuation.~~ For patients who discontinue study drug prematurely~~, a~~ *but continue study assessments per Appendix 3, TD visits and/or* follow-up visits may be combined with the next scheduled visit (as outlined in Appendix 3), provided that the timing of the scheduled visit coincides with the specified timing for the ~~follow up visit. In this case~~*TD or follow-up visit. If a TD visit is being combined with another visit, only the TD visit assessments need to be completed. If a follow-up visit is being combined with the next scheduled visit in Appendix 3*, the efficacy assessments required at the scheduled visit, as well as safety assessments from the follow-up visit will be performed.

Patients who discontinue study drug prematurely in both the double-blind period and the open-label period will undergo two sets of TD and follow up visits.

SECTION 3.1.2: Escape Therapy and Other Concomitant Treatments for SSc

Escape therapy will be available from Week 24 for patients with worsening of skin thickening, and from Week 16 for patients with decline in FVC (confirmed on two separate occasions within a 4-week period; see Section 4.4.1.1 for details). The

decision to initiate escape therapy will be based on predefined criteria, investigator judgment, and discussion with the Medical Monitor. Patients will continue to receive study drug in addition to escape therapy. Upon completion of the 48-week double-blind treatment period, patients receiving escape therapy in addition to study drug can enter the open-label treatment period to receive TCZ. *These patients may remain on escape therapy during the open-label period at the discretion of the investigator.*

SECTION 4.3.4: Open-Label Treatment for Patients Who Discontinue Study Drug in the Double-Blind Treatment Period

If a patient discontinues study drug prematurely during the double-blind treatment period of the study (prior to Week 48), they may be eligible to participate in the open-label treatment period of the study and receive TCZ (as per Appendix 2), beginning at Week 48, if they meet the following criteria:

- Adhered to the study visits shown in Appendix 3
- Did not receive any prohibited medication as described in Section 4.1.2
- ~~Adhered to appropriate washout times for other treatments as described in Section 4.1.2~~
- Did not develop a concurrent condition that would preclude participation as described in Section 4.1.2
- Did not develop a safety issue that would preclude receipt of TCZ as determined by the Principal Investigator and Medical Monitor
- Did not discontinue the study drug during the double-blind treatment period due to non-compliance

Patients who are eligible and wish to receive open-label study drug at Week 48 must complete all Week 48 assessments (as per Appendix 1). If these patients discontinue after TCZ treatment in the open-label period, they should undergo a second TD visit and complete the 4 and 8 week follow-up visits.

Patients who start other medications for systemic sclerosis (e.g., DMARDs) between treatment discontinuation and Week 48 may remain on these medications during the open-label period at the discretion of the investigator.

Patients who do not participate in the open-label period should complete only the reduced schedule of assessments (as per Appendix 3). These patients are not required to undergo a second TD visit or complete Week 4 or Week 8 follow-up visits.

SECTION 4.4.1.1: Escape Therapy for Worsening mRSS or FVC

Patients who initiate escape therapy during the double-blind period may remain on escape therapy during the open-label period, at the discretion of the investigator.

Patients may initiate escape therapy during the open-label period if they meet the escape therapy criteria.

SECTION 4.5.2: Dual Assessor Approach

To prevent potential unblinding because of observed efficacy and laboratory changes, a dual-assessor approach will be used to evaluate these data. *To ensure consistency of assessments and limit inter-observer variability, it is essential that the same assessor conduct the mRSS evaluations for a given patient at all study visits.* Details regarding the dual-assessor approach are provided in a separate manual.

SECTION 4.5.12: Pulmonary Function Tests

The acceptability of the FVC and DLco data, including the graphic representations of the maneuvers, will be determined centrally by over-readers blinded to treatment assignment. Calculations for the reproducibility of the acceptable maneuvers will be performed and reviewed centrally by the blinded over-readers.

The over-readers will state whether a session has been accepted or rejected. If rejected, the following sessions should be repeated within 4 weeks:

- *FVC session from Week 8 onwards*
- *DL_{CO} session at Week 48 and/or Week 96*
- *Session at any TD visit*

SECTION 4.5.14: Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- *TB testing at screening (see Section 4.5.15)*

Samples for the following laboratory tests will be sent to one or several central laboratories for analysis:

- Chemistry panel: ~~(serum or plasma)~~ BUN or urea, uric acid, creatinine, random glucose, potassium, sodium, chloride, calcium, phosphorus, total protein, albumin, creatine phosphokinase, C3, C4

The following samples will be sent to the Sponsor or a designee for analysis:

- Serum samples for analysis of the following PD biomarkers: IL-6, sIL-6R, CRP

  Central CRP will be blinded to the site and Sponsor for all post-baseline visits until after the primary analysis. Local CRP testing should only be performed if deemed clinically necessary by the investigator. Local CRP results should not be shared with the Sponsor or entered into the eCRF until after the primary analysis.

SECTION *4.5.15*: *Tuberculosis Screening*

All patients will be evaluated for TB at screening. Testing must be repeated at Week 36, and the result confirmed, prior to initiation of open-label TCZ at Week 48 (except for patients who discontinued study drug prematurely who had a TB test performed at the

TD visit). The test method (e.g. PPD or QuantiFERON® test) is at the discretion of the investigator.

Patients who test positive for TB at screening should be evaluated for evidence of active TB per local standard practice. A patient with a positive TB test may be eligible for study inclusion only if diagnosed with latent TB and treated per local standard practice.

Patients who test positive for TB at screening and were treated for latent TB must undergo repeat TB testing at the Week 36 visit. However, since no applicable clinical practice guidelines currently exist regarding how to further evaluate patients who have had a positive TB test, a clinical evaluation at Week 36 and prompt local review of the Week 48 HRCT to evaluate for any evidence of active TB is required. Investigators will be asked to confirm this assessment.

Patients who test negative for TB at screening must undergo repeat TB testing at the Week 36 visit. If the Week 36 visit TB test is positive, dosing of study drug must be interrupted and patients evaluated for evidence of active TB per local standard practice. If a patient is diagnosed with latent TB and has started TB treatment, the patient may recommence dosing with study drug.

SECTION 5.3.5.8: Deaths

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. ~~The term "sudden death" should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable.~~ If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. *The term "sudden death" should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").*

SECTION 5.3.5.11: Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., in-patient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

- ~~The following hospitalization scenarios are not considered to be adverse events~~*An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:*
- Hospitalization for respite care

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event

~~The following hospitalization scenarios are not considered to be serious adverse events, but should be reported as adverse events instead:~~*An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead.*

SECTION 5.4.3.1: Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 8 weeks after the last dose of study drug. ~~A Pregnancy Report eCRF should be completed by the investigator~~ *A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee* immediately (i.e., no more than 24 hours after learning of the pregnancy) *either by faxing or by scanning and emailing the form with use of the fax number or email address provided to investigators.*~~and submitted via the EDC system. A pregnancy report will automatically be generated and sent to Roche Safety Risk Management.~~ Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. *In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.*

~~In the event that the EDC system is unavailable, the Clinical Trial Pregnancy Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.~~

SECTION 9.2: PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. *The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require*

reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

SECTION 9.5: PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

~~http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf~~

http://www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

APPENDIX 1: Schedule of Assessments: Screening, Baseline, and Double-Blind Treatment Period

The schedule of assessments for the screening, baseline, and double-blind treatment period has been revised to reflect the changes to the protocol.

APPENDIX 2: Schedule of Assessments: Open-Label Treatment Period

The schedule of assessments for the open-label treatment period has been revised to reflect the changes to the protocol.

APPENDIX 3: Schedule of Assessments: Patients Who Have Discontinued Study Drug Prematurely

The schedule of assessments for patients who have discontinued study drug prematurely has been revised to reflect the changes to the protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO ASSESS THE EFFICACY AND SAFETY OF TOCILIZUMAB VERSUS PLACEBO IN PATIENTS WITH SYSTEMIC SCLEROSIS**
PROTOCOL NUMBER:	WA29767
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IND NUMBER:	112406
TEST PRODUCT:	Tocilizumab (RO4877533)
MEDICAL MONITOR:	[redacted]
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy as instructed by the Sponsor representative.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO ASSESS THE EFFICACY AND SAFETY OF TOCILIZUMAB VERSUS PLACEBO IN PATIENTS WITH SYSTEMIC SCLEROSIS**
PROTOCOL NUMBER:	WA29767
VERSION NUMBER:	6
EUDRACT NUMBER:	2015-000424-28
IND NUMBER:	112406
TEST PRODUCT:	Tocilizumab (RO4877533)
PHASE:	III
INDICATION:	Systemic sclerosis
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives

Efficacy Objectives

The primary efficacy objective for this study is as follows:

- To evaluate the efficacy of tocilizumab (TCZ) compared with placebo on skin sclerosis, as measured by modified Rodnan Skin Score (mRSS) at Week 48

The secondary efficacy objectives for this study are as follows:

- To evaluate the efficacy of TCZ compared with placebo on pulmonary function, as measured by forced vital capacity (FVC) at Week 48
- To evaluate the efficacy of TCZ compared with placebo on patient-reported outcomes (PROs), as measured by the Health Assessment Questionnaire Disability Index (HAQ-DI) and Patient's Global Assessment at Week 48
- To evaluate the efficacy of TCZ compared with placebo as measured by the Physician's Global Assessment at Week 48
- To evaluate the efficacy of TCZ compared with placebo by assessment of time to treatment failure (death, worsening of mRSS and/or FVC, or clinically significant systemic sclerosis [SSc] complication) up to Week 48

Safety Objectives

The safety objectives for this study are as follows:

- To evaluate the safety of TCZ compared with placebo, focusing on the nature, frequency, and severity of serious and non-serious adverse events, the frequency of SSc-related complications, and effects on vital signs, physical findings, and clinical laboratory results
- To evaluate the safety of TCZ compared with placebo by assessing the number of digital ulcers
- To assess the long-term safety of TCZ

Immunogenicity Objectives

The immunogenicity objectives for this study are as follows:

- To characterize the immunogenic potential of TCZ by measuring anti-TCZ antibodies
- To assess the potential relationship between development of anti-TCZ antibodies and efficacy, safety, or pharmacokinetic (PK) outcome measures

Pharmacodynamic Objectives

The pharmacodynamic (PD) objectives for this study are as follows:

- To compare changes in levels of PD biomarkers following treatment with TCZ versus placebo

Pharmacokinetic Objectives

The PK objectives for this study are as follows:

- To characterize the pharmacokinetics of TCZ
- To evaluate potential relationships between PK parameters for TCZ and efficacy, safety, or immunogenicity outcome measures

Exploratory Objectives

The exploratory objectives for this study are as follows:

- To evaluate the efficacy of TCZ compared with placebo on skin sclerosis, as measured by mRSS at Week 24
- To evaluate the efficacy of TCZ versus placebo measured by the proportion of responders as defined by the Combined Response Index for Systemic Sclerosis (CRISS) at Week 48
- To evaluate the efficacy of TCZ compared with placebo, as measured by the visual analog scale (VAS) component of the Scleroderma Health Assessment Questionnaire (SHAQ) at Weeks 24 and 48
- To evaluate the efficacy of TCZ compared with placebo, as measured by the Work Productivity and Activity Impairment—General Health (WPAI-GH) questionnaire at Weeks 24 and 48
- To evaluate the efficacy of TCZ compared with placebo, as measured by the EuroQol 5-Dimension Questionnaire with three levels of severity (EQ-5D-3L) at Weeks 24 and 48
- To evaluate the efficacy of TCZ compared with placebo, as measured by the Saint George's Respiratory Questionnaire (SGRQ) at Week 48
- To evaluate the effect of TCZ compared with placebo on fatigue as measured by Functional Assessment of Chronic Illness Therapy (FACIT)–Fatigue score at Week 48.
- To evaluate the efficacy of TCZ compared with placebo, as measured by the Scleroderma Skin Patient-Reported Outcome (SkinPRO) questionnaire at Week 48 (for North America only)
- To evaluate the efficacy of TCZ compared with placebo on the basis of change in pulmonary fibrosis, as determined using high-resolution computed tomography (HRCT) scans at Week 48
- To evaluate the efficacy of TCZ compared with placebo, as measured by diffusion capacity of the lung for carbon monoxide (DL_{CO}) at Week 48, and FVC at Week 24
- To evaluate the maintenance of efficacy of TCZ, as measured by mRSS and FVC at Week 96
- To assess whether non-inherited biomarkers are predictive of response to TCZ (i.e., predictive biomarkers), susceptibility to developing adverse events, or progression to a more severe disease state (i.e., prognostic biomarkers), can provide evidence of TCZ activity, or can increase the knowledge and understanding of disease biology

Study Design

Description of Study

This is a Phase III, multicenter, randomized, double-blind, placebo-controlled, two-arm, parallel-group study designed to assess the efficacy and safety of TCZ in patients with SSc.

Number of Patients

Approximately *212* patients with diffuse cutaneous systemic sclerosis (dcSSc) will be enrolled at approximately *75* global sites.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years at baseline (Day 1)
- Able to comply with the study protocol, in the investigator's judgment
- Diagnosis of SSc, as defined using the American College of Rheumatology [ACR]/European League Against Rheumatism [EULAR] criteria
- SSc disease duration of ≤ 60 months (defined as time from the first non–Raynaud phenomenon manifestation)
- mRSS of ≥ 10 and ≤ 35 units at screening
- Active disease that meets at least one of the following criteria at screening:
  - Disease duration of ≤ 18 months defined as time from the first non–Raynaud phenomenon manifestation
  - Increase in mRSS of ≥ 3 units compared with the most recent assessment performed within the previous 6 months
  - Involvement of one new body area and an increase in mRSS of ≥ 2 units compared with the most recent assessment performed within the previous 6 months
  - Involvement of two new body areas within the previous 6 months
  - Presence of at least one tendon friction rub
- Presence of at least one of the following at screening:
  - C-reactive protein (CRP) ≥ 0.6 mg/dL (≥ 6 mg/L)
  - Erythrocyte sedimentation rate (ESR) ≥ 28 mm/hr
  - Platelet count $\geq 330 \times 10^9$/L (330,000/μL)
- Uninvolved or mildly thickened skin at one of the following possible injection-site locations:
  - Front, middle region of the thigh
  - Abdomen, except for the 2-inch area directly around the navel
  - Outer area of the upper arm (if a patient caregiver is giving the injection)
- For women who are not postmenopausal (≥ 12 months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or use single or combined contraceptive methods that result in a failure rate of $< 1\%$ per year during the treatment period and for up to 3 months after the last dose of study drug

  Abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

  Examples of contraceptive methods with a failure rate of $< 1\%$ per year include tubal ligation, male sterilization, hormonal implants, established, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices.

  Alternatively, it is acceptable to combine the use of two methods (e.g., two barrier methods such as a condom and a cervical cap). Barrier methods must always be supplemented with the use of a spermicide.

- For men: agreement to remain abstinent or use contraceptive measures and agreement to refrain from donating sperm, as defined below:

  With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 8 weeks after the last dose of study drug.

  Abstinence is acceptable only if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

  Men must refrain from donating sperm during the treatment period and for at least 8 weeks after the last dose of study drug.

Exclusion Criteria

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

- Pregnant or lactating, or intending to become pregnant during the study
- Women who are not postmenopausal ($\geq$ 12 months of non-therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test at screening and a negative urine pregnancy test at baseline.
- Major surgery (including joint surgery) within 8 weeks prior to screening or planned major surgery within 12 months following randomization
- Skin thickening (scleroderma) limited to the face or areas distal to the elbows or knees at screening
- Rheumatic autoimmune disease other than SSc, including but not limited to rheumatoid arthritis (RA) (diagnosed using ACR/EULAR criteria), systemic lupus erythematosus, mixed connective tissue disorder, polymyositis, dermatomyositis, eosinophilic fasciitis, primary Sjögren's syndrome, and eosinophilic myalgia syndrome, as determined by the investigator
- Treatment with non-investigational or investigational cell-depleting therapies, including but not limited to alemtuzumab, anti-CD4, anti-CD5, anti-CD3, anti-CD19, and anti-CD20 within 18 months of baseline; or if treatment prior to 18 months from baseline, evidence of peripheral depletion of targeted lymphocyte subset at screening
- Previous treatment with chlorambucil, bone marrow transplantation, or total lymphoid irradiation
- Previous treatment with anti-IL6 therapy (including and not limited to TCZ)
- Previous treatment with thalidomide, antithymocyte globulin, plasmapheresis, or extracorporeal photopheresis
- Treatment with anakinra within 1 week prior to baseline
- Treatment with etanercept within 2 weeks prior to baseline
- Treatment with oral, intramuscular, or intravenous corticosteroids ($>$ 10 mg/day of prednisone or equivalent) within 2 weeks prior to baseline
- Treatment with methotrexate, hydroxychloroquine, cyclosporine A, azathioprine, mycophenolate mofetil, rapamycin, colchicine, or D-penicillamine, within 4 weeks prior to baseline
- Immunization with a live or live attenuated vaccine within 4 weeks prior to baseline
- Treatment with any investigational agent within 5 elimination half-lives of the investigational drug prior to baseline
- Chronic treatment with any of the following within 5 elimination half-lives of the drug prior to baseline:
  - Pirfenidone
  - Nintedanib
  - Endothelin-receptor antagonists, terguride
  - Tyrosine-kinase inhibitors (e.g., imatinib, nilotinib, dasatinib)
  - Janus-kinase inhibitors

- Treatment with IV prostacyclin within 1 week prior to baseline
- Treatment with ultraviolet phototherapy within 6 weeks prior to baseline
- Treatment with infliximab, certolizumab, golimumab, abatacept, or adalimumab within 8 weeks prior to baseline
- Treatment with cyclophosphamide within 6 months prior to baseline
- History of severe allergic or anaphylactic reactions to human, humanized, or murine monoclonal antibodies
- Evidence of moderately severe concurrent nervous system, renal, endocrine, or gastrointestinal (GI) disease not related to SSc, as determined by the investigator
- Pulmonary disease with FVC $\leq$ 55% of predicted (best of three acceptable and repeatable measurements as described in the site's Pulmonary Function Testing Manual)

  OR

  $DL_{CO} \leq 45\%$ of predicted (corrected for hemoglobin, and the average of the 2 highest acceptable and repeatable measurements as described in the Pulmonary Function Testing Manual)
- Class II or higher pulmonary arterial hypertension (PAH), as defined by the World Health Organization
- Evidence of other moderately severe pulmonary disease (e.g., asthma, emphysema), as determined by the investigator
- Cardiovascular disease with significant arrhythmia, congestive heart failure (New York Heart Association Class II–IV), unstable angina, uncontrolled hypertension, cor pulmonale, or symptomatic pericardial effusion
- History of myocardial infarction in the last 6 months prior to screening
- Current liver disease, as determined by the investigator
- History of diverticulitis or chronic ulcerative lower GI disease, such as Crohn disease, ulcerative colitis, or other symptomatic lower GI conditions that might predispose a patient to perforations
- Known active current or significant history of recurrent bacterial, viral, fungal, mycobacterial, or other infections, including but not limited to atypical mycobacterial disease, hepatitis B or C, herpes zoster, infected digital ulcers, and osteomyelitis
- Any major episode of infection requiring hospitalization or treatment with IV antibiotics within 4 weeks prior to screening or oral antibiotics within 2 weeks prior to screening
- Significant history of recurrent tuberculosis (TB), active TB requiring treatment within the previous 3 years, or untreated latent TB

  Patients should be screened for latent TB, and, if positive, will be eligible for the study after treatment per local standard practices.
- History of or currently active primary or secondary immunodeficiency
- Evidence of malignant disease, or malignancies diagnosed within the previous 5 years (with the exception of local basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix uteri that has been excised and cured)
- History of alcohol, drug, or chemical abuse within 1 year prior to screening
- Neuropathies or other conditions that might interfere with pain evaluation, as determined by the investigator

- At screening:

  Body weight $>$ 150 kg

  Glomerular filtration rate $<$ 45 mL/min

  Alanine transaminase (ALT) or Aspartate aminotransferase (AST) $>$ 1.5 $\times$ the upper limit of normal (ULN)

  Total bilirubin $>$ ULN

  Platelet count $<$ 100 $\times$ 10^9/L (100,000/μL)

  Hemoglobin $<$ 85 g/L (8.5 g/dL; 5.3 mmol/L)

  White blood cell (WBC) count $<$ 3.0 $\times$ 10^9/L (3000/μL)

  Absolute neutrophil count (ANC) $<$ 2.0 $\times$ 10^9/L (2000/μL)

  Absolute lymphocyte count $<$ 0.5 $\times$ 10^9/L (500/μL)

  Positive hepatitis B surface antigen or hepatitis C antibody

Length of Study

The length of the study, from screening of the first subject to the end of the study, is expected to be approximately 4 years.

End of Study

The end of the study will occur when the last participating patient completes the last scheduled visit of the follow-up period. This is expected to occur 2 years after the last patient is enrolled.

Outcome Measures

Efficacy Outcome Measures

The primary efficacy outcome measure for this study is as follows:

- Change in mRSS from baseline to Week 48

The secondary efficacy outcome measures for this study are as follows:

- Proportions of patients with $\geq$20%, $\geq$40%, and $\geq$60% improvement in mRSS at Week 48 compared with baseline
- Change in FVC from baseline to Week 48
- Change in HAQ-DI from baseline to Week 48
- Change in Patient's Global Assessment from baseline to Week 48
- Change in Physician's Global Assessment from baseline to Week 48
- Time to treatment failure, defined as the time from randomization to the time of one of the following events (whichever occurs first) during the 48-week double-blind treatment period:

  death,

  decline in percent-predicted FVC $>$10% relative to baseline,

  $>$20% increase in mRSS **and** an increase in mRSS of $\geq$5 points

  occurrence of a predefined SSc-related complication as adjudicated by the Clinical Adjudication Committee

Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Frequency of deaths
- Nature, frequency, and severity of adverse events
- Incidence of specific laboratory abnormalities
- Change from baseline in digital ulcer count

Immunogenicity Outcome Measures

The immunogenicity outcome measures for this study are as follows:

- Incidence of anti-TCZ antibodies during the study relative to the prevalence of anti-TCZ antibodies at baseline
- Correlation between anti-TCZ–antibody status and efficacy, safety, or PK outcome measures

Pharmacodynamic Outcome Measures

The PD outcome measure for this study is as follows:

- Predose ESR and serum IL-6, soluble IL-6 receptor (sIL-6R), and CRP levels at baseline and at subsequent timepoints after initiation of study drug

Pharmacokinetic Outcome Measures

The PK outcome measures for this study are as follows:

- Predose serum TCZ concentration at baseline and at specified timepoints thereafter
- Correlation between PK parameters for TCZ and efficacy, safety, or immunogenicity outcome measures

Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- Proportions of patients who achieve a response, as determined by the investigator using CRISS, at Week 48
- Change in the VAS component of the SHAQ from baseline to Week 24 and baseline to Week 48
- Change in WPAI-GH score from baseline to Week 24 and baseline to Week 48
- Change in EQ-5D-3L score from baseline to Week 24 and baseline to Week 48
- Change in total score and subscores of the SGRQ from baseline to Week 48.
- Change in total and domain scores of the SkinPRO questionnaire from baseline to Week 48 (for North America only)
- Change in FACIT-Fatigue score from baseline to Week 48.
- Change in HRCT fibrosis score from baseline (based on HRCT scan performed within 3 months prior to screening) to Week 48
- Change in DL_{CO} from baseline to Week 48
- Proportion of patients with $\geq$ 15% decline in observed DL_{CO} at Week 48
- Proportion of patients with $\geq$ 15% decline in percentage of predicted DL_{CO} at Week 48
- Change in FVC from baseline to Week 24
- Proportion of patients with $\geq$ 10% decline in observed FVC at Week 24 and at Week 48
- Proportion of patients with $\geq$ 10% decline in percentage of predicted FVC at Week 24 and at Week 48
- Change in mRSS from baseline to Week 24 and Week 96
- Change in observed and percentage of predicted FVC from baseline to Week 96
- Correlation between non-inherited biomarkers (serum levels of CCL18, sVCAM-1, COMP, and autotaxin; plasma levels of CXCL4; and whole blood gene signatures associated with plasmablasts and IFN) and efficacy, safety, PK, or immunogenicity outcome measures

Investigational Medicinal Products

Test Product (Investigational Drug)

Patients assigned to the TCZ group will receive *a single* subcutaneous (SC) *injection* of 162 mg of TCZ once weekly (QW) for 48 weeks during the double-blind treatment period. All patients will receive SC injections of 162 mg of TCZ QW for 48 weeks during the open-label treatment period.

Comparator

Patients assigned to the placebo group will receive SC injections of placebo QW for 48 weeks during the double-blind treatment period.

Non-Investigational Medicinal Products

From Week 24, escape therapy will be permitted for patients with worsening of skin thickening, and from Week 16, escape therapy will be permitted for patients with decline in FVC compared with baseline. Patients may receive other concomitant treatments for SSc, including treatments for new and existing organ complications.

Statistical Methods

Primary Analysis

The estimand of interest for the primary analysis is the difference between treatment arms in the mean change in the mRSS at Week 48 for the intent to treat (ITT) population. The study has been designed to continue to capture efficacy data on patients who discontinue study drug prematurely or receive escape therapies during the double-blind treatment period. These data will be included in the primary analysis.

Determination of Sample Size

A sample size of approximately 105 patients in the TCZ group and 105 patients in the placebo group (a total of 210 patients) will give power in the range of $>$75% to 80%, (allowing for an estimated patient dropout rate of approximately 15% to 20%) to detect a between-group difference of 3.55 units (common standard deviation of 8.43) in mean change in mRSS from baseline to Week 48 using a two-group t-test, with a 5% two-sided significance level. The minimal detectable difference in mRSS (smallest treatment difference that would give a statistically significant result) under these assumptions, and with a patient dropout rate of 20%, is approximately 2.6 units.

Interim Analyses

The Sponsor will define a futility analysis to which the Sponsor will remain blinded. The futility analysis will be conducted by an external statistical group and reviewed by the iDMC. The futility analysis will be based on the treatment difference for change from baseline in mRSS at Week 24; the stopping boundary will be determined by a beta spending function. The study will be stopped for futility if the endpoint meets the futility criterion.

The futility analysis will be conducted when approximately 76 patients have either reached the Week 24 visit or have withdrawn. Since a repeated measures analysis will be used for the futility criterion, partial data from additional patients enrolled at (but not yet completed) Week 24 will also be utilized in the analysis. Thus, although only approximately one-third of the patients will have reached Week 24, the timing of the futility analysis approximates half of the final expected information (I) at Week 24, where I is the inverse of the expected variance of the treatment difference when all patients have reached Week 24.

Full statistical details of the futility analysis, along with the rationale, and timing will be documented in the iDMC charter. The iDMC charter will be made available to the relevant health authorities.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACR	American College of Rheumatology
ALT	alanine transaminase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATS	American Thoracic Society
CRP	C-reactive protein
CRISS	Combined Response Index for Systemic Sclerosis
CYP450	cytochrome P450
dcSSc	diffuse cutaneous systemic sclerosis
DL_{CO}	diffusion capacity of the lung for carbon monoxide
DMARD	disease-modifying anti-rheumatic drug
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
ePRO	electronic patient-reported outcome
EQ-5D-3L	EuroQol 5-Dimension Questionnaire with three levels of severity
ERS	European Respiratory Society
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
EUSTAR	Scleroderma Trials and Research
FACIT	Functional Assessment of Chronic Illness Therapy
FDA	U.S. Food and Drug Administration
FVC	forced vital capacity
GI	gastrointestinal
HAQ-DI	Health Assessment Questionnaire Disability Index
HIPAA	Health Insurance Portability and Accountability Act
HN	home nursing
HRCT	high-resolution computed tomography
ICH	International Council for Harmonisation
iDMC	independent Data Monitoring Committee
IL-6	interleukin 6
IL-6R	interleukin 6 receptor
ILD	interstitial lung disease
IM	intramuscular
IMP	investigational medicinal product

Abbreviation	Definition
IND	Investigational New Drug (application)
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous
IxRS	interactive voice- or web-based response system
lcSSc	limited cutaneous systemic sclerosis
LDL	low-density lipoprotein
ΔLSM	least-squares mean
MCH	mean corpuscular hemoglobin
MCP	metacarpal phalangeal
mIL-6R	membrane-bound interleukin 6 receptor
mRSS	modified Rodnan Skin Score
NCEP	National Cholesterol Education Program
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHANES	National Health and Nutrition Examination Survey
PAH	pulmonary arterial hypertension
PD	pharmacodynamic
PFS	prefilled syringe
PIP	proximal interphalangeal
pcJIA	polyarticular course juvenile idiopathic arthritis
PK	pharmacokinetic
PRO	patient-reported outcome
PY	patient-years
QW	once weekly
RA	rheumatoid arthritis
RCR	Roche Clinical Repository
SAP	Statistical Analysis Plan
SC	subcutaneous
SGRQ	Saint George's Respiratory Questionnaire
SHAQ	Scleroderma Health Assessment Questionnaire
sIL-6R	soluble interleukin 6 receptor
sJIA	systemic juvenile idiopathic arthritis
SkinPRO	Scleroderma Skin Patient-Reported Outcome
SSc	systemic sclerosis
TB	tuberculosis
TCZ	tocilizumab

Abbreviation	Definition
ULN	upper limit of normal
VAS	visual analog scale
WPAI-GH	Work Productivity and Activity Impairment—General Health

1. BACKGROUND

1.1 BACKGROUND ON SYSTEMIC SCLEROSIS

Systemic sclerosis (SSc) is a rare connective tissue disease involving the skin, underlying tissues, blood vessels, and major organs. It is characterized by microvascular damage and fibrosis of the skin and of various internal organs. Although the pathogenesis of SSc is not yet fully understood, it is believed to result from increased systemic fibrosis, vasculopathy, and immune dysfunction.

1.1.1 Epidemiology

SSc is most prevalent in adults aged 30–50 (Chifflot et al. 2008; National Institute of Arthritis and Musculoskeletal and Skin Diseases 2012). SSc primarily affects women (Nikpour et al. 2014) and has an incidence and prevalence that varies by geographic region and ethnicity. In the United States, the incidence is estimated to be 14–21 cases per 1,000,000 in 1 year (Steen et al. 1997; Mayes et al. 2003; Barnes and Mayes 2012). Multiple population-based studies estimate the prevalence of SSc in the United States at 105–300 cases per 1,000,000 (Ranque and Mouthon 2010; Furst et al. 2012). In a systematic literature review, Chifflot et al. (2008) identified a north–south gradient of prevalence in Europe. There were fewer cases in England and Iceland compared with France and Greece (England: 88 cases per 1,000,000 in 2000; Iceland: 71 cases per 1,000,000 in 1990; France: 158 cases per 1,000,000 in 2001; Greece: 154 cases per 1,000,000 in 2002).

1.1.2 Clinical Manifestations

SSc is characterized by initial acral skin sclerosis of the hands, feet, and face that can progress to involve the entire body diffusely. There are two major subsets of patients, divided according to the extent of skin involvement: limited cutaneous system sclerosis (lcSSc) and diffuse cutaneous systemic sclerosis (dcSSc). dcSSc is associated with a greater extent of skin involvement, and often-rapid progression of internal organ manifestations. Patients who have early onset of disease often have a more severe course (Gabrielli et al. 2009). The extent and severity of skin sclerosis have been shown to be predictive of internal organ involvement and overall survival (Clements et al. 1995, 2000; Steen and Medsger 2001). In lcSSc, skin sclerosis is restricted to distal extremities; however, these patients also develop internal organ complications, most often interstitial lung disease and pulmonary hypertension. These complications often occur later in the disease compared to patients with dcSSc.

Raynaud phenomenon, one of the earliest and most common clinical symptoms, can result in digital pits, painful fingertip ulcers, and dry gangrene. About 50% of all patients with SSc will experience a digital ulcer at some stage in their disease course (Ennis et al. 2013). Infections are common complications of digital ulcers.

The gastrointestinal (GI) tract, heart, lungs, and kidneys are the internal organs with significant involvement in this disease. Reflux disease, heartburn, dysphagia, and

odynophagia are typical GI symptoms, with cardiac findings including arrhythmia, heart block, and pericardial effusions. Interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) are the two most common pulmonary manifestations of SSc. ILD develops in up to 75% of patients with SSc overall (Bussone and Mouthon 2011). Clinical symptoms include tachypnea, exertional dyspnea, and dry cough. PAH develops in approximately 20% of patients. Symptoms include dyspnea, fatigue, atypical chest pain, lower extremity swelling, and syncope. Renal crisis associated with SSc is characterized by sudden onset of arterial hypertension and rapidly progressive renal insufficiency. Renal, cardiac, and pulmonary involvement and complications are known predictors of mortality (Ioannidis et al. 2005).

Musculoskeletal involvement is more frequent than expected in patients with SSc and is a major cause of disability (Randone et al. 2008). Symptoms include myalgia, muscle weakness, arthralgia, and generalized fatigue. Approximately 20%–30% of patients have SSc-associated polyarthritis. The proximal interphalangeal (PIP) and metacarpal phalangeal (MCP) joints, wrist joints, and ankle joints are affected the most often. In contrast to other autoimmune diseases, joint effusions are not common, but thickening and fibrosis of the periarticular tissue may result in joint contractures. Flexion contractures of the fingers can lead to severe impairment of hand function and muscle weakness. Tendon friction rubs are palpable signs of overlying tendon sheath inflammation and/or fibrosis and occur most commonly at the fingers, wrists, elbows, knees, and ankles. They have been associated with active disease and are predictive of further disease progression. Friction rubs have been reported in approximately 20% of patients with diffuse cutaneous sclerosis and 40% of patients with disease duration of $<$5 years (Avouac et al. 2010).

Infections are a well-known disease complication in SSc. Risk factors for infection may include skin and internal organ system involvement, such as esophageal and pulmonary involvement, severe Raynaud phenomenon, severe calcinosis, and immunosuppressive treatments used for disease management (Juárez et al. 2003). In addition, infected ulcers and osteomyelitis were seen in patients in Study WA27788, an ongoing Phase II/III study of tocilizumab (TCZ) versus placebo in patients with SSc.

1.1.3 Mortality

The life expectancy for patients with SSc is reduced (Fett and Werth 2011). The mortality rate for patients with SSc is higher than the rate for patients with other rheumatic diseases, with a 10-year survival of $<$70% from the time of diagnosis (Steen and Medsger 2007). The primary causes of SSc-related deaths are pulmonary fibrosis, PAH, heart failure, and cardiac arrhythmia. Deaths not directly related to SSc are most frequently from infections, malignancies, and cardiovascular disease (Tyndall et al. 2010).

1.1.4 Treatment for Systemic Sclerosis

The treatment of patients with SSc can be challenging, given the heterogeneity of the disease. To date, no therapy has been shown to modify disease progression. However, recent advances have been made in the treatment of organ manifestations, and formal treatment guidelines have been published on the basis of both evidence from the literature and expert opinion (Kowal-Bielecka et al. 2009).

Several lines of evidence support the role of interleukin 6 (IL-6) in the pathogenesis of SSc, as presented in Section 1.2. Blockade of IL-6 may therefore be a treatment path for SSc. This evidence, along with the unmet medical need in patients with SSc, builds the framework for this study.

1.2 INTERLEUKIN-6 AS DRUG TARGET

The pro-inflammatory, multifunctional cytokine IL-6 is produced by a variety of cell types, including T cells, B cells, monocytes, fibroblasts, keratinocytes, and synovial and endothelial cells, leading to local production of IL-6 in joints affected by inflammatory processes such as rheumatoid arthritis (RA) and SSc. It has been shown to be involved in diverse physiological processes, such as T-cell activation, B-cell differentiation, induction of immunoglobulin secretion, acute-phase protein production, stimulation of hematopoietic precursor cell growth and differentiation, osteoclast differentiation from precursor cells, proliferation of hepatic, dermal, and neural cells, and bone and lipid metabolism (Dayer and Choy 2010). It exerts its effects through the IL-6 receptor (IL-6R), which is present both in soluble (sIL-6R) and membrane-bound (mIL-6R) forms.

In vitro data from fibroblast cultures (Duncan and Berman 1991; Atamas 2002) and in vivo data from animal models of SSc (Hasegawa 2006; Kitaba et al. 2012) support a pathogenic role of IL-6 in the development of fibrosis, the histologic correlate of sclerosis. Kitaba et al. (2012) demonstrated the effectiveness of a murine anti-IL-6R antibody in preventing development of skin fibrosis in a mouse model of SSc. The same antibody also showed efficacy for treatment of existing skin fibrosis in a bleomycin-induced mouse model for SSc.

Increased levels of circulating IL-6, elevated levels of IL-6 in bronchoalveolar lavage fluid, and overexpression of IL-6 in endothelial cells and fibroblasts from involved skin have all been reported in patients with SSc (Koch et al. 1993). Dermal fibroblasts from patients with SSc, compared with those from healthy controls, constitutively express higher levels of IL-6 (Kadono et al. 1998). In addition, serum IL-6 levels correlate with the modified Rodnan skin score (mRSS; Ong and Denton 2010), a validated measure of the extent and severity of skin sclerosis (Furst et al. 1998). Elevated serum IL-6 levels are also predictive of the extent and severity of skin involvement 3 years after disease onset (Ong and Denton 2010).

1.3 BACKGROUND ON TOCILIZUMAB

TCZ is a recombinant, humanized, anti-human monoclonal antibody of the IgG1 subclass directed against the IL-6R. Humanization was performed by grafting the complementary-determining region of the mouse anti-human IL-6R monoclonal antibody onto a human IgG1κ antibody framework, followed by transfection of both light- and heavy-chain genes into Chinese hamster ovary cells to produce a humanized antibody.

TCZ binds specifically to sIL-6R and mIL-6R and has been shown to inhibit both membrane-bound and IL-6–mediated *trans*-signaling through the IL-6R. As described previously, elevated tissue and serum levels of IL-6 have been implicated in the pathogenesis of SSc and are correlated with skin sclerosis, the hallmark of SSc disease. Thus, inhibition of the biological activity of IL-6 and/or its receptor represents a promising new approach for the treatment of SSc.

Intravenous (IV) TCZ has been approved in more than 100 countries, including the United States, Japan, and the European Union, for the treatment of moderate to severe RA. In several countries, including the United States and Canada, TCZ has been approved in combination with disease-modifying anti-rheumatic drugs (DMARDs) or as monotherapy at a recommended starting dose of 4 mg/kg followed by an increase to 8 mg/kg on the basis of clinical response (Actemra® [tocilizumab] Package Insert). In all other countries, including the European Union, TCZ has been approved at a dose of 8 mg/kg. The dose can be reduced to 4 mg/kg if necessary. IV TCZ has been approved in 3 regions so far, including the European Union, Switzerland, and Australia for the treatment of early RA. IV TCZ has also been approved for the treatment of systemic juvenile idiopathic arthritis (sJIA) in the United States and the European Union, as well as for sJIA, polyarticular course juvenile idiopathic arthritis (pcJIA), and Castleman's disease in India and Japan.

Subcutaneous (SC) TCZ has been approved in more than 10 countries, including the United States, Japan, and European Union, for the treatment of moderate to severe RA. In several countries, including the United States and Canada, TCZ has been approved in combination with DMARDs or as monotherapy at a recommended starting dose of 162 mg every 2 weeks (Q2W) followed by an increase to once weekly (QW) on the basis of clinical response. In other regions, including the European Union, TCZ has been approved at a dose of 162 mg QW. The dose can be reduced to Q2W if necessary.

Information on the safety and efficacy of TCZ in clinical studies is provided below. See the Tocilizumab Investigator's Brochure for information on nonclinical studies and additional details on clinical studies.

1.3.1 Clinical Safety and Immunogenicity of Tocilizumab in Patients with Rheumatoid Arthritis

1.3.1.1 Intravenous Administration

In patients with RA treated with IV TCZ, the most frequently reported adverse events by System Organ Class were infections and infestations, and GI disorders. The most frequently reported serious adverse events by System Organ Class were infections and infestations, of which pneumonia and cellulitis were the most common.

Clinically significant hypersensitivity events (defined as any adverse event within 24 hours of infusion, not deemed "unrelated" to trial treatment, and leading to treatment discontinuation) have been reported in 60 patients leading to a rate of 0.38 (95% CI: 0.29, 0.48) events per 100 PY. Anaphylaxis occurred in 8 patients.

1.3.1.2 Subcutaneous versus Intravenous Administration

In Study WA22762, patients received TCZ 162 mg SC QW plus placebo IV every 4 weeks (Q4W), or TCZ 8 mg/kg IV Q4W plus placebo SC QW in a double-blind fashion for 24 weeks, in combination with non-biologic DMARDs. All SC injections were given by prefilled syringe (PFS). At Week 24, all patients were re-randomized to open-label TCZ 162 mg SC QW or TCZ 8 mg/kg IV Q4W for 72 weeks.

The safety profiles of TCZ SC and TCZ IV were similar in Study WA22762, with the exception of injection-site reactions. At Week 24, injection-site reactions were more common in the SC arm than in the IV arm (treated with SC placebo; 57.97 vs. 32.59 events per 100 PY). Clinically significant hypersensitivity reactions occurred at a rate of 4.16 per 100 patient-years (PY) in the IV arm and 2.07 per 100 PY in the SC arm. At Week 97, the rate of injection-site reactions per 100 PY was 26.05 in the SC arm, 33.63 in the IV arm, 93.45 in the IV-to-SC arm, and 0 in the SC-to-IV arm. The rate of clinically significant hypersensitivity reactions was comparable in the SC and IV arms at Week 97. There were no events of anaphylaxis during the 2-year study.

During the study, serious adverse events occurred at similar rates in the SC arm and the IV arm (14.61 vs. 15.43 per 100 PY), with the most common events being infections (3.95 vs. 3.92 per 100 PY). The rate of deaths per 100 PY was 0.39 in the SC arm, 0.49 in the IV arm, 0.78 in the IV-to-SC arm, and 0 in the SC-to-IV arm.

Decreased mean platelet count and neutrophil count occurred in both the SC arm and IV arm, but mean levels remained within the normal range. Decreases to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade 1 or 2 values were numerically greater in the SC arm than in the IV arm. At Week 97, analysis of laboratory parameters showed that cases of neutropenia, leukopenia, and thrombocytopenia were comparable across all four treatment arms. Shifts in laboratory parameters for alanine transaminase (ALT), aspartate aminotransferase (AST), total bilirubin, and alkaline phosphatase levels were similar in both the SC and IV treatment arms; although adverse shifts in total cholesterol,

low-density lipoprotein (LDL) cholesterol, and triglycerides were numerically more frequent in the SC arm compared with the IV arm.

The proportion of patients who developed anti-TCZ antibodies through Week 97 was consistently low across all four treatment arms (range, 0%–1.6%). Among the patients who developed anti-TCZ antibodies, only 1 patient in the IV arm had a clinically significant hypersensitivity reaction and 2 patients in the SC arm experienced injection-site reactions. Among patients across all treatment arms who developed anti-TCZ antibodies with neutralizing potential (range, 0%–1.3%), none were classified as having loss of efficacy or withdrew because of lack of efficacy.

1.3.2 Clinical Studies in Patients with Systemic Sclerosis

Efficacy and safety data are available from Study WA27788, an ongoing Phase II/III, randomized, double-blind study of 87 patients with SSc who were treated with SC injections of TCZ 162 mg or placebo.

1.3.2.1 Clinical Safety and Immunogenicity of Tocilizumab in Patients with Systemic Sclerosis

The overall safety profile for TCZ in SSc, emerging after 48 weeks of treatment in Study WA27788, is consistent with the natural history of SSc and the known safety profile for TCZ. Treatment with TCZ was generally well tolerated. Except for a higher incidence of serious infections with TCZ, the observed adverse event profile was comparable between the placebo and active treatment arms. No new or unexpected safety findings were observed.

Adverse events and serious adverse events were reported in 90.9% and 34.1%, respectively, of placebo-treated patients compared with 97.7% and 32.6%, respectively, of TCZ-treated patients. Four deaths were reported in the first 48 weeks of Study WA27788 (1 in the placebo arm and 3 in the TCZ arm). The death in the placebo arm was attributed to cardiac failure, and the deaths in the TCZ arm were attributed to lung infection (considered to be related to TCZ), arrhythmia (considered to be unrelated to TCZ), and multi-organ failure (considered to be unrelated to TCZ).

Injection-site reactions occurred in 4.5% of placebo-treated patients and 7.0% of TCZ-treated patients. Injection-site reactions were reported in 2 placebo-treated patients (events of bruising and hematoma) and 3 TCZ-treated patients (2 patients with erythema and 1 with rash and contusion).

Hypersensitivity events were defined as adverse events occurring immediately after or within 24 hours of the end of injection (excluding injection-site reaction events) that were not deemed to be unrelated to study drug. According to this definition, over the 48-week treatment period, 3 patients (6.8%) in the placebo arm and 6 patients (14.0%) in the TCZ arm experienced a hypersensitivity event. The reported events on TCZ were fatigue, pruritus, headache, somnolence, tension headache, hot flush, vertigo, and pollakiuria.

There were no clinically significant hypersensitivity events. There were no events of anaphylaxis.

Serious infections were more common in the TCZ arm (7 patients; 16.3%) than in the placebo arm (2 patients; 4.5%). A total of 8 events of serious infections were considered to be related to study drug: 6 events in TCZ-treated patients (lung infection, infected skin ulcer [2 events in the same patient], osteomyelitis in 2 different patients, and sepsis) and 2 events in placebo-treated patients (lower respiratory tract infection and osteomyelitis). None of the serious infections were associated with neutropenia.

There were no events of GI perforation, demyelination, or malignancy.

Four patients in the placebo arm and 5 patients in the TCZ arm discontinued because of adverse events.

At Week 48, 1 TCZ-treated patient had tested positive for neutralizing anti-TCZ antibodies. The patient completed 96 weeks of treatment with TCZ and did not experience obvious worsening of mRSS after developing anti-TCZ antibodies. The patient did not experience any adverse events indicative of a hypersensitivity reaction.

1.3.2.2 Clinical Efficacy of Tocilizumab in Patients with Systemic Sclerosis

The primary endpoint for Study WA27788 is change in the mRSS at Week 24. The analysis at 24 weeks showed a numerically but not statistically significantly greater improvement in mRSS with TCZ versus placebo treatment (TCZ, −3.92; placebo, −1.22; adjusted difference in least-squares mean [ΔLSM], −2.70 [95% confidence interval [CI]: −5.85, 0.45]; p = 0.0915). Consistent with the Week 24 results, there was a numerically but not statistically significantly greater improvement in mRSS with TCZ versus placebo treatment at Week 48 (TCZ, −6.33; placebo, −2.77; ΔLSM, −3.55 [95% CI: −7.23, 0.12], p = 0.0579). A greater proportion of patients on TCZ compared with placebo showed benefit on an individual patient level, because more TCZ-treated than placebo-treated patients showed at least a 20%, 40%, or 60% reduction in mRSS at Week 48: in the TCZ arm, 17 (39.5%), 9 (20.9%), and 5 (11.6%) patients improved by at least 20%, 40%, or 60%, respectively, compared with 12 (27.3%), 3 (6.8%), and 0 (0%), respectively, in the placebo arm.

Clinical improvements in most patient- and physician-reported outcomes were observed over the 48-week treatment period. However, none of these results achieved statistical significance. A worsening in the Health Assessment Questionnaire Disability Index (HAQ-DI) was noted in the placebo arm, whereas in the TCZ arm no change from baseline was apparent at Week 48 (TCZ, −0.002; placebo, 0.205, ΔLSM = −0.207 [95% CI: −0.471, 0.056]; p = 0.1212). There was a greater improvement in Physician's Global Assessment (TCZ, −18.41; placebo, −9.39, ΔLSM = −9.02 [95% CI: −19.04, 1.00]; p = 0.0768) and in Patient's Global Assessment (TCZ, −11.00; placebo, −2.70,

ΔLSM $= -8.30$ [95% CI: -19.31, 2.71]; $p = 0.1371$) in the TCZ arm compared with the placebo arm at Week 48.

Exploratory analyses of forced vital capacity (FVC) data from Study WA27788 showed that at Week 48 there was a decline of 6.6% (SD, 9.4%) from baseline in percent-predicted FVC in the placebo arm compared with a 2.1% (SD, 4.8 %) decline in the TCZ arm. In addition, 28.1% of placebo-treated patients (9 of 32 patients) compared with 10.0% of TCZ-treated patients (3 of 30 patients) experienced a decline of ≥ 10 % in observed FVC at Week 48 compared with baseline.

1.4 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

SSc is a rare and devastating disease with no approved treatment options. To date, no therapy has been shown to modify overall disease progression in SSc. The data from Study WA27788, a double-blind, placebo-controlled study, demonstrated a clinically meaningful effect of TCZ on mRSS and FVC, as well as improvements in HAQ-DI, Physician's Global Assessment, and Patient's Global Assessment at Week 48. This Phase III study is designed to confirm clinically and statistically the findings from Study WA27788. Overall, no new or unexpected safety signals were observed in Study WA27788. The benefit–risk profile for TCZ in SSc is considered to be positive on the basis of clinically meaningful, albeit not statistically significant, effects of TCZ on skin sclerosis and pulmonary function, the concordance of positive clinical and patient-reported outcomes (PROs), as well as the absence of safety findings that would be prohibitive of further development.

2. OBJECTIVES

This study will evaluate the efficacy and safety of TCZ compared with placebo in patients with SSc. Specifically, 210 patients with dcSSc will be enrolled in this study. Objectives and corresponding outcome measures for the study are outlined below.

2.1 EFFICACY OBJECTIVES

The primary efficacy objective for this study is as follows:

- To evaluate the efficacy of TCZ compared with placebo on skin sclerosis, as measured by mRSS at Week 48

The secondary efficacy objectives for this study are as follows:

- To evaluate the efficacy of TCZ compared with placebo on pulmonary function, as measured by FVC at Week 48
- To evaluate the efficacy of TCZ compared with placebo on PROs, as measured by the HAQ-DI and Patient's Global Assessment at Week 48
- To evaluate the efficacy of TCZ compared with placebo, as measured by the Physician's Global Assessment at Week 48

- To evaluate the efficacy of TCZ compared with placebo by assessment of time to treatment failure (death, worsening of mRSS and/or FVC [see Section 4.4.1.1], or clinically significant SSc complication) up to Week 48

2.2 SAFETY OBJECTIVES

The safety objectives for this study are as follows:

- To evaluate the safety of TCZ compared with placebo, focusing on the nature, frequency, and severity of serious and non-serious adverse events, the frequency of SSc-related complications, and effects on vital signs, physical findings, and clinical laboratory results
- To evaluate the safety of TCZ compared with placebo by assessing the number of digital ulcers
- To assess the long-term safety of TCZ

2.3 IMMUNOGENICITY OBJECTIVES

The immunogenicity objectives for this study are as follows:

- To characterize the immunogenic potential of TCZ by measuring anti-TCZ antibodies
- To assess the potential relationship between development of anti-TCZ antibodies and efficacy, safety, or pharmacokinetic (PK) outcome measures

2.4 PHARMACODYNAMIC OBJECTIVE

The pharmacodynamic (PD) objective for this study is as follows:

- To compare changes in levels of PD biomarkers following treatment with TCZ versus placebo

2.5 PHARMACOKINETIC OBJECTIVES

The PK objectives for this study are as follows:

- To characterize the pharmacokinetics of TCZ
- To evaluate potential relationships between PK parameters for TCZ and efficacy, safety, or immunogenicity outcome measures

2.6 EXPLORATORY OBJECTIVES

The exploratory objectives for this study are as follows:

- To evaluate the efficacy of TCZ compared with placebo on skin sclerosis, as measured by mRSS at Week 24
- To evaluate the efficacy of TCZ versus placebo measured by the proportion of responders as defined by the Combined Response Index for Systemic Sclerosis (CRISS) at Week 48
- To evaluate the efficacy of TCZ compared with placebo, as measured by the visual analog scale (VAS) component of the Scleroderma Health Assessment Questionnaire (SHAQ) at Weeks 24 and 48

- To evaluate the efficacy of TCZ compared with placebo, as measured by the Work Productivity and Activity Impairment—General Health (WPAI-GH) questionnaire at Weeks 24 and 48
- To evaluate the efficacy of TCZ compared with placebo, as measured by the EuroQol 5-Dimension Questionnaire with three levels of severity (EQ-5D-3L) at Weeks 24 and 48
- To evaluate the efficacy of TCZ compared with placebo, as measured by the Saint George's Respiratory Questionnaire (SGRQ) at Week 48
- To evaluate the effect of TCZ compared with placebo on fatigue as measured by Functional Assessment of Chronic Illness Therapy (FACIT)–Fatigue score at Week 48.
- To evaluate the efficacy of TCZ compared with placebo, as measured by the Scleroderma Skin Patient-Reported Outcome (SkinPRO) questionnaire at Week 48 (for North America only)
- To evaluate the efficacy of TCZ compared with placebo on the basis of change in pulmonary fibrosis, as determined using high-resolution computed tomography (HRCT) scans at Week 48
- To evaluate the efficacy of TCZ compared with placebo, as measured by diffusion capacity of the lung for carbon monoxide (DL_{CO}) at Week 48 and FVC at Week 24
- To evaluate the maintenance of efficacy of TCZ, as measured by mRSS and FVC at Week 96
- To assess whether non-inherited biomarkers are predictive of response to TCZ (i.e., predictive biomarkers), susceptibility to developing adverse events, or progression to a more severe disease state (i.e., prognostic biomarkers), can provide evidence of TCZ activity, or can increase the knowledge and understanding of disease biology

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

3.1.1 Overview of Study

This Phase III, multicenter, randomized, double-blind, placebo-controlled, two-arm, parallel-group study is designed to assess the efficacy and safety of TCZ in patients with SSc. The study consists of two periods: a 48-week, double-blind, placebo-controlled period, followed by a 48-week open-label treatment period. Patients will be randomized in a 1:1 ratio to receive SC injections of 162 mg of TCZ QW or placebo QW for 48 weeks during the double-blind treatment period. During the open-label treatment period, all patients will receive SC injections of 162 mg of TCZ QW for up to 48 weeks. Patients receive their first dose of open-label treatment at Week 48. Approximately *212* patients with dcSSc will be enrolled at approximately *75* global sites. The study design is presented schematically in Figure 1.

The screening visit may occur up to 40 days prior to the baseline visit (Day 1). Patients will be randomized at Day 1 through an interactive voice- or Web-based response system (IxRS). Randomization will be centralized and stratified by IL-6 level (<10; ≥ 10 pg/mL) at screening.

Efficacy parameters will be assessed from baseline through Week 96, as described in the schedules of assessments (see Appendix 1–Appendix 3). The primary analysis will occur after all patients have completed the Week 48 visit.

All patients will be closely monitored for adverse events throughout the study and for at least 8 weeks after the last dose of study drug (see Section 5.3.1). Adverse events will be graded according to the NCI CTCAE, Version 4.0.

All patients who discontinue study drug prematurely at any time during the study will undergo a treatment discontinuation (TD) visit as soon as possible after the decision to discontinue study drug. These patients *will also undergo follow-up assessments within 4 weeks of study drug discontinuation and at 8 weeks after study drug discontinuation.*

Patients who discontinue study drug during the double-blind period will be encouraged to remain in the study and undergo safety monitoring and key efficacy assessments at all remaining scheduled visits through Week 48. The schedule of assessments for patients who discontinue study drug is outlined in Appendix 3. These patients will be eligible to enter the open-label treatment period of the study at Week 48 and receive TCZ (as per Appendix 2), beginning at Week 48, if they meet specified eligibility criteria (described in Section 4.3.4). For patients who discontinue study drug prematurely *but continue study assessments per Appendix 3, TD visits and/or* follow-up visits may be combined with the next scheduled visit (as outlined in Appendix 3), provided that the timing of the scheduled visit coincides with the specified timing for the *TD or follow-up visit. If a TD visit is being combined with another visit, only the TD visit assessments need to be completed. If a follow-up visit is being combined with the next scheduled visit in Appendix 3*, the efficacy assessments required at the scheduled visit, as well as safety assessments from the follow-up visit will be performed.

Patients who discontinue study drug prematurely in both the double-blind period and the open-label period will undergo two sets of TD and follow up visits.

3.1.2 Escape Therapy and Other Concomitant Treatments for SSc

Escape therapy will be available from Week 24 for patients with worsening of skin thickening, and from Week 16 for patients with decline in FVC (confirmed on two separate occasions within a 4-week period; see Section 4.4.1.1 for details). The decision to initiate escape therapy will be based on predefined criteria, investigator judgment, and discussion with the Medical Monitor. Patients will continue to receive study drug in addition to escape therapy. Upon completion of the 48-week double-blind treatment period, patients receiving escape therapy in addition to study drug can enter

the open-label treatment period to receive TCZ. *These patients may remain on escape therapy during the open-label period at the discretion of the investigator.*

Patients may receive other concomitant treatments for SSc including treatments for new and existing organ complications as described in Section 4.4.1.

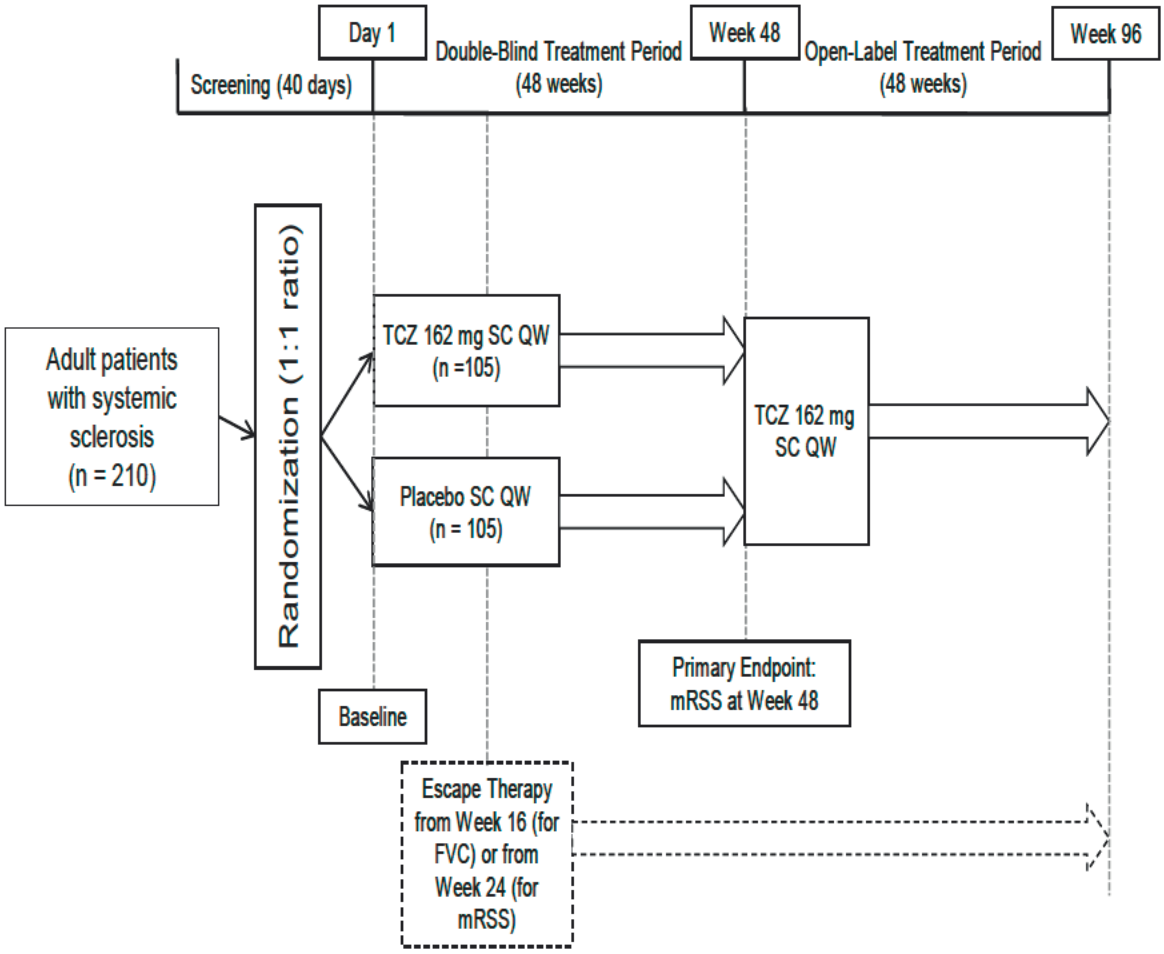
3.1.3 Independent Data Monitoring Committee

An external independent Data Monitoring Committee (iDMC) will be established to perform regular review of the safety data at least two times per year to ensure the ongoing safety of participating patients until the last patient completes the double-blind treatment period. Analyses required for the iDMC's review will be performed by an independent data coordinating center/Contract Research Organization as described in the iDMC Charter. The committee's composition and a description of its responsibilities will be provided in the iDMC Charter.

3.1.4 Clinical Adjudication Committee

A Clinical Adjudication Committee, an independent and blinded expert clinician panel, will adjudicate predefined serious adverse events with regard to their classification as SSc complications. The definition of events for independent assessment and criteria for adjudication of the predefined SSc-related complications will be provided in a charter. The clinical expert panel's composition and a description of its responsibilities will also be provided in the charter.

Figure 1 Study Schema



FVC = forced vital capacity; mRSS = modified Rodnan Skin Score; n = number; QW = once weekly; SC = subcutaneous; TCZ = tocilizumab.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of the study will occur when the last participating patient completes the last scheduled visit of the follow-up period. This is expected to occur 2 years after the last patient is enrolled.

The total length of the study, from screening of the first subject to the end of the study, is expected to be approximately 4 years.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Tocilizumab Dose and Schedule

Study WA27788 assessed the pharmacokinetics, pharmacodynamics, efficacy, and safety of TCZ 162 mg SC QW.

Steady-state TCZ concentrations and PD responses (IL-6, sIL-6R, C-reactive protein [CRP], and erythrocyte sedimentation rate [ESR]) in patients with SSc were similar to those observed in patients with RA receiving the same dosing regimen, with saturation of the target (IL-6R) at steady-state concentrations.

As described in Section 1.3.2.2, numerically favorable, albeit not statistically significant, improvements in mRSS, PROs, Physician's Global Assessment, and pulmonary function were demonstrated at Week 48 with TCZ 162 mg SC QW. Although the study did not show statistically significant results, the difference in mean change from baseline in mRSS was 3.55 units in favor of TCZ over placebo. More TCZ-treated patients than placebo-treated patients showed at least a 20%, 40%, or 60% reduction in mRSS at Week 48, indicating an effect of TCZ on skin sclerosis. An important observation from the exploratory analysis indicated a possible beneficial effect of TCZ on pulmonary function and progression of lung disease: at Week 48, the mean change in the percent-predicted FVC for placebo ($n=31$) and TCZ ($n=30$), respectively, was -6.6% ($SD=9.4\%$, median $=-5.7\%$) and -2.1% ($SD=4.8\%$, median $=-1.5\%$). More placebo-treated than TCZ-treated patients had a $\geq 10\%$ decline from baseline in the observed FVC at Week 48: 9 of 32 placebo-treated patients (28.1%) compared with 3 of 30 TCZ-treated patients (10.0%). Overall, these data indicate a consistent effect of TCZ 162 mg SC QW across several endpoints in patients with SSc.

Treatment with TCZ was generally well tolerated (see Section 1.3.2.1). Except for a higher incidence of serious infections with TCZ, the observed adverse event profile was comparable between the placebo and active treatment arms. No new or unexpected safety findings were observed. Overall, the adverse events observed in patients receiving TCZ 162 mg SC QW in Study WA27788 were consistent with the natural history of SSc and the known safety profile for TCZ in other indications.

The safety of SC TCZ was assessed in patients with RA in Studies WA22762 and NA25520. Overall, the safety profile of TCZ 162 mg SC QW was consistent with that of TCZ 162 mg SC Q2W, and the incidence of serious infections was low and comparable with both SC regimens.

In summary, the use of TCZ 162 mg SC QW in this study is supported by the benefit–risk ratio demonstrated in Study WA27788 and the known safety profile of TCZ in patients with RA from the TCZ RA clinical trial program and the postmarketing setting.

3.3.2 Rationale for Patient Population

SSc is a heterogeneous disease, and clinical development has been affected by the variable course of the disease. Patients with dcSSc have more rapidly progressive skin sclerosis compared with patients with lcSSc. In general, peak skin scores of patients with dcSSc occur 24–40 months after onset, followed by regression of skin scores later in the course of the disease when skin atrophy may occur (Merkel et al. 2005). In addition, a major loss of lung function occurs within the first 4–6 years after the onset of SSc (Steen and Medsger 2007). In order to target patients with progressive skin disease and those who are at risk of developing internal organ complications, as well as exclude patients who may have spontaneous improvement of skin sclerosis, enrollment in this Phase III study will be restricted to patients with time $\leq$60 months since the onset of non-Raynaud symptoms and patients with active progressive skin disease.

3.3.3 Rationale for Control Group

No drugs are approved for the treatment of SSc, and no adequate and well-controlled trials 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 patients with SSc have been developed by the European League Against Rheumatism (EULAR) and Scleroderma Trials and Research (EUSTAR) group, a group of experts from the United States and the European Union (Kowal-Bielecka et al. 2009). The EUSTAR consensus statement includes 14 recommendations for the treatment of organ-specific complications. 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 (Kowal-Bielecka et al. 2009).

In the absence of treatment options that change the overall course of the disease or have a substantial effect on skin thickening, and based on the treatment effect of TCZ observed in Study WA27788, a placebo-controlled study design is proposed. In the lessons-learned publication from the D-penicillamine study, Clements et al. (2004) concluded that definite answers are difficult to achieve when there is no placebo control, even in a randomized, controlled trial.

3.3.4 Rationale for Efficacy Endpoints

The primary endpoint for this study (consistent with Study WA2788) is mean change in mRSS, a measure of skin thickness. The extent and degree of skin thickness in patients with SSc have been shown to be predictive of SSc disease outcome. Greater skin involvement is associated with internal organ complications and decreased survival (Bryan et al. 1999; Clements et al. 2000; Steen and Medsger 2000; Walker et al. 2007; Muangchan et al. 2012). Improvement in skin thickness has been associated with increased survival, improvements in overall functioning, as well as improvement in Physician's Global Assessment of disease (Clements et al. 2000;

Steen and Medsger 2001). Thus, skin thickness can be considered a measure that reflects overall disease severity. The mRSS has been used as the primary endpoint in several clinical trials in dcSSc (Denton et al. 2007; Postlethwaite et al. 2008; Khanna et al. 2009) and has shown sensitivity to change. The proportions of patients with ≥20%, ≥40%, and ≥60% improvement in mRSS at Week 48 compared with baseline will complement the primary endpoint of mean change in mRSS in the assessment of clinically meaningful changes in the progression of disease.

Assessment of lung function is of clinical importance in patients with SSc because of high morbidity and mortality in patients with SSc-associated ILD. Change in observed and percentage of predicted FVC from baseline to Week 48 will provide clinically important insight on the effect of TCZ on the development or progression of SSc-associated ILD in patients with SSc. Change in HAQ-DI, Patient's Global Assessment, and Physician's Global Assessment from baseline to Week 48 will provide information on the patient- and physician-reported outcomes, reflecting physical functioning, emotional well-being, and general health status.

3.3.5 Rationale for Biomarker Assessments

SSc is a rare and heterogeneous disease characterized by fibrosis of the skin and internal organs, vasculopathy, and dysregulated immune functions. An increasing number of biomarkers have been associated with different features of SSc (Doran and Veale 2008; Castro and Jimenez 2010). These biomarkers have provided new means to identify specific subsets of SSc patients, to predict the course of the disease and its complications, and to elucidate the underlying biological mechanisms of the disease. Examples of SSc-related biomarkers are described below:

- Plasma levels of the chemokine CXCL4 have been associated with the severity of disease (skin fibrosis, lung fibrosis, and PAH) and with the risk of progression of the disease (lung fibrosis and PAH; van Bon et al. 2014)
- Serum levels of the chemokine CCL18 have been associated with higher risk of worsening of lung fibrosis in SSc patients (Tiev et al. 2011)
- Serum soluble VCAM-1 levels have been associated with the severity of cardiac dysfunction in SSc patients (Shahin et al. 2000)
- Serum COMP levels have been associated with the degree of skin fibrosis and with overall mortality in SSc patients (Hesselstrand et al. 2008, 2012)

In this study, the aim of the exploratory biomarker assessment is to assess whether non-inherited biomarkers:

- can provide evidence of TCZ activity;
- are predictive of response to TCZ (i.e., predictive biomarkers);
- can increase the knowledge and understanding of disease biology; and
- are predictive of progression to a more severe disease state (i.e., prognostic biomarkers).

3.4 OUTCOME MEASURES

3.4.1 Efficacy Outcome Measures

The primary efficacy outcome measure for this study is as follows:

- Change in mRSS from baseline to Week 48

The secondary efficacy outcome measures for this study are as follows:

- Proportions of patients with $\geq 20\%$, $\geq 40\%$, and $\geq 60\%$ improvement in mRSS at Week 48 compared with baseline
- Change in FVC from baseline to Week 48
- Change in HAQ-DI from baseline to Week 48
- Change in Patient's Global Assessment from baseline to Week 48
- Change in Physician's Global Assessment from baseline to Week 48
- Time to treatment failure, defined as the time from randomization to the time of one of the following events (whichever occurs first) during the 48-week double-blind treatment period:

  death,

  decline in percent-predicted FVC $> 10\%$ relative to baseline,

  $> 20\%$ increase in mRSS **and** an increase in mRSS of ≥ 5 points

  occurrence of a predefined SSc-related complication as adjudicated by the Clinical Adjudication Committee

3.4.2 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Frequency of deaths
- Nature, frequency, and severity of adverse events
- Incidence of specific laboratory abnormalities
- Change from baseline in digital ulcer count

3.4.3 Immunogenicity Outcome Measures

The immunogenicity outcome measures for this study are as follows:

- Incidence of anti-TCZ antibodies during the study relative to the prevalence of anti-TCZ antibodies at baseline
- Correlation between anti-TCZ–antibody status and efficacy, safety, or PK outcome measures

3.4.4 Pharmacodynamic Outcome Measure

The PD outcome measure for this study is as follows:

- Predose ESR and serum IL-6, sIL-6R, and CRP levels at baseline and at subsequent timepoints after initiation of study drug

3.4.5 Pharmacokinetic Outcome Measures

The PK outcome measures for this study are as follows:

- Predose serum TCZ concentration at baseline and at specified timepoints thereafter
- Correlation between PK parameters for TCZ and efficacy, safety, or immunogenicity outcome measures

3.4.6 Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- Proportions of patients who achieve a response, as determined by the investigator using CRISS, at Week 48
- Change in the VAS component of the SHAQ from baseline to Week 24 and baseline to Week 48
- Change in WPAI-GH score from baseline to Week 24 and baseline to Week 48
- Change in EQ-5D-3L score from baseline to Week 24 and baseline to Week 48
- Change in total score and subscores of the SGRQ from baseline to Week 48
- Change in total and domain scores of the SkinPRO questionnaire from baseline to Week 48 (for North America only)
- Change in FACIT-Fatigue score from baseline to Week 48.
- Change in HRCT fibrosis score from baseline (based on HRCT scan performed within 3 months prior to screening) to Week 48
- Change in DL_{CO} from baseline to Week 48
- Proportion of patients with $\geq$15% decline in observed DL_{CO} at Week 48
- Proportion of patients with $\geq$15% decline in percentage of predicted DL_{CO} at Week 48
- Change in FVC from baseline to Week 24
- Proportion of patients with $\geq$10% decline in observed FVC at Week 24 and at Week 48

- Proportion of patients with ≥10% decline in percentage of predicted FVC at Week 24 and at Week 48
- Change in mRSS from baseline to Week 24 and Week 96
- Change in observed and percentage of predicted FVC from baseline to Week 96
- Correlation between non-inherited biomarkers (serum levels of CCL18, sVCAM-1, COMP, and autotaxin; plasma levels of CXCL4; and whole blood gene signatures associated with plasmablasts and IFN) and efficacy, safety, PK, or immunogenicity outcome measures

4. MATERIALS AND METHODS

4.1 PATIENTS

This study will enroll approximately 210 patients with active progressive SSc.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥18 years at baseline (Day 1)
- Able to comply with the study protocol, in the investigator's judgment
- Diagnosis of SSc, as defined using the American College of Rheumatology/EULAR criteria (van den Hoogen et al. 2013a; van den Hoogen et al. 2013b)
- SSc disease duration of ≤60 months (defined as time from the first non–Raynaud phenomenon manifestation)
- mRSS of ≥10 and ≤35 units at screening
- Active disease that meets at least one of the following criteria at screening:
  - Disease duration of ≤18 months defined as time from the first non–Raynaud phenomenon manifestation
  - Increase in mRSS of ≥3 units compared with the most recent assessment performed within the previous 6 months
  - Involvement of one new body area and an increase in mRSS of ≥2 units compared with the most recent assessment performed within the previous 6 months
  - Involvement of two new body areas within the previous 6 months
  - Presence of at least one tendon friction rub
- Presence of at least one of the following at screening:
  - CRP ≥0.6 mg/dL (≥6 mg/L)
  - ESR ≥28 mm/hr
  - Platelet count ≥330×10^9/L (330,000/μL)

- Uninvolved or mildly thickened skin at one of the following possible injection-site locations:
  - Front, middle region of the thigh
  - Abdomen, except for the 2-inch area directly around the navel
  - Outer area of the upper arm (if a patient caregiver is giving the injection)
- For women who are not postmenopausal (≥ 12 months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or use single or combined contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for up to 3 months after the last dose of study drug

  Abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

  Examples of contraceptive methods with a failure rate of < 1% per year include tubal ligation, male sterilization, hormonal implants, established, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices.

  Alternatively, it is acceptable to combine the use of two methods (e.g., two barrier methods such as a condom and a cervical cap). Barrier methods must always be supplemented with the use of a spermicide.
- For men: agreement to remain abstinent or use contraceptive measures and agreement to refrain from donating sperm, as defined below:

  With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 8 weeks after the last dose of study drug.

  Abstinence is acceptable only if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

  Men must refrain from donating sperm during the treatment period and for at least 8 weeks after the last dose of study drug.

4.1.2 Exclusion Criteria

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

- Pregnant or lactating, or intending to become pregnant during the study

  Women who are not postmenopausal (≥ 12 months of non-therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test at screening and a negative urine pregnancy test at baseline.
- Major surgery (including joint surgery) within 8 weeks prior to screening or planned major surgery within 12 months following randomization

- Skin thickening (scleroderma) limited to the face or areas distal to the elbows or knees at screening
- Rheumatic autoimmune disease other than SSc, including but not limited to RA (diagnosed using ACR/EULAR criteria), systemic lupus erythematosus, mixed connective tissue disorder, polymyositis, dermatomyositis, eosinophilic fasciitis, primary Sjögren's syndrome, and eosinophilic myalgia syndrome, as determined by the investigator
- Treatment with non-investigational or investigational cell-depleting therapies, including but not limited to alemtuzumab, anti-CD4, anti-CD5, anti-CD3, anti-CD19, and anti-CD20 within 18 months of baseline; or if treatment prior to 18 months from baseline, evidence of peripheral depletion of targeted lymphocyte subset at screening
- Previous treatment with chlorambucil, bone marrow transplantation, or total lymphoid irradiation
- Previous treatment with anti-IL6 therapy (including and not limited to TCZ)
- Previous treatment with thalidomide, antithymocyte globulin, plasmapheresis, or extracorporeal photopheresis
- Treatment with anakinra within 1 week prior to baseline
- Treatment with etanercept within 2 weeks prior to baseline
- Treatment with oral, intramuscular, or intravenous corticosteroids ($>$10 mg/day of prednisone or equivalent) within 2 weeks prior to baseline
- Treatment with methotrexate, hydroxychloroquine, cyclosporine A, azathioprine, mycophenolate mofetil, rapamycin, colchicine, or D-penicillamine, within 4 weeks prior to baseline
- Immunization with a live or live attenuated vaccine within 4 weeks prior to baseline
- Treatment with any investigational agent within 5 elimination half-lives of the investigational drug prior to baseline
- Chronic treatment with any of the following within 5 elimination half-lives of the drug prior to baseline:
  - Pirfenidone
  - Nintedanib
  - Endothelin-receptor antagonists, terguride
  - Tyrosine-kinase inhibitors (e.g., imatinib, nilotinib, dasatinib)
  - Janus-kinase inhibitors
- Treatment with IV prostacyclin within 1 week prior to baseline
- Treatment with ultraviolet phototherapy within 6 weeks prior to baseline
- Treatment with infliximab, certolizumab, golimumab, abatacept, or adalimumab within 8 weeks prior to baseline
- Treatment with cyclophosphamide within 6 months prior to baseline

- History of severe allergic or anaphylactic reactions to human, humanized, or murine monoclonal antibodies
- Evidence of moderately severe concurrent nervous system, renal, endocrine, or GI disease not related to SSc, as determined by the investigator
- Pulmonary disease with FVC ≤ 55% of predicted (best of three acceptable and repeatable measurements as described in the site's Pulmonary Function Testing Manual)

  OR

  DL_{CO} ≤45% of predicted (corrected for hemoglobin, and the average of the 2 highest acceptable and repeatable measurements as described in the Pulmonary Function Testing Manual)
- Class II or higher PAH, as defined by the World Health Organization (Galiè et al. 2009)
- Evidence of other moderately severe pulmonary disease (e.g., asthma, emphysema), as determined by the investigator
- Cardiovascular disease with significant arrhythmia, congestive heart failure (New York Heart Association Class II–IV), unstable angina, uncontrolled hypertension, cor pulmonale, or symptomatic pericardial effusion
- History of myocardial infarction in the last 6 months prior to screening
- Current liver disease, as determined by the investigator
- History of diverticulitis or chronic ulcerative lower GI disease, such as Crohn disease, ulcerative colitis, or other symptomatic lower GI conditions that might predispose a patient to perforations
- Known active current or significant history of recurrent bacterial, viral, fungal, mycobacterial, or other infections, including but not limited to atypical mycobacterial disease, hepatitis B or C, herpes zoster, infected digital ulcers, and osteomyelitis
- Any major episode of infection requiring hospitalization or treatment with IV antibiotics within 4 weeks prior to screening or oral antibiotics within 2 weeks prior to screening
- Significant history of recurrent tuberculosis (TB), active TB requiring treatment within the previous 3 years, or untreated latent TB

  Patients should be screened for latent TB, and, if positive, will be eligible for the study after treatment per local standard practices.
- History of or currently active primary or secondary immunodeficiency
- Evidence of malignant disease, or malignancies diagnosed within the previous 5 years (with the exception of local basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix uteri that has been excised and cured)
- History of alcohol, drug, or chemical abuse within 1 year prior to screening
- Neuropathies or other conditions that might interfere with pain evaluation, as determined by the investigator

- At screening:

  Body weight >150 kg

  Glomerular filtration rate <45 mL/min

  ALT or AST $>1.5\times$ the upper limit of normal (ULN)

  Total bilirubin $>$ ULN

  Platelet count $<100\times10^9$/L (100,000/μL)

  Hemoglobin <85 g/L (8.5 g/dL; 5.3 mmol/L)

  WBC count $<3.0\times10^9$/L (3000/μL)

  Absolute neutrophil count (ANC) $<2.0\times10^9$/L (2000/μL)

  Absolute lymphocyte count $<0.5\times10^9$/L (500/μL)

  Positive hepatitis B surface antigen or hepatitis C antibody

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

Prior to the Week 48 database lock, patients, investigators, other study site personnel, and Sponsor personnel (including monitors, project statisticians, and project team members) will remain blinded to treatment assignment. To prevent potential unblinding because of observed efficacy and laboratory changes, a dual-assessor approach will be used to evaluate these data. Details regarding the dual-assessor approach are provided in a separate manual.

If unblinding is necessary for patient management (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. Treatment codes should not be broken except in emergency situations. If the investigator wishes to know the identity of the study drug for any other reason, he or she should contact the Medical Monitor directly. The investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event).

For regulatory reporting purposes, and if required by local health authorities, the Sponsor will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 5.7) that are considered by the investigator or Sponsor to be related to study drug.

While PK samples must be collected from patients assigned to the comparator arm to maintain the blinding of treatment assignment, PK assay results for these patients are generally not needed for the safe conduct or proper interpretation of this trial. Sponsor personnel responsible for performing PK assays will be unblinded to patients' treatment assignments to identify appropriate PK samples to be analyzed. Samples from patients assigned to the comparator arm will not be analyzed except by request (i.e., to evaluate a possible error in dosing).

4.3 STUDY TREATMENT

Patients will be randomized in a 1:1 ratio to receive SC injections of TCZ 162 mg QW or placebo QW for 48 weeks during the double-blind treatment period. Patients will receive their first dose of open-label TCZ at Week 48. During the open-label treatment period, all patients will receive SC injections of TCZ 162 mg QW for up to 48 weeks.

4.3.1 Formulation, Packaging, and Handling

TCZ or placebo will be supplied in 1-mL, ready-to-use, single-use PFSs (prefilled syringes), each delivering either 162 mg (0.9 mL) of TCZ solution or 0.9 mL of matching placebo when the plunger is fully depressed. The placebo PFSs will resemble the active TCZ PFSs as closely as possible. A patient will use one PFS for each dosing per week.

The study drug must be stored according to the details on the product label. The drug label indicates the storage temperature. Local packaging in some countries may be different. Upon arrival of investigational products at the site, site personnel should check for damage and verify proper identity, quantity, integrity of seals, and temperature conditions, and report any deviations or product complaints to the monitor upon discovery.

All study drug PFS must be stored at a controlled temperature of 2°C–8°C. PFS should be handled according to Good Manufacturing Practice and GCP procedures.

Used PFS with study drug will be stored at room temperature in designated sharps containers and returned to the site for disposal per local schedule. Under no circumstances is the investigator to allow study drug to be used other than as directed by the protocol.

For information on the formulation and handling of TCZ, see the most recent Tocilizumab Investigator's Brochure or local prescribing information for Actemra.

4.3.2 Dosage, Administration, and Compliance

A single SC *injection* should be given to patients on the same day once weekly (QW), whenever possible. If for any reason the weekly schedule cannot be kept (e.g., SC injections have to be postponed or moved forward to coincide with the next scheduled site visit), injections may be given a minimum of 5 days and a maximum of 11 days apart.

The first SC injection in both study periods (double-blind and open-label) will be administered to patients at the site under close supervision. Patients (and patient caregivers, if applicable) will be trained on how to perform SC injections at the Day 1 visit. After the patient or the patient's caregiver has demonstrated competence in giving the injection correctly, SC injections may be administered by the patient or the patient's caregiver at home. If a patient is unable or does not wish to administer study drug at home, clinic staff may administer injections to the patient at the study site. For patients and caregivers at applicable sites who require additional training, study drug may be

administered (or guidance provided) at Weeks 1 and 2 by a home nursing (HN) professional or (at sites with established teams) appropriately qualified site personnel at the patient's home or another suitable location (see Section 4.5.1 for details on HN services). Provision of HN services is at the discretion of the investigator, and the patient must provide written informed consent to participate in HN services.

The recommended injection sites are uninvolved (or mildly thickened) areas of skin at the front, middle region of the thigh, the abdomen except for the 2-inch area directly around the navel, and, if a caregiver is giving the injection, the outer area of the upper arm. Injections should not be made into areas where the skin is not intact or is tender, bruised, red, or hard. Injection sites will be inspected by site personnel or the HN professional, as applicable, at each visit and any injection-site reactions should be documented appropriately on the Adverse Event electronic Case Report From (eCRF).

Patients will record details of their home-administered study drug injections in an electronic diary (e-diary). Site personnel will monitor the medication records from the e-diary via an online portal. Sharps containers will be provided for home usage, and patients will be instructed to place used PFSs immediately into the sharps container. The sharps containers should be returned to the clinic at each clinic visit and will be discarded by site staff per local practice. Patients will be asked to return all unused PFSs in the provided boxes at each clinic visit. Patients should also bring their e-diary to clinic visits. Patient compliance will be assessed by maintaining adequate drug dispensing logs and return records (see Section 4.3.3), and by reviewing patient e-diary entries.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.

Any overdose or incorrect administration of study drug should be noted in the patient e-diary. Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

4.3.3 Investigational Medicinal Product Accountability

All investigational medicinal product (IMP) required for completion of this study (i.e., TCZ) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMP, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.4 Open-Label Treatment for Patients Who Discontinue Study Drug in the Double-Blind Treatment Period

If a patient discontinues study drug prematurely during the double-blind treatment period of the study (prior to Week 48), they may be eligible to participate in the open-label treatment period of the study and receive TCZ (as per Appendix 2), beginning at Week 48, if they meet the following criteria:

- Adhered to the study visits shown in Appendix 3
- Did not receive any prohibited medication as described in Section 4.1.2
- Did not develop a concurrent condition that would preclude participation as described in Section 4.1.2
- Did not develop a safety issue that would preclude receipt of TCZ as determined by the Principal Investigator and Medical Monitor
- Did not discontinue the study drug during the double-blind treatment period due to non-compliance

Patients who are eligible and wish to receive open-label study drug at Week 48 must complete all Week 48 assessments (as per Appendix 1). If these patients discontinue after TCZ treatment in the open-label period, they should undergo a second TD visit and complete the 4 and 8 week follow-up visits.

Patients who start other medications for systemic sclerosis (e.g., DMARDs) between treatment discontinuation and Week 48 may remain on these medications during the open-label period at the discretion of the investigator.

Patients who do not participate in the open-label period should complete only the reduced schedule of assessments (as per Appendix 3). These patients are not required to undergo a second TD visit or complete Week 4 or Week 8 follow-up visits.

4.3.5 Post-Trial Access to Tocilizumab

The Sponsor will offer post-trial access to the study drug (TCZ) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive study drug after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued study drug treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A patient will not be eligible to receive study drug after completing the study if any of the following conditions are met:

- The study drug is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the study drug or data suggest that the study drug is not effective for SSc
- The Sponsor has reasonable safety concerns regarding the study drug as treatment for SSc
- Provision of study drug is not permitted under the laws and regulations of the patient's country

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following Web site:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

Concomitant therapy includes any medication (e.g., prescription drugs, preventative vaccinations, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 4 weeks prior to screening until 8 weeks after the last dose of study drug or until completion of the last scheduled visit, whichever occurs later. In addition, all medications taken for SSc since diagnosis will be recorded at screening. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

Use of lipid-lowering agents in patients with elevated lipids is strongly encouraged at any time during the study in conjunction with the investigator's clinical judgment and based on guidelines such as the third report from the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (NCEP 2001).

4.4.1 Treatments for Systemic Sclerosis

Treatment with investigational agents, cell-depleting therapies, biologic agents (e.g., tumor necrosis factor antagonists), tyrosine-kinase inhibitors, endothelin receptor antagonists, terguride, alkylating agents such as chlorambucil, cyclophosphamide, bone marrow transplantation with total lymphoid irradiation, thalidomide, IV gamma globulin, antithymocyte globulin, plasmapheresis, or extracorporeal photopheresis is prohibited during the study.

Patients will be allowed to receive escape treatment for worsening of skin thickening and/or deterioration in FVC, as described in Section 4.4.1.1. Concomitant therapies for

treatment of other SSc complications and disease manifestations are permitted as described in Sections 4.4.1.2 and 4.4.1.3. It is important that dose regimens of medications taken by patients during the double-blind treatment period (through Week 48) 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 (in Sections 4.4.1.1–4.4.1.3) may be initiated for management of SSc complications after discussion with the Medical Monitor.

4.4.1.1 Escape Therapy for Worsening mRSS or FVC

At or after the Week 24 visit, escape therapy will be permitted in patients with worsening mRSS of a minimum of 5 points and at least 20% increase, relative to baseline.

At or after the Week 16 visit, escape therapy will be permitted in patients with a decrease of >10 relative percentage points in percentage of predicted FVC compared with baseline, with a decline from baseline confirmed on two separate occasions within a 4-week period.

Initiation of escape therapy for eligible patients will be based on investigator assessment but should be discussed with the Medical Monitor.

Patients who initiate escape therapy during the double-blind treatment period should continue to receive blinded study drug and remain on escape therapy throughout the double-blind treatment period.

Patients who initiate escape therapy during the double-blind period may remain on escape therapy during the open-label period, at the discretion of the investigator.

Patients may initiate escape therapy during the open-label period if they meet the escape therapy criteria.

The following are permitted escape therapies:

<u>Worsening in mRSS at or after Week 24:</u>

- Methotrexate

  After initial dose escalation, patients should remain on a stable dose of methotrexate ($\leq$25 mg/wk by mouth or parenterally) throughout the study unless a dose reduction is required for safety reasons. To minimize methotrexate toxicity, all patients treated with methotrexate must receive folic acid or equivalent at a dose of ≥ 5 mg/wk (refer to local package insert).

- Hydroxychloroquine

  Initial and maintenance doses of hydroxychloroquine should not exceed maximum recommended doses (refer to local package insert).

In patients who are intolerant or inadequate responders to methotrexate or hydroxychloroquine, other DMARDs (such as mycophenolate mofetil) may be used as escape therapy after discussion with the Medical Monitor.

Worsening in FVC at or after Week 16:

- Treatment of SSc-associated ILD should be initiated as indicated per local treatment guidelines (excluding cyclophosphamide)
- The choice of escape therapy for worsening of FVC should be discussed with the Medical Monitor prior to initiation of treatment.

Only one escape therapy can be added to blinded study drug treatment. A change in escape therapy is permitted after discussion with the Medical Monitor.

4.4.1.2 Treatments for Other Systemic Sclerosis Complications

Initiation of treatments for SSc complications (except prohibited therapies, per Section 4.4.1) should be discussed with the Medical Monitor unless an urgent intervention is necessary as a result of the patient's medical condition.

Patients receiving IV prostacyclin at study entry for treatment of Raynaud phenomenon or digital ulcers may continue to receive such treatment. Initiation of IV prostacyclin during the study is permitted for treatment of worsening Raynaud phenomenon or severe digital ulcers. However, no IV prostacyclin therapy is to be administered at or within 1 week prior to the Day 1 or Week 48 visits.

4.4.1.3 Medications Commonly Used in Systemic Sclerosis

NSAIDs and Analgesics

Patients may be treated with NSAIDs, including cyclooxygenase-2 inhibitors, during the study. The dose should remain stable through Week 48, 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 H_2-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 for pain. However, patients should be discouraged from using analgesics, including NSAIDs, within 12 hours prior to performance of efficacy assessments at a clinic visit.

Oral Corticosteroids

Patients 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 such as

asthma, doses of oral corticosteroids up to ≤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.

Intravenous or Intramuscular Corticosteroids

IV or intramuscular (IM) corticosteroids are not permitted up to and including Week 48 of the study. After the Week 48 visit, treatment with IV or IM corticosteroids is discouraged. However, if deemed medically necessary, IV or IM corticosteroids may be administered after discussion with the Medical Monitor.

DMARDs

All biologic or other conventional DMARDs must be discontinued with appropriate washout prior to the initiation of study drug as described in Section 4.1.2 and are prohibited during the study, except when given as escape therapy as described in Section 4.4.1.1 or after Week 24 for other significant systemic sclerosis complications as described in Section 4.4.1.2.

4.4.2 Drug-Drug Interactions

The formation of cytochrome P450 (CYP450) enzymes may be suppressed by increased levels of cytokines (e.g., IL-6) during chronic inflammation. Therefore, for molecules that antagonize cytokine activity, such as TCZ, it is expected that the formation of CYP450 enzymes could be normalized. When starting or stopping therapy with TCZ, patients taking medications that are individually dose adjusted and metabolized by means of CYP450, 3A4, 1A2, or 2C9 (e.g., atorvastatin, calcium-channel blockers, theophylline, warfarin, phenytoin, cyclosporine, or benzodiazepines) should be monitored, as doses may need to be adjusted to maintain their therapeutic effect. Given its long elimination half-life, the effect of TCZ on CYP450 enzyme activity may persist for several weeks after stopping therapy.

4.5 STUDY ASSESSMENTS

Please see Appendix 1–Appendix 3 for schedules of assessments performed during the study.

Assessments and procedures should be performed in the sequence that is most practical for the site, as long as PROs are performed first and study drug administration is performed last. The study visits should follow the schedule as much as possible and should occur on the same day of the week. Study drug is also to be administered on the same day of the week; however, the timing of study drug administration can be altered to allow for an injection to be performed at a scheduled site visit, as long as the injection is 5–11 days after the prior injection.

4.5.1 Home Nursing Services

At applicable sites, certain study assessments may be performed by an HN professional or (at sites with established teams) by appropriately qualified site personnel at the patient's home or another suitable location, to improve access and convenience for patients participating in the study. The investigator at a participating site will determine if HN services are appropriate for a patient, and the patient must provide written informed consent to participate in HN services. HN services will be scheduled on specified visit days, to allow for relevant assessments to be performed by the HN professional. The schedules of assessments (see Appendix 1–Appendix 3) will specify the assessments that may be performed by an HN professional.

For participating sites without established HN teams, the Sponsor will select a health care company that will be responsible for providing HN services for participating sites (the HN vendor). The HN vendor is responsible for ensuring that all HN professionals are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed. The HN network will communicate with the patient, the patient's caregiver (if applicable), and the patient's site to coordinate HN services.

4.5.2 Dual Assessor Approach

To prevent potential unblinding because of observed efficacy and laboratory changes, a dual-assessor approach will be used to evaluate these data. *To ensure consistency of assessments and limit inter-observer variability, it is essential that the same assessor conduct the mRSS evaluations for a given patient at all study visits.* Details regarding the dual-assessor approach are provided in a separate manual.

4.5.3 Informed Consent Forms

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

4.5.4 Screening

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.4.1 Re-Testing for Laboratory Eligibility Criteria

Laboratory tests and pulmonary function tests (FVC and DLco) may be repeated twice during the screening period if they do not meet the eligibility criteria. If a patient's results do not satisfy the eligibility criteria on the third assessment, the patient will not be able to

enter the study. It will not be considered a re-testing if blood samples have to be re-drawn because of sample handling problems.

4.5.4.2 Re-Screening

Re-screening (i.e., repeating the entire screening process) is required if a patient has not met all of the eligibility criteria within 40 days of the original screening visit. Patients are allowed to be re-screened once. Each patient must be re-consented before re-screening can occur. It will not be considered a re-screening if blood samples have to be re-drawn because of sample handling problems. During the screening period, it will not be considered a re-screening if pulmonary function tests need to be repeated.

4.5.5 Medical History and Demographic Data

Medical history includes clinically significant diseases (including SSc complications), reproductive status, smoking history, and use of alcohol and drugs of abuse. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 4 weeks prior to the screening visit and all SSc-related medications used by the patient since diagnosis will be recorded.

Demographic data will include age, sex, and self-reported race and ethnicity.

The National Health and Nutrition Examination Survey (NHANES) III reference values as described by Hankinson and colleagues (1999) will be used to calculate percentage of predicted FVC values. The NHANES data sets have been standardized on the basis of key demographic information that includes race and ethnicity. It is therefore necessary to record patient race and ethnicity to ensure that the most appropriate reference equation is used to establish the predicted values.

4.5.6 Physical Examinations

A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, GI, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in patient notes. New or worsened abnormalities after screening should be recorded as adverse events if appropriate.

Physical examinations may be performed by an HN professional.

4.5.7 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressures while the patient is in a seated position, and temperature.

Additional measurements may be performed in the event of an adverse event, at the discretion of the investigator.

Vital signs may be performed by an HN professional.

4.5.8 Digital Ulcer Count

A digital ulcer is defined as an ulcer at or distal to the MCP joint on either the dorsal or volar surface, with loss of surface epithelialization. This does not include fissures, cracks, or calcium extrusions from calcinosis cutis. The number of fingers (0–10) with digital ulcers and the number of digital (or finger) ulcers will be counted and recorded by the investigator.

Digital ulcers will be classified as active, indeterminate, or healed (Baron et al. 2014).

Digital ulcer counts may be performed by an HN professional.

4.5.9 Modified Rodnan Skin Score

Skin thickness will be assessed by palpation and rated using an mRSS that ranges from 0 (normal) to 3 (severe skin thickening) across 17 different body sites. The total score is the sum of the individual skin scores from all of these sites and ranges from 0 to 51 units. The instrument has been validated for patients with dcSSc.

4.5.10 Physician's Global Assessment

The Physician's Global Assessment is to be completed on the basis of examination and overall assessment of the patient. The physician's assessment of the patient's SSc status will be scored on a 100-mm horizontal VAS (see Appendix 5). The extreme left end of the line represents "has no effect at all" (symptom free), and the extreme right end represents "worst possible effect."

4.5.11 Combined Response Index for Systemic Sclerosis

CRISS represents a composite measure of patient and physician reported outcomes, presence of SSc symptoms, and their severity. The details on analysis of CRISS will be described in the Statistical Analysis Plan (SAP).

4.5.12 Pulmonary Function Tests

Pulmonary function tests will include DL_{CO} and FVC. Pulmonary function tests will be conducted as per the study Pulmonary Function Manual, which is based on the American Thoracic Society/European Respiratory Society (ATS/ERS) Consensus Statement. The manual will include information on equipment, procedures, patient instructions, and precautions. Spirometry tests will be performed on a centralized spirometry system (provided to all sites by a central spirometry vendor) configured to the requirements of the study and in accordance with ATS/ERS guidelines. The DLco tests will be performed using the investigator site's own PFT equipment. DLco test results

and reports will be entered into the centralized spirometry system software as described in the Pulmonary Function Manual.

The acceptability of the FVC and DLco data, including the graphic representations of the maneuvers, will be determined centrally by over-readers blinded to treatment assignment. Calculations for the reproducibility of the acceptable maneuvers will be performed and reviewed centrally by the blinded over-readers.

The over-readers will state whether a session has been accepted or rejected. If rejected, the following sessions should be repeated within 4 weeks:

- *FVC session from Week 8 onwards*
- *DL_{CO} session at Week 48 and/or Week 96*
- *Session at any TD visit*

The NHANES III reference values, standardized on the basis of key demographic information (including race and ethnicity), will be used to calculate percentage of predicted FVC values (Hankinson et al. 1999).

The Miller et al. 1983, reference values will be used for the predicted DLco values.

Percentage of predicted DL_{CO} values will be calculated by visit. Predicted DL_{CO} values will be derived using height at screening, age at screening, and patient sex. The predicted value is then adjusted for the hemoglobin level at each visit (Macintyre et al. 2005).

4.5.13 High-Resolution Computed Tomography Scans

HRCT scans will be obtained at baseline and at Week 48 to assess for pulmonary fibrosis (unless prohibited by local regulations). Good-quality (as determined by the site radiologist and/or investigator) standard-of-care HRCT scans obtained within 3 months prior to screening and in accordance with study image acquisition guidelines can be used for baseline. Existing scans should be sent to the vendor during the screening period so that acceptability can be assessed and scheduling of a new scan at the baseline visit can occur, if required, prior to study drug administration. The HRCT films will be centrally reviewed and scored on the basis of texture-based analysis for changes in lung fibrosis, using validated qualitative and quantitative methods.

4.5.14 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Dipstick urinalysis: pH, specific gravity, glucose, protein, ketones, blood

  Microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria), if indicated, will be performed at a central laboratory.

- ESR (PD biomarker)
- Pregnancy test during treatment

  All women who are not postmenopausal (≥12 months of non-therapy-induced amenorrhea) or surgically sterile will have urine pregnancy tests performed at specified visits during treatment. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

- *TB testing at screening (see Section 4.5.15)*

Samples for the following laboratory tests will be sent to one or several central laboratories for analysis:

- Hematology: hemoglobin, hematocrit, mean corpuscular hemoglobin (MCH), MCH concentration, mean corpuscular volume, WBC count, RBC count, platelet count, absolute differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry panel: BUN or urea, uric acid, creatinine, random glucose, potassium, sodium, chloride, calcium, phosphorus, total protein, albumin, creatine phosphokinase, C3, C4
- Liver profile: AST, ALT, alkaline phosphatase, total bilirubin (direct and indirect will be performed if total bilirubin is greater than the ULN)
- Serum lipids: fasting total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides
- Serology: anti-nuclear antibodies, SSc-specific auto-antibodies (e.g., anti-PM/Scl, anti-topoisomerase, anti-RNA polymerase, anti-histone, anti-U1 snRP, and anti-centromere), hepatitis B surface antigen, and hepatitis C antibody

  Hepatitis B surface antigen and hepatitis C antibody serology will be performed at screening only, unless clinically indicated during the study.

- Microscopic urinalysis (only if indicated after local dipstick urinalysis): sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria
- Creatinine clearance
- Pregnancy test at screening

  All women who are not postmenopausal (≥12 months of non-therapy-induced amenorrhea) or surgically sterile will have a serum pregnancy test at screening.

The following samples will be sent to the Sponsor or a designee for analysis:

- Serum samples for analysis of anti-TCZ antibodies
- Serum samples for PK analysis
- Serum samples for analysis of the following PD biomarkers: IL-6, sIL-6R, CRP

  Central CRP will be blinded to the site and Sponsor for all post-baseline visits until after the primary analysis. Local CRP testing should only be performed if deemed clinically necessary by the investigator. Local CRP results should not be shared with the Sponsor or entered into the eCRF until after the primary analysis.
- Serum samples for analysis of candidate biomarkers, including but not limited to CCL18, sVCAM-1, COMP, autotaxin, and other candidate biomarkers
- Plasma (EDTA) samples for analysis of candidate biomarkers, including but not limited to CXCL4
- Whole blood samples for RNA extraction for analysis of candidate biomarkers, including but not limited to gene signatures associated with plasmablasts and IFN

Additional samples for PK analysis and analysis of anti-TCZ antibodies and sIL-6R will be collected prior to resuming study drug for patients who have missed at least three consecutive doses and at the time of anaphylaxis or a serious hypersensitivity reaction.

Collection of blood and urine samples may be performed by an HN professional.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Samples will be destroyed when the final clinical study report has been completed, with the following exceptions:

- Biomarker samples will be destroyed no later than 5 years after the date of final closure of the clinical database unless the patient gives specific consent for the remainder of the samples to be stored for optional exploratory research. If the patient provides consent for optional exploratory research, the samples will be destroyed no later than 15 years after the date of final closure of the clinical database.

4.5.15 *Tuberculosis Screening*

All patients will be evaluated for TB at screening. Testing must be repeated at Week 36, and the result confirmed, prior to initiation of open-label TCZ at Week 48 (except for patients who discontinued study drug prematurely who had a TB test performed at the TD visit). The test method (e.g. PPD or QuantiFERON® test) is at the discretion of the investigator.

Patients who test positive for TB at screening should be evaluated for evidence of active TB per local standard practice. A patient with a positive TB test may be eligible for study inclusion only if diagnosed with latent TB and treated per local standard practice.

Patients who test positive for TB at screening and were treated for latent TB must undergo repeat TB testing at the Week 36 visit. However, since no applicable clinical practice guidelines currently exist regarding how to further evaluate patients who have had a positive TB test, a clinical evaluation at Week 36 and prompt local review of the Week 48 HRCT to evaluate for any evidence of active TB is required. Investigators will be asked to confirm this assessment.

Patients who test negative for TB at screening must undergo repeat TB testing at the Week 36 visit. If the Week 36 visit TB test is positive, dosing of study drug must be interrupted and patients evaluated for evidence of active TB per local standard practice. If a patient is diagnosed with latent TB and has started TB treatment, the patient may recommence dosing with study drug.

4.5.16 Electrocardiograms

Single ECG recordings will be obtained at screening and may be obtained at unscheduled timepoints if indicated. ECG recordings should be performed after the patient has been resting in a supine position for at least 10 minutes.

4.5.17 Patient-Reported Outcomes

Patients will use an electronic PRO (ePRO) device to capture PRO data. The appropriate PRO assessments will be programmed to appear at specific visits, as noted in the schedule of assessments. Not all assessments are included at every visit. All assessments will be translated into the appropriate local language.

The PRO assessments are to be completed by patients without assistance at the investigational site prior to the completion of other study assessments and the administration of study drug. PRO assessments are completed in this manner to minimize any bias that may come from investigational site staff assessments. However, site staff or patient caregivers may assist patients who are physically unable to complete the questionnaires by recording responses selected by patients. Site staff (and patient caregivers, if applicable) will be trained on how to teach patients to use the ePRO device, as well as how to avoid providing interpretation of questions or selection of responses.

4.5.17.1 Health Assessment Questionnaire Disability Index

The HAQ-DI consists of 20 questions referring to eight component sets: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities (Wolfe 1989; see Appendix 6). The total score indicates the patient's self-assessed level of disability. A negative change from baseline indicates improvement.

4.5.17.2 Scleroderma Health Assessment Questionnaire

The SHAQ is composed of the HAQ-DI scale with the addition of five scleroderma-specific VAS scales (Steen and Medsger 1997; see Appendix 6 for an example) to assess additional elements of SSc disease and the impact each element has on a patient's daily life. Each VAS item is rated separately, with higher scores indicating more severe disease. The five VAS scales are: 1) intestinal disease, 2) breathing problems, 3) Raynaud syndrome, 4) digital ulcers, and 5) overall disease.

4.5.17.3 Patient's Global Assessment

The Patient's Global Assessment represents the patient's overall assessment of his or her current SSc status on a 100-mm horizontal VAS (see Appendix 7). The extreme left end of the scale indicates "has no effect at all" (symptom free), and the extreme right end indicates "worst possible effect."

4.5.17.4 Saint George's Respiratory Questionnaire

The SGRQ (see Appendix 10) is a self-administered questionnaire that contains 50 items distributed over three scales. Symptom scale assesses the severity of respiratory symptoms; activity scale examines impairment in patient activity as a result of respiratory symptoms; and impact scale evaluates effects of respiratory symptoms on overall function and wellbeing. Each scale can be scored from 0 to 100 and a total score represents the weighted average of these three subscores. This questionnaire has been recently validated in early dcSSc (Wallace et al. 2015).

4.5.17.5 FACIT-Fatigue

The FACIT-Fatigue is a 13-item measure of fatigue, with patients scoring each item on a 5-point scale (see Appendix 8). The assessment was originally developed for chronic illnesses and has been validated for patients with RA.

4.5.17.6 SkinPRO Questionnaire

The SkinPRO is a 22-item, patient-completed questionnaire developed to measure skin health status as experienced by scleroderma patients with skin involvement. There are 4 separate domains: skin symptoms, physical function, social function, and emotional response. The recall period is "over the PAST 4 WEEKS," and the response set for all items is a 7-point ordinal scale, ranging from "Not at all" to "Very much." The SkinPRO questionnaire is a new, exploratory measure developed specifically for scleroderma patients. The SkinPRO questionnaire will be administered only in North America (see Appendix 1, Appendix 2, and Appendix 11).

4.5.17.7 EuroQol 5-Dimension Questionnaire

The EQ-5D-3L is a generic, preference-based health utility measure with questions about mobility, self-care, usual activities, pain/discomfort, and anxiety/depression that are used to build a composite of the patient's health status (see Appendix 9). It is a concise scale that has performed well for patients with SSc (Gualtierotti et al. 2009). The EQ-5D-3L will be utilized in this study for economic modeling.

4.5.17.8 Work Productivity and Activity Impairment–General Health

The WPAI-GH questionnaire is a six-item scale, asking patients to estimate the amount of time that their work and daily activities were affected by their health over the previous 7 days (Reilly et al. 1993). The WPAI-GH assesses absenteeism as well as "presenteeism," which accounts for the time when patients were present for work or activities but believed their health had a negative effect on their ability to perform at the usual level (see Appendix 4).

4.5.18 Samples for Roche Clinical Repository

4.5.18.1 Overview of the Roche Clinical Repository

The Roche Clinical Repository (RCR) is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection and analysis of RCR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Specimens for the RCR will be collected from patients who give specific consent to participate in this optional research. RCR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.18.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RCR is contingent upon the review and approval of the exploratory research and the RCR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RCR sampling, this section of the protocol (Section 4.5.17) will not be applicable at that site.

4.5.18.3 Sample Collection

The following RCR samples will be collected for research purposes, including but not limited to research on dynamic (non-inherited) biomarkers related to TCZ mode of action, IL-6 biology, SSc biology, or biology of related diseases (e.g., systemic lupus erythematosus, dermatomyositis):

- Residual plasma and serum samples, including biomarker, PK, and anti-TCZ antibody samples
- Residual whole blood for RNA extraction, including derivatives
- Optional skin biopsy tissues: Patients who consent to the RCR sampling will be asked to provide two 3-mm skin punch biopsies at the baseline and at the Week 48 visits (see Appendix 1). The first biopsy will be used to evaluate the gene expression in the skin of patients with SSc before and after treatment with TCZ. It has been shown that in skin biopsies, the expression of a four-gene signature, reflecting the activity of the TGFb and IFN pathways, correlates closely with the degree of skin fibrosis (Farina et al. 2010). In addition, genome-wide gene expression analysis revealed that SSc patients can be categorized according to intrinsic gene signatures reflecting different biological mechanisms (Milano et al. 2008). The second biopsy will be used to evaluate protein biomarkers in the skin of SSc patients before and after treatment with TCZ. It has been shown that, in skin biopsies, the detection of alpha smooth muscle actin-expressing cells is highly correlated with the development of skin fibrosis (Sappino et al. 1990)

The following RCR samples will be collected for research purposes, including but not limited to research on genetic (inherited) biomarkers related to TCZ mode of action, IL-6 biology, SSc biology, or biology of related diseases (e.g., systemic lupus erythematosus, dermatomyositis):

- Whole blood for DNA extraction

For all samples, dates of consent and specimen collection should be recorded on the associated RCR page of the eCRF. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RCR specimens will be destroyed no later than 15 years after the date of final closure of the associated clinical database. The RCR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

The dynamic biomarker specimens will be subject to the confidentiality standards described in Section 8.4. The genetic biomarker specimens will undergo additional processes to ensure confidentiality, as described below.

4.5.18.4 Confidentiality

Given the sensitive nature of genetic data, Roche has implemented additional processes to ensure patient confidentiality for RCR specimens and associated data. Upon receipt

by the RCR, each specimen is "double-coded" by replacing the patient identification number with a new independent number. Data generated from the use of these specimens and all clinical data transferred from the clinical database and considered relevant are also labeled with this same independent number. A "linking key" between the patient identification number and this new independent number is stored in a secure database system. Access to the linking key is restricted to authorized individuals and is monitored by audit trail. Legitimate operational reasons for accessing the linking key are documented in a standard operating procedure. Access to the linking key for any other reason requires written approval from the Pharma Repository Governance Committee and Roche's Legal Department, as applicable.

Data generated from RCR specimens must be available for inspection upon request by representatives of national and local health authorities, and Roche monitors, representatives, and collaborators, as appropriate.

Patient medical information associated with RCR specimens is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Data derived from RCR specimen analysis on individual patients will generally not be provided to study investigators unless a request for research use is granted. The aggregate results of any research conducted using RCR specimens will be available in accordance with the effective Roche policy on study data publication.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RCR data will become and remain the exclusive and unburdened property of Roche, except where agreed otherwise.

4.5.18.5 Consent to Participate in the Roche Clinical Repository

The Informed Consent Form will contain a separate section that addresses participation in the RCR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RCR. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RCR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate by completing the RCR Research Sample Informed Consent eCRF.

In the event of an RCR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RCR research.

4.5.18.6 Withdrawal from the Roche Clinical Repository

Patients who give consent to provide RCR specimens have the right to withdraw their specimens from the RCR at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the RCR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RCR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study WA29767 does not, by itself, constitute withdrawal of specimens from the RCR. Likewise, a patient's withdrawal from the RCR does not constitute withdrawal from Study WA29767.

4.5.18.7 Monitoring and Oversight

RCR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Roche monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RCR for the purposes of verifying the data provided to Roche. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RCR samples.

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient’s safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.
A study retention plan will be put in place to minimize early discontinuation from the study and to encourage patients to follow the reduced schedule of assessments (see Appendix 3) even if study drug has been discontinued prematurely.

4.6.2 Study Drug Discontinuation

Patients must discontinue study drug if they experience any of the following:

- Pregnancy
- GI perforations (see Section 5.1.2)
- Neutropenia <500 cells/μL still present after repeat testing (see Section 5.1.4)
- Thrombocytopenia $<50{,}000/\mu$L still present after repeat testing (see Section 5.1.4)
- ALT or AST $>5\times$ ULN or as specified in Section 5.1.5
- Malignancies (with the exception of local basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix uteri that has been excised and cured; see Section 5.1.7)
- Anaphylaxis or serious hypersensitivity (see Section 5.1.9)
- Patient non-compliance, defined as missing multiple scheduled visits, not adhering to protocol requirements for permitted or prohibited concomitant therapy, or not adhering to safety risk mitigation strategies

The primary reason for study drug discontinuation should be documented on the appropriate eCRF. Patients who discontinue study drug prematurely will not be replaced. A study retention plan will be put in place to minimize early discontinuation from the study and to encourage patients to follow the reduced schedule of assessments (see Appendix 3) even if study drug has been discontinued prematurely. These patients will be eligible to enter the open-label treatment period of the study at Week 48 and receive TCZ (as per Appendix 2), beginning at Week 48, if they meet specified eligibility criteria (described in Section 4.3.4).

4.6.3 Study and Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Measures will be taken to ensure the safety of patients participating in this trial. Eligibility criteria have been designed to exclude patients at higher risk for toxicities (see Section 4.1.2). In addition, patients will undergo safety monitoring during the study as described in Section 4.5, Section 5, and the schedules of assessments (see Appendix 1–Appendix 3).

The following information is based on results from clinical studies. Please refer to the Tocilizumab Investigator's Brochure for a complete summary of safety information.

5.1.1 Opportunistic Infections and Serious Infections

Physicians should exercise caution when considering the use of TCZ in patients with a history of recurring infections or with underlying conditions (e.g., diabetes mellitus), which may predispose patients to infections. TCZ should not be administered to patients with active infection. The effects of TCZ on CRP and neutrophils, and the signs and symptoms of infection, should be considered when evaluating a patient for a potential infection. Although rarely reported within the TCZ program because of the exclusion criteria at study entry, reactivation of viral and other serious infections (e.g., Epstein–Barr virus or TB) has been observed with biologic therapies for RA, including TCZ.

Patients with SSc may be susceptible to certain serious infections and underlying conditions such as SSc-associated ILD and digital ulcers can increase this risk. Patients enrolled in this study will be provided with a Patient Information Card, informing them and health care providers of the importance of recognition of early signs of infections, so that appropriate diagnostic and therapeutic measures can be introduced.

Vigilance for timely detection of serious infection is recommended for patients receiving biologic agents, as signs and symptoms of acute inflammation may be lessened because of suppression of the acute-phase reaction. Patients must be instructed to

contact their physician immediately when any symptoms suggesting infection appear, to ensure rapid evaluation and appropriate treatment.

If a patient develops a serious infection, administration of TCZ is to be interrupted until the infection is controlled. The clinician should consider the benefits and risks to the patient before resuming treatment with TCZ.

5.1.2 Gastrointestinal Perforations

Symptomatic diverticulosis, diverticulitis, or chronic ulcerative lower GI disease, such as Crohn's disease, ulcerative colitis, or other chronic lower GI conditions, might predispose patients to GI perforations. Therefore, patients with these conditions are excluded from this study (see Section 4.1.2). Timely diagnosis and appropriate treatment may reduce the potential for complications of diverticular disease and thus reduce the risk of GI perforations. As a result, patients should be made aware of the symptomatology potentially indicative of diverticular disease and instructed to alert their health care provider as soon as possible if these symptoms arise. Discontinuation of TCZ is required for patients who develop GI perforations.

5.1.3 Demyelinating Disorders

The effect of treatment with TCZ on demyelinating disorders is not known; events have rarely been reported. Patients should be closely monitored for signs and symptoms potentially indicative of central demyelinating disorders. Physicians should exercise caution when considering the use of TCZ in patients with preexisting or recent-onset demyelinating disorders. Treatment with TCZ should be interrupted during assessment of a potential demyelization event and be resumed only if the balance of benefits and risks of continuing study drug is favorable.

5.1.4 Hematologic Abnormalities

Decreases in neutrophil and platelet counts have been observed following treatment with TCZ in combination with methotrexate. In addition, there may be an increased risk of neutropenia for patients who have been previously treated with a tumor necrosis factor antagonist.

Risk mitigation strategies for neutropenia and thrombocytopenia are summarized in Table 1 and Table 2, respectively.

Table 1 Risk Mitigation for Neutropenia

ANC	Action
> 1000 cells/μL	• Maintain dose.
500–1000 cells/μL	• If neutropenia persists, interrupt TCZ dosing (or reduce TCZ dosing frequency to Q2W). • When ANC increases to > 1000 cells//μL, resume TCZ (or increase dosing frequency to QW), as clinically appropriate.
< 500 cells/μL	• If confirmed by repeat testing, discontinue TCZ.

ANC = absolute neutrophil count; QW = once weekly; Q2W = every 2 weeks; TCZ = tocilizumab.

Note: Patients withdrawn from the study because of a reduced ANC must be followed closely for signs of infection, with treatment as deemed appropriate by the investigator, and must have a repeat WBC count with differential count performed weekly until the ANC is > 1000 cells/μL. If the ANC does not return to > 1000 cells/μL within 2 months (or sooner if deemed necessary by the investigator), a hematology referral is recommended.

Table 2 Risk Mitigation for Thrombocytopenia

Platelet count	Action
> 100,000/μL	• Maintain dose.
50,000–100,000/μL	• If thrombocytopenia persists, interrupt TCZ dosing (or reduce TCZ dosing frequency to Q2W). • When platelet count increases to > 100,000/μL, resume TCZ (or increase dosing frequency to QW), as clinically appropriate.
< 50,000/μL	• If confirmed by repeat testing, discontinue TCZ.

QW = once weekly; Q2W = every 2 weeks; TCZ = tocilizumab.

Note: Patients withdrawn from the study because of a reduced platelet count must repeat platelet tests weekly until the count is > 100,000/μL. If platelets do not return to > 100,000/μL within 2 months (or sooner if deemed necessary by the investigator), a hematology referral is recommended.

For patients receiving concomitant medications associated with hematologic toxicity, reduction or interruption of the suspected medication is recommended prior to modifying TCZ.

5.1.5 Elevated Liver Enzymes

Risk mitigation strategies for patients with elevated ALT or AST are presented in Table 3.

Table 3 Hepatic Enzyme Elevation Risk Mitigation

ALT or AST Values	Action
ULN [a] to 3 × ULN	• Reduce the dose of and, if necessary, interrupt treatment with concomitant DMARD and other hepatotoxic drugs. If ALT/AST levels return to baseline, DMARD dosing may be resumed. • For persistent increases in this range, interrupt TCZ dosing (or reduce TCZ dosing frequency to Q2W). • When ALT/AST levels return to baseline, resume TCZ (or increase dosing frequency to QW), with or without the DMARD, as clinically appropriate.
> 3 to 5 × ULN	• Interrupt TCZ dosing until ≤ 3 × ULN (confirmed by repeat testing) and then follow the instructions above. • For persistent increases in this range, TCZ should be discontinued.
> 5 × ULN	• If confirmed by repeat testing, discontinue TCZ.

DMARD = disease-modifying anti-rheumatic drug; QW = once weekly; Q2W = every 2 weeks; TCZ = tocilizumab; ULN = upper limit of normal.

[a] ULN or the patient's baseline value, whichever is higher.

Discontinuation of study drug treatment is recommended with ALT or AST elevation > 3 × ULN combined with at least one of the following:

- Total bilirubin > 2 × ULN
- International normalized ratio > 1.5
- Alkaline phosphatase > 2 × ULN
- Presence of worsening fatigue, nausea, vomiting, fever, rash, or eosinophilia

The Sponsor should be contacted for further discussion of the case.

Patients withdrawn from the study because of elevated liver function tests must have repeat tests performed as clinically indicated until levels return to baseline. If the patient's liver function tests have not returned to normal or the patient's baseline level within 6 months (or sooner if deemed necessary by the investigator), the investigator should consider referral to a specialist. If the specialist deems a liver biopsy necessary, the prepared histologic slides will be requested by the Sponsor for central review by a third party and the biopsy report should be forwarded to the Sponsor.

5.1.6 Elevated Lipids

For patients with LDL cholesterol levels of ≥ 160 mg/dL, it is strongly recommended that investigators advise therapeutic lifestyle changes that may include initiation of lipid-lowering agents. Lipid-lowering agents should also be considered for patients with lower LDL cholesterol levels as part of their therapeutic lifestyle changes, depending on their overall risk as defined by the NCEP Adult Treatment Panel III (NCEP 2001) or other national guidelines.

5.1.7 Malignancies

The effect of IL-6R–signaling inhibition on the development of malignancies is not known. Although no imbalance of malignancies was observed in controlled clinical trials of TCZ in patients with RA, malignancies have been identified as a concern for other biologic agents. It is recognized that identification of such events in TCZ-treated patients may require a longer period of surveillance. TCZ administration should be discontinued for patients with malignancies (with the exception of local basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix uteri that has been excised and cured).

5.1.8 Local Injection-Site Reactions

Local injection-site reactions, including but not limited to erythema, induration, pain, and SC emphysema, should be reported as described in Section 5.3.5.1. If needed, injection-site reactions should be treated topically and the treatments should be reported on the eCRF.

5.1.9 Hypersensitivity and Anaphylaxis after TCZ Injection

A systemic injection reaction is typically defined as an adverse event occurring during and within 24 hours after the SC injection of TCZ. This may include hypersensitivity reactions or anaphylactic reactions.

Signs of a possible hypersensitivity reaction include, but are not limited to, the following:

- Fever, chills, pruritus, urticaria, angioedema, and skin rash
- Cardiopulmonary reactions, including chest pain, dyspnea, hypotension, or hypertension

Health care professionals administering TCZ injections should: be trained in the appropriate procedures for TCZ administration, be able to recognize the symptoms associated with potential anaphylactic or hypersensitivity reactions, and have the appropriate medication available for immediate use in case of anaphylaxis or hypersensitivity reaction during or after administration of TCZ.

If a patient has symptoms of anaphylaxis or serious hypersensitivity, or requires an interruption of the study drug because of symptoms of anaphylaxis or hypersensitivity, administration of TCZ must be discontinued permanently and the patient should be withdrawn from the study. The patient should be treated according to the standard of care for management of the hypersensitivity reaction. Blood samples for the presence of anti-TCZ antibodies and PK or PD assessment should be obtained at the time of the event and 8 weeks after the final dose, as outlined in Appendix 1 and Appendix 2.

The first SC injection in both study periods (double-blind and open-label) will be administered to patients at the site under close supervision.

Study site personnel should educate patients about the signs and symptoms of hypersensitivity and anaphylaxis and instruct them to seek immediate medical attention if they experience such symptoms. If anaphylaxis or serious hypersensitivity reaction occurs, injection of TCZ must be discontinued permanently and any remaining PFSs should be returned to the study site.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.10
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE criteria; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study include the following:

- Serious or medically significant hepatic events, including cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.5.7)

- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Serious, opportunistic, or medically significant infections
- Myocardial infarction or acute coronary syndrome
- GI perforations
- Malignancies
- Anaphylaxis or hypersensitivity reactions (as defined in Section 5.1.9)
- Demyelinating disorders
- Stroke
- Serious or medically significant bleeding events

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until 8 weeks after the last dose of study drug or until completion of the last scheduled visit, whichever occurs later. After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment (see Section 5.6).

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v4.0) will be used for assessing adverse event severity. Table 4 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 4 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug, indicating "yes" or

"no" accordingly. The following guidance should be taken into consideration (see also Table 5):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 5 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Injection Reactions

Adverse events that occur during or within 24 hours after study drug administration should be captured as individual signs and symptoms on the Adverse Event eCRF rather than an overall diagnosis (e.g., record dyspnea and hypotension as separate events rather than a diagnosis of injection reaction).

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than injection reactions (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 $\times$ ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2). For management of study drug and abnormal liver function tests, please refer to Section 5.1.5.

5.3.5.8 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of SSc.

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should

be replaced by the established cause of death. *The term "sudden death" should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").*

If the death is attributed to progression of SSc, "systemic sclerosis progression" should be recorded on the Adverse Event eCRF.

5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of Systemic Sclerosis

Medical occurrences or symptoms of deterioration that are anticipated as part of SSc should be recorded as an adverse event if judged by the investigator to have worsened in severity or frequency or changed in nature at any time during the study. When recording a worsening of SSc on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by describing a worsening of a symptom or syndrome (e.g., "worsening gastrointestinal reflux disease") instead of a general "worsening of systemic sclerosis."

Worsening of skin thickening as measured by mRSS will be captured as efficacy assessment data only and should not be recorded as an adverse event. Worsening of FVC, if not accompanied by clinical symptoms, will be captured as efficacy data only and should not be recorded as an adverse event. Every effort should be made to document disease progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., in-patient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization for an adverse event that would ordinarily have been treated in an outpatient setting had an outpatient clinic been available

5.3.5.12 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.3.5.13 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. However, if any PRO responses suggestive of a possible adverse event are identified during site review of the PRO data, the investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF.

5.3.5.14 Adverse Events in Individuals Not Enrolled in the Study

If an adverse event inadvertently occurs in an individual not enrolled in the study (e.g., during administration of study drug), the Adverse Event Form provided to investigators should be completed and submitted to the Sponsor or its designee, either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (see Section 5.4.2 for further details)
- Adverse events of special interest (see Section 5.4.2 for further details)
- Pregnancies (see Section 5.4.3 for further details)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information for North America

Medical Monitor: [redacted]

Telephone No.: +[redacted]

Mobile Telephone No.: [redacted]

Medical Monitor Contact Information for Ex-North America

Medical Monitor: [redacted]

Telephone No.: +[redacted]

Mobile Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Monitor, and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor contact information, will be distributed to all investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event / Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 8 weeks after the last dose of study drug or until completion of the last scheduled visit, whichever occurs later. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the Serious Adverse Event / Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting post-study adverse events are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 8 weeks after the last dose of study drug. *A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee* immediately (i.e., no more than 24 hours after learning of the pregnancy) *either by faxing or by scanning and emailing the form with use of the fax number or email address provided to investigators.* Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. *In addition, the investigator will submit a Clinical Trial*

Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Abortions

Any abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.3.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 5.4.3.1.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 POST-STUDY ADVERSE EVENTS

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 8 weeks after the last dose of study drug or completion of the last scheduled visit, whichever occurs later), if the event is believed to be related to prior study drug treatment.

The investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the Serious Adverse Event / Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document:

- Tocilizumab Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Full details about all statistical issues and planned statistical analyses will be specified in a separate SAP. A database lock will occur when the last patient has completed his or her Week 48 assessments or has been withdrawn from the study. The original SAP will detail the reporting of data up to and including Week 48 and will be finalized prior to unblinding. The SAP may be amended to describe analyses of data collected after Week 48, if deemed necessary.

6.1 DETERMINATION OF SAMPLE SIZE

A sample size of approximately 105 patients in the TCZ group and 105 patients in the placebo group (a total of 210 patients) will give power in the range of $>$75% to 80%, (allowing for an estimated patient dropout rate of approximately 15% to 20%) to detect a between-group difference of 3.55 units (common standard deviation of 8.43) in mean change in mRSS from baseline to Week 48 using a two-group t-test, with a 5% two-sided significance level. The minimal detectable difference in mRSS (smallest treatment difference that would give a statistically significant result) under these assumptions, and with a patient dropout rate of 20%, is approximately 2.6 units.

6.2 SUMMARIES OF CONDUCT OF STUDY

Patient exclusions from the safety and intent-to-treat (ITT) populations, including the reason for exclusion, will be summarized by treatment group. A summary of enrollment by country and investigator name will be produced.

The number of patients that completed or discontinued from the study by Week 48, including a reason for discontinuation, will be summarized by treatment group. A listing of withdrawals, including reason and study day of withdrawal, will be produced.

The treatment duration within the study (defined as the time from the first dose of study drug to the last dose of study drug) will be summarized for the safety population at Week 48. Compliance will be summarized by dose intensity (the number of doses actually received divided by the expected number of doses), cumulative dose, and number of patients with missed doses.

The number and percentage of patients receiving escape therapy will be summarized by visit through Week 48.

A listing of patients in each treatment group who were randomized according to an incorrect stratification value given at baseline will be produced for the Week 48 analysis (IxRS stratification data will be compared with data entered in the eCRF).

A summary of all major protocol deviations will be produced.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

To descriptively assess the comparability of treatment arms (TCZ versus placebo) at baseline, clinically important baseline demographic and disease characteristics will be summarized for the safety population, with patients grouped according to the treatment actually received. If it is found that there is a large difference in the number of patients in the safety population compared with the intent to treat (ITT) population, additional summaries will be produced with patients grouped according to the treatment assigned at randomization.

These summary tables will include number of patients, mean, standard deviation, median, and range for continuous demographic/disease characteristics and number and percentage of patients for categorical characteristics.

Baseline demographics will include, but not be limited to, the following variables: sex, age, height, weight, race, ethnicity, country, reproductive status, and smoking history. Baseline disease characteristics will include, but are not be limited to, the following variables: duration of SSc, mRSS, CRP level, ESR level, platelet level, HAQ-DI, percentage of predicted FVC, percentage of predicted DL_{CO} (hemoglobin-corrected), auto-antibody status, and IL-6 status at Day 1.

Medical history data, including surgery and procedures and baseline conditions, will be summarized descriptively by treatment group using the safety population. Previous and concomitant treatment will be summarized descriptively by treatment group.

6.4 EFFICACY ANALYSES

The primary analysis population for efficacy will be the ITT population, which includes all patients who are randomized and who receive any study drug. Patients in the ITT population will be grouped according to the treatment assigned at randomization.

Statistical hypotheses will be tested at a nominal 5% significance level (allowing for adjustments for multiplicity as detailed in the SAP) against two-sided alternatives, and 95% CIs will be reported as appropriate. Full details of adjustments for multiplicity and/or sequential order of analyses will be predefined in the SAP prior to unblinding of the treatment groups.

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the mean change in mRSS from baseline to Week 48. The primary hypotheses to be tested are the following:

- H_0 (null hypothesis): There is no difference between the TCZ group and the placebo group in mean change in mRSS from baseline to Week 48.
- H_1 (alternative hypothesis): There is a difference between the TCZ group and the placebo group in mean change in mRSS from baseline to Week 48.

Similar hypotheses will be tested for the secondary efficacy parameters.

The mean change from baseline will be analyzed using a restricted maximum likelihood–based repeated-measures approach. The analysis will include fixed, categorical effects for treatment, IL-6 stratification level (< 10; ≥ 10 pg/mL) at screening, visit, IL-6 level at screening–by-visit interaction, and treatment-by-visit interaction, as well as continuous covariates of baseline mRSS and baseline mRSS–by-visit interaction. An unstructured covariance structure will be used to model within-patient errors.

The primary treatment comparison will be the contrast between treatment arms at Week 48. Analyses will be implemented in SAS® using PROC MIXED and the Kenward-Roger approximation (Kenward and Roger 1997).

The estimand of interest for the primary analysis is the difference between treatment arms in the mean change in the mRSS at Week 48 for the ITT population. The study has been designed to continue to capture efficacy data on patients who discontinue study drug prematurely or receive escape therapies during the double-blind treatment period. These data will be included in the primary analysis. However, it is unrealistic to assume that complete data will be obtained from patients who discontinue study drug prematurely, and the primary analysis specified above assumes a missing-at-random missing-data mechanism whereby patients who are lost to follow-up from the TCZ arm

will tend to have similar efficacy to that of patients on TCZ who remained in the study. Sensitivity analyses using missing-not-at-random models will be implemented. Specifically, a pattern-mixture model will be implemented, using multiple imputations, whereby missing data in the placebo arm will be imputed using a missing-at-random assumption and missing data in the TCZ arm will be imputed in a stepwise fashion using multiple calls to PROC MI with a monotone regression statement using data from placebo-treated patients as the basis for the imputation (Ratitch and O'Kelly 2011). This imputation method assumes that patients who are lost to follow-up in the TCZ arm will have a trajectory similar to that of patients in the placebo arm. Other clinically plausible MNAR models may be implemented, and full details will be specified in the SAP.

As appropriate, depending on the numbers of patients, analyses or summaries of the mean change in mRSS by clinically meaningful subgroups, including but not limited to disease duration and disease severity at baseline, will be carried out.

6.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints for this study are as follows:

- Difference in proportions of patients with $\geq$20%, $\geq$40%, and $\geq$60% improvement in mRSS at Week 48 compared with baseline
- Difference in mean change in FVC from baseline to Week 48
- Difference in mean change in HAQ-DI from baseline to Week 48
- Difference in mean change in Patient's Global Assessment from baseline to Week 48
- Difference in mean change in Physician's Global Assessment from baseline to Week 48
- Time to treatment failure, defined as the time from randomization to the time of one of the following events (whichever occurs first) during the 48-week double-blind treatment period:

  death,

  decline in percent-predicted FVC $>$10% relative to baseline

  $>$20% increase in mRSS **and** an increase in mRSS of $\geq$5 points

  occurrence of a predefined SSc-related complication as adjudicated by the Clinical Adjudication Committee

For the secondary efficacy endpoints, the TCZ treatment group will be compared with the placebo group using the following methods, which will be specified further in the SAP:

- Continuous variables, such as difference in mean change in observed FVC from baseline to Week 48, will be analyzed using the same methodology as specified for the primary analysis (see Section 6.4.1). For the FVC, additional analyses using non-parametric methods will be used alongside cumulative density plots.

- For binary response variables, such as the proportion of patients with $\geq 20\%$ improvement in mRSS at Week 48 compared with baseline, the weighted difference in proportion for the specified treatment group comparison will be presented, together with a 95% CI using the extended Mantel-Haenszel method and the p-value calculated using the Cochran-Mantel-Haenszel test, adjusting for the stratification factor, IL-6 level (< 10; ≥ 10 pg/mL) at screening. Patients who receive escape therapy between baseline and Week 48 or have a missing Week 48 assessment will be considered non-responders in the analysis.

6.4.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are listed in Section 3.4.6 and will be analyzed as appropriate.

6.5 SAFETY ANALYSES

The population for safety analyses will be the safety population. The safety population is defined as all randomized patients who received at least one dose of study drug and provide data from at least one post dose safety assessment. Patients will be grouped according to the treatment actually received.

The safety outcome measures for this study are as follows:

- Frequency of deaths
- Nature, frequency, and severity of adverse events
- Incidence of specific laboratory abnormalities
- Change from baseline in digital ulcer count

All data relating to safety will be summarized by treatment group for the 48-week double-blind treatment period. The long-term safety will be summarized for the entire treatment period (i.e., through Week 96).

Adverse events will be summarized by mapped term, appropriate thesaurus level, and toxicity grade. All adverse events will be coded and tabulated by System Organ Class and Preferred Term for individual events within each body system and will be presented in descending frequency. Adverse events will also be tabulated by severity and relationship to the study drug. Serious adverse events will be summarized separately.

Associated laboratory parameters, such as hepatic function, renal function, and hematologic values, will be grouped and presented together. Marked abnormalities will be tabulated for each laboratory test by treatment group.

The change from baseline for each vital sign variable will be computed and summarized using descriptive statistics. Physical examination and ECG data will also be summarized descriptively.

6.6 IMMUNOGENICITY ANALYSES

The immunogenicity outcome measures for this study are the incidence of anti-TCZ antibodies during the study relative to the prevalence of anti-TCZ antibodies at baseline and the correlation between anti-TCZ–antibody status and efficacy, safety, or PK outcome measures.

The immunogenicity analyses will include patients with at least one ATA assessment. The numbers and proportions of ATA-positive patients and ATA-negative patients during both the treatment and follow-up periods will be summarized by treatment group. Patients are considered to be ATA positive if they are ATA negative at baseline but develop an ATA response following study drug administration (treatment-induced ATA response), or if they are ATA positive at baseline and the titer of one or more postbaseline samples is at least 4-fold greater (i.e., $\geq$0.60 titer units) than the titer of the baseline sample (treatment-enhanced ATA response). Patients are considered to be ATA negative if they are ATA negative at baseline and all postbaseline samples are negative, or if they are ATA positive at baseline but do not have any postbaseline samples with a titer that is at least 4-fold greater than the titer of the baseline sample (treatment unaffected).

The relationship between ATA status and safety, efficacy, PK, and biomarker endpoints will be analyzed and reported descriptively via subgroup analyses.

6.7 PHARMACODYNAMIC ANALYSES

The PD outcome measure for this study is predose ESR and serum IL-6, sIL-6R, and CRP levels at baseline and at subsequent timepoints after initiation of study drug.

Data for all PD biomarkers will be presented using descriptive summary statistics, including mean, median, range, standard deviation, and coefficient of variation.

6.8 PHARMACOKINETIC ANALYSES

The PK outcome measures for this study are predose serum TCZ concentration at baseline and at specified timepoints thereafter, and the correlation between PK parameters for TCZ and efficacy, safety, or immunogenicity outcome measures

Predose concentrations of TCZ will be presented descriptively, including arithmetic means, median, range, standard deviations, and coefficients of variation.

6.9 INTERIM ANALYSIS

The Sponsor will define a futility analysis to which the Sponsor will remain blinded. The futility analysis will be conducted by an external statistical group and reviewed by the iDMC. The futility analysis will be based on the treatment difference for change from baseline in mRSS at Week 24; the stopping boundary will be determined by a beta

spending function. The study will be stopped for futility if the endpoint meets the futility criterion.

The futility analysis will be conducted when approximately 76 patients have either reached the Week 24 visit or have withdrawn. Since a repeated measures analysis will be used for the futility criterion, partial data from additional patients enrolled at (but not yet completed) Week 24 will also be utilized in the analysis. Thus, although only approximately one-third of the patients will have reached Week 24, the timing of the futility analysis approximates half of the final expected information (I) at Week 24, where I is the inverse of the expected variance of the treatment difference when all patients have reached Week 24.

Full statistical details of the futility analysis, along with the rationale and timing will be documented in the iDMC charter. The iDMC charter will be made available to the relevant health authorities.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data and other electronic data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 ELECTRONIC PATIENT-REPORTED OUTCOME DATA

Patients will use an ePRO device to capture PRO data. The data will be transmitted to a centralized database at the ePRO vendor.

Once the study is complete, the ePRO data, audit trail, and trial and system documentation will be archived. The investigator will receive patient data for the site in both human- and machine-readable formats on an archival-quality compact disc that must be kept with the study records as source data. Acknowledgement of receipt of the compact disc is required. In addition, the Sponsor will receive all patient data in a machine-readable format on a compact disc.

7.4 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.5 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, ePRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. Food and Drug Administration (FDA) regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Informed Assent Form or Home Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms

or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., when the last participating patient completes the last scheduled visit).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. *The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.*

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This study will be sponsored by Roche. Approximately 210 patients are expected be enrolled in this study, at approximately 120 global sites. Patients will be enrolled using an IxRS.

Central facilities will be used for the majority of the laboratory assessments. An iDMC will perform regular review of the safety data. A Clinical Adjudication Committee will adjudicate predefined serious adverse events with regard to their classification as SSc complications.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all

requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

http://www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective clinical study report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Assessments: Screening, Baseline, and Double-Blind Treatment Period

Assessment or Procedure	Screen. (up to 40 d)	Double-Blind Treatment Period (± 7 d, except Day 1)							Unsch. Visit	Treat. Discon. [c]	Follow-Up [a]	
		Day 1, BL	Wk 4 [b]	Wk 8 [b]	Wk 16 [b]	Wk 24 [b]	Wk 36 [b]	Wk 48 [b]			Wk 4	Wk 8 [a]
Informed consent	x [d]											
Demographics	x											
Medical history [e]	x											
Review of inclusion and exclusion criteria	x	x										
Electronic device training (PROs and study drug compliance)		x										
PRO assessments [f]		x		x	x	x	x	x				
Review study drug compliance			x	x	x	x	x	x	x	x		
Urinalysis [g, h]	x		x	x	x	x	x	x	x	x		
Pregnancy test [g, i]	x	x	x	x	x	x	x	x		x		
HBsAg and HCV serology	x											
Tuberculosis screening [j]	x						x			x		
Serum sample for IL-6 for stratification purposes	x											
Hematology [g, k]	x	x	x	x	x	x	x	x	x	x		
Chemistry panel (serum or plasma) and creatinine clearance [g, l]	x	x	x	x	x	x	x	x	x	x		
Liver profile [g, m]	x	x	x	x	x	x	x	x	x	x		
Lipid panel [g,*n*]		x		x		x		x	x	x		
ANA sample		x										

Appendix 1
Schedule of Assessments: Screening, Baseline, and Double-Blind Treatment Period (cont.)

Assessment or Procedure	Screen. (up to 40 d)	Double-Blind Treatment Period (± 7 d, except Day 1)							Unsch. Visit	Treat. Discon. [c]	Follow-Up [a]	
		Day 1, BL	Wk 4 [b]	Wk 8 [b]	Wk 16 [b]	Wk 24 [b]	Wk 36 [b]	Wk 48 [b]			Wk 4	Wk 8 [a]
SSc-specific auto-antibody panel [g, o]		x						x	x	x		
Serum anti-TCZ antibody sample [g, p]		x		x	x	x	x	x	x	x		x
Serum sample for PK analysis [g, p, q]		x	x	x	x	x	x	x	x	x		x
IL-6 sample [g, q]		x	x	x	x	x	x	x		x		
sIL-6R sample [g,p,q]		x	x	x	x	x	x	x	x	x		x
High-sensitivity CRP [g]	x	x	x			x		x	x	x		
ESR [g]	x	x	x			x		x	x	x		
Serum sample for candidate biomarkers [g]		x				x		x				
Plasma (EDTA) sample for candidate biomarkers [g]		x				x		x				
Whole blood sample for RNA extraction [g]		x				x		x				
Skin biopsies (RCR sample, optional) [r]		x						x				
Whole blood RCR sample for DNA exaction (optional)		x										
mRSS	x	x		x	x	x	x	x	x	x		
Forced vital capacity	x	x		x	x	x	x	x	x	x		
DL_{CO}	x	x				x		x	x	x		
Physician's Global Assessment [s]		x		x	x	x	x	x	x	x		
High-resolution CT scan [t]		x						x				

Appendix 1
Schedule of Assessments: Screening, Baseline, and Double-Blind Treatment Period (cont.)

Assessment or Procedure	Screen. (up to 40 d)	Double-Blind Treatment Period (± 7 d, except Day 1)							Unsch. Visit	Treat. Discon. [c]	Follow-Up [a]	
		Day 1, BL	Wk 4 [b]	Wk 8 [b]	Wk 16 [b]	Wk 24 [b]	Wk 36 [b]	Wk 48 [b]			Wk 4	Wk 8 [a]
Physical examination [u]	x	x							x	x		
Height	x [v]											
Body weight [g]	x	x						x	*x*	x		
Vital signs [g, w]	x	x	x	x	x	x	x	x	*x*	x		
Digital ulcer count [g]		x		x	x	x	x	x	x	x		
ECG	x								x			
Echocardiogram	x								x	x		
Adverse events [g, x, y]	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications [g, z]	x	x	x	x	x	x	x	x	x	x	x	x
Study drug distribution and administration [g, aa]		x [bb, cc]	x	x	x	x	x	x [bb]				

ANA = anti-nuclear antibody; BL = baseline; CBC = complete blood count; CRP = C-reactive protein; CT = computed tomography; d = day; Discon. = discontinuation; DL_{CO} = diffusing capacity of the lung for carbon monoxide; eCRF = electronic Case Report Form; ESR = erythrocyte sedimentation rate; EQ-5D-3L = EuroQol 5-Dimension Questionnaire (three levels of severity); FVC = forced vital capacity; HAQ-DI = Health Assessment Questionnaire Disability Index; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HRCT = high-resolution computed tomography; IL = interleukin; mRSS = modified Rodnan Skin Score; PK = pharmacokinetic; PRO = patient-reported outcome; RCR = Roche Clinical Repository; Screen. = screening; SGRQ = Saint George's Respiratory Questionnaire; SHAQ = Scleroderma Health Assessment Questionnaire; SkinPRO = Scleroderma Skin Patient-Reported Outcome; SSc = systemic sclerosis; TCZ = tocilizumab; Treat. = treatment; Unsch. = unscheduled; Wk = week; WPAI-GH = Work Productivity and Activity Impairment—General Health.

Appendix 1
Schedule of Assessments: Screening, Baseline, and Double-Blind Treatment Period (cont.)

Note: Assessments and procedures should be performed in the sequence that is most practical for the site, as long as PROs are performed first and study drug administration is performed last.

[a] All patients will undergo follow-up assessments within 4 weeks of study drug discontinuation and at 8 weeks after study drug discontinuation. For patients who discontinue study drug prematurely, a follow-up visit can be combined with the next scheduled visit (as outlined in Appendix 3), provided that the timing of the scheduled visit coincides with the specified timing for the follow-up visit. The follow-up visit at 4 weeks may be conducted by telephone.

[b] For patients at participating sites who have provided written informed consent to participate in home nursing services, specified assessments at Weeks 4, 8, 16, 24, 36, and 48, as well as Week 8 of the Follow-up Period may be performed by a trained home nursing professional or (at sites with established teams) by appropriately qualified site personnel at the patient's home or another suitable location.

[c] Patients who discontinue study drug prematurely should undergo assessments as outlined in Appendix 3, with the timing of those visits being relative to baseline. Assessments at the early treatment discontinuation visit should be performed *as soon as possible after discontinuing* study drug.

[d] Informed consent must be documented before any study-specific screening procedure is performed.

[e] Medical history includes clinically significant diseases (including SSc complications) reproductive status, smoking history, and use of alcohol and drugs of abuse.

[f] PRO questionnaires are to be completed prior to all other assessments during the study visit, with the exception of ECGs. Patients will use an electronic PRO device to capture PRO data. The appropriate PRO assessments will be programmed to appear at specific visits. The HAQ-DI, will be completed at baseline and at Weeks 8, 16, 24, 36, and 48. The Patient's Global Assessment, SHAQ, SGRQ, FACIT-Fatigue, and SkinPRO questionnaire will be completed at baseline and at Weeks 8, 16, 24, and 48. The SkinPRO questionnaire will only be administered in North America. The WPAI-GH and EQ-5D-3L will be completed at baseline and at Weeks 24 and 48.

[g] For patients at participating sites who have provided written informed consent to participate in home nursing services, this assessment or procedure may be performed by a trained home nursing professional or (at sites with established teams) by appropriately qualified site personnel at the patient's home or another suitable location.

[h] Urinalysis includes dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, and bacteria).

[i] All women who are not postmenopausal (≥12 months of non-therapy-induced amenorrhea) or surgically sterile will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[j] Tuberculosis screening *must* be performed *at screening and at Week 36. The screening method (e.g. PPD or QuantiFERON® test) is at the discretion of the investigator.*

Appendix 1
Schedule of Assessments: Screening, Baseline, and Double-Blind Treatment Period (cont.)

[k] Hematology includes hemoglobin, hematocrit, RBC count (with morphology), WBC count, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[l] Chemistry panel includes total protein, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN or urea, serum creatinine, C3, and C4. Creatinine clearance will be calculated by a central laboratory.

[m] Liver profile consists of AST, ALT, alkaline phosphatase, and total bilirubin (direct and indirect bilirubin will be performed if total bilirubin greater than the upper limit of normal).

[n] Overnight fasting (> 8 hours) is required. An additional fasting lipid panel should be obtained 8 weeks after initiation of lipid-lowering therapy.

[o] SSc-specific autoantibody panel includes anti-topoisomerase, anti-RNA polymerase, anti-PM/Scl, anti-histone, anti-U1 snRP, and anti-centromere antibodies.

[p] Additional samples for PK analysis and analysis of anti-TCZ antibodies and sIL-6R will be collected prior to resuming study drug for patients who have missed at least three consecutive doses and at the time of anaphylaxis or a serious hypersensitivity reaction.

[q] Samples for PK analysis and analysis of IL-6, sIL-6R, and candidate biomarkers will be obtained at a single blood draw and aliquoted according to the procedures in the Sample Handling and Logistics Manual.

[r] Two 3-mm punch biopsies are to be obtained from clinically involved skin, preferably at the forearm (optional).

[s] Physician's Global Assessment is to be completed by the investigator on the basis of examination and overall assessment of the patient.

[t] As accepted by the local regulations. Good-quality (as determined by the site radiologist and/or investigator), standard-of-care HRCT scans obtained within 3 months prior to screening and in accordance with study image acquisition guidelines can be used for baseline.

[u] A physical examination will be performed but will not be recorded on the eCRF, if normal; any abnormality will be reported either on the Medical History eCRF (for screening examination) or Adverse Event eCRF (for examinations after the screening).

[v] Height is required at screening only and will be recorded on the Vital Signs eCRF.

[w] Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressures while the patient is in a seated position, and temperature. Additional measurements may be performed in the event of an adverse event, at the discretion of the investigator. Temperature readings (as part of vital signs) will be measured but will not be recorded on the eCRF, if normal; any abnormal body temperature will be reported on the Adverse Event eCRF.

[x] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 8 weeks after the last dose of study drug or until completion of the last scheduled visit, whichever occurs later. However, for patients who discontinue study drug prematurely but continue scheduled visits, all adverse events will be reported until completion of the last scheduled visit or 8 weeks after the last dose of study drug, whichever occurs later. After this period, the investigator should report any serious adverse events that are believed to be related to prior study

drug treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

[y] For all serious infectious adverse events, CBC, differentials, and platelets should be determined during the disease episode. Every effort should be made to collect appropriate specimens for serology, polymerase chain reaction, or culture to identify the infectious organism. The results of all laboratory assessments performed locally, except for CRP, should be reported on the eCRF.

[z] Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 4 weeks prior to screening until 8 weeks after the last dose of study drug or until completion of the last scheduled visit, whichever occurs later. In addition, all medications taken for SSc since diagnosis will be recorded at screening.

[aa] If for any reason the weekly schedule cannot be kept (e.g., SC injections have to be administered to patients during a site visit), injections may be given a minimum of 5 days and a maximum of 11 days apart.

[bb] The first SC injection in both study periods (double-blind and open-label) will be administered to patients at the site under close supervision. The Week 48 injection is the first dose for the open-label treatment period.

[cc] Patients (and patient caregivers, if applicable) will be trained on how to perform SC injections at the Day 1 visit. For patients and caregivers at applicable sites who require additional training, study drug may be administered (or guidance provided) at Weeks 1 and 2 by a home nursing professional or by appropriately qualified site personnel.

Appendix 2
Schedule of Assessments: Open-Label Treatment Period

Assessment or Procedure	Open-Label Treatment Period (± 7 d)					Unsch. Visit	Treat. Discon. [b]	Follow-Up [c]	
	Wk 52 [a]	Wk 60 [a]	Wk 72 [a]	Wk 84 [a]	Wk 96 [a]			Wk 4	Wk 8 [a]
PRO assessments [d]			x		x				
Review study drug compliance	x	x	x	x	x	x	x		
Urinalysis [e,f]		x	x	x	x	x	x		
Pregnancy test [e,g]	x	x	x	x	x		x		
Tuberculosis screening [h]							x		
Hematology [e,i]	x	x	x	x	x	x	x		
Chemistry panel (serum or plasma) and creatinine clearance [e,j]	x	x		x		x	x		
Liver profile [e,k]	x	x	x	x	x	x	x		
Lipid panel [e,l]		x	x		x	x	x		
SSc-specific auto-antibody panel [e,m]					x	x	x		
Serum anti-TCZ antibody sample [e,n]					x	x	x		x
Serum sample for PK analysis [e,n,o]					x	x	x		x
IL-6 sample [e,o]					x		x		
sIL-6R sample [e,n,o]					x	x	x		x
High-sensitivity CRP [e]			x		x	x	x		
ESR [e]			x		x	x	x		
mRSS			x		x	x	x		
Forced vital capacity			x		x	x	x		
DL_{CO}			x		x	x	x		

Appendix 2
Schedule of Assessments: Open-Label Treatment Period (cont.)

Assessment or Procedure	Open-Label Treatment Period (± 7 d)					Unsch. Visit	Treat. Discon. [b]	Follow-Up [c]	
	Wk 52 [a]	Wk 60 [a]	Wk 72 [a]	Wk 84 [a]	Wk 96 [a]			Wk 4	Wk 8 [a]
Physician's Global Assessment [p]			x		x	x	x		
Physical examination [q]						x	x		
Body weight [e]					x	*x*	x		
Vital signs [e,r]	x	x	x	x	x	x	x		
Digital ulcer count [e]			x		x	x	x		
Echocardiogram						x	x		
Adverse events [e,s,t]	x	x	x	x	x	x	x	x	x
Concomitant medications [e,u]	x	x	x	x	x	x	x	x	x
Study drug distribution and administration [e,v]	*x*[w]	x	x	x					

CBC = complete blood count; CRP = C-reactive protein; d = day; Discon. = discontinuation; DL_{CO} = diffusing capacity of the lung for carbon monoxide; eCRF = electronic Case Report Form; ESR = erythrocyte sedimentation rate; EQ-5D-3L = EuroQol 5-Dimension Questionnaire (three levels of severity); FVC = forced vital capacity; HAQ-DI = Health Assessment Questionnaire Disability Index; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HRCT = high-resolution computed tomography; IL = interleukin; mRSS = modified Rodnan Skin Score; PK = pharmacokinetic; PRO = patient-reported outcome; RCR = Roche Clinical Repository; SHAQ = Scleroderma Health Assessment Questionnaire; SGRQ = Saint George's Respiratory Questionnaire; SkinPRO = Scleroderma Skin Patient-Reported Outcome; SSc = systemic sclerosis; TCZ = tocilizumab; Treat. = treatment; Unsch. = unscheduled; Wk = week; WPAI-GH = Work Productivity and Activity Impairment—General Health.

Note: Assessments and procedures should be performed in the sequence that is most practical for the site, as long as PROs are performed first and study drug administration is performed last.

[a] For patients at participating sites who have provided written informed consent to participate in home nursing services, specified assessments at Weeks 52, 60, 72, 84, and 96, as well as Week 8 of the Follow-up Period may be performed by a trained home nursing professional or (at sites with established teams) by appropriately qualified site personnel at the patient's home or another suitable location.

[b] Discontinued patients should undergo *a treatment discontinuation visit as soon as possible after discontinuing study drug*.

Appendix 2
Schedule of Assessments: Open-Label Treatment Period (cont.)

[c] All patients will undergo follow-up assessments within 4 weeks of study drug discontinuation and at 8 weeks after study drug discontinuation, *except for patients who reach Week 96 but who transition onto locally provided TCZ prior to the follow up visit.* The follow-up visit at 4 weeks may be conducted by telephone.

[d] PRO questionnaires are to be completed prior to all other assessments during the study visit. Patients will use an electronic PRO device to capture PRO data. The appropriate PRO assessments will be programmed to appear at specific visits. The HAQ-DI, Patient's Global Assessment, SHAQ, SGRQ, FACIT-Fatigue, and SkinPRO questionnaire will be completed at Weeks 72 and 96. The SkinPRO questionnaire will only be administered in North America. The WPAI-GH and EQ-5D-3L will be completed at Week 96.

[e] For patients at participating sites who have provided written informed consent to participate in home nursing services, this assessment or procedure may be performed by a trained home nursing professional or (at sites with established teams) by appropriately qualified site personnel at the patient's home or another suitable location.

[f] Urinalysis includes dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, and bacteria).

[g] Urine pregnancy tests will be conducted for all women who are not postmenopausal (≥ 12 months of non-therapy-induced amenorrhea) or surgically sterile. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[h] Tuberculosis screening *must* be performed *at screening and at Week 36. The screening method (e.g. PPD or QuantiFERON® test) is at the discretion of the investigator.*

[i] Hematology includes hemoglobin, hematocrit, RBC count (with morphology), WBC count, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[j] Chemistry panel includes total protein, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN or urea, serum creatinine, C3, and C4. Assessment of creatinine clearance is to be performed every 12 weeks and will be calculated by the central laboratory. Creatinine clearance will be calculated by a central laboratory.

[k] Liver profile consists of AST, ALT, alkaline phosphatase, and total bilirubin (direct and indirect bilirubin will be performed if total bilirubin greater than the upper limit of normal).

[l] Overnight fasting (> 8 hours) is required. An additional fasting lipid panel should be obtained 8 weeks after initiation of lipid-lowering therapy.

[m] SSc-specific autoantibody panel includes anti-topoisomerase, anti-RNA polymerase, anti-PM/Scl, anti-histone, anti-U1 snRP, and anti-centromere antibodies.

[n] Additional samples for PK analysis and analysis of anti-TCZ antibodies and sIL-6R will be collected prior to resuming study drug for patients who have missed at least three consecutive doses and at the time of anaphylaxis or a serious hypersensitivity reaction.

Appendix 2
Schedule of Assessments: Open-Label Treatment Period (cont.)

[o] Samples for PK analysis and analysis of IL-6 and sIL-6R will be obtained at a single blood draw and aliquoted according to the procedures in the Sample Handling and Logistics Manual.

[p] Physician's Global Assessment is to be completed by the investigator on the basis of examination and overall assessment of the patient.

[q] A physical examination will be performed but will not be recorded on the eCRF, if normal; any abnormality will be reported on the Adverse Event eCRF.

[r] Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressures while the patient is in a seated position, and temperature. Additional measurements may be performed in the event of an adverse event, at the discretion of the investigator. Temperature readings (as part of vital signs) will be measured but will not be recorded on the eCRF, if normal; any abnormal body temperature will be reported on the Adverse Event eCRF.

[s] After initiation of study drug, all adverse events will be reported until 8 weeks after the last dose of study drug or until completion of the last scheduled visit, whichever occurs later. However, for patients who discontinue study drug prematurely but continue scheduled visits, all adverse events will be reported until completion of the last scheduled visit or 8 weeks after the last dose of study drug, whichever occurs later. After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

[t] For all serious infectious adverse events, CBC, differentials and platelets should be determined during the disease episode. Every effort should be made to collect appropriate specimens for serology, polymerase chain reaction, or culture to identify the infectious organism. The results of all laboratory assessments performed locally, except for CRP, should be reported on the eCRF.

[u] Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 4 weeks prior to screening until 8 weeks after the last dose of study drug or until completion of the last scheduled visit, whichever occurs later.

[v] If for any reason the weekly schedule cannot be kept (e.g., SC injections have to be administered to patients during a site visit), injections may be given a minimum of 5 days and a maximum of 11 days apart.

[w] Study drug administration only; no study drug distribution at this visit.

Appendix 3
Schedule of Assessments: Patients Who Have Discontinued Study Drug Prematurely

Assessment or Procedure	Timing of Visit Relative to Baseline (Day 1)				
	Wk 8 [a] (±7d)	Wk 16 [a] (±7d)	Wk 24 [a] (±7d)	Wk 36 [a] (±7d)	Wk 48 [a, e] (±7d)
mRSS	x	x	x	x	x
Forced vital capacity	x	x	x	x	x
HAQ-DI	x	x	x	x	x
Adverse events [a,b,c]	x	x	x	x	x
Concomitant medications [a,d]	x	x	x	x	x

Appendix 3
Schedule of Assessments: Patients Who Have Discontinued Study Drug Prematurely (cont.)

CBC = complete blood count; CRP = C-reactive protein; d; eCRF = electronic Case Report Form; HAQ-DI = Health Assessment Questionnaire Disability Index; mrSS = modified Rodnan Skin Score; Wk = week.

Note: Patients who discontinue study drug prematurely but continue to attend scheduled study visits should follow a reduced assessment schedule as outlined above, starting with the first scheduled visit following discontinuation of study drug. *These patients should also undergo a treatment discontinuation (TD) visit as soon as possible after discontinuing study drug, and follow-up assessments within 4 weeks of study drug discontinuation and at 8 weeks after study drug discontinuation. A TD and/or follow-up visit may be combined with the next scheduled visit (as outlined above in Appendix 3), provided that the timing of the scheduled visit coincides with the specified timing for the TD or follow-up visit.*

[a] For patients at participating sites who have provided written informed consent to participate in home nursing services, specified assessments at each visit may be performed by a trained home nursing professional or (at sites with established teams) by appropriately qualified site personnel at the patient's home or another suitable location.

[b] After initiation of study drug, all adverse events will be reported until 8 weeks after the last dose of study drug or until completion of the last scheduled visit, whichever occurs later. However, for patients who discontinue study drug prematurely but continue scheduled visits, all adverse events will be reported until completion of the last scheduled visit or 8 weeks after the last dose of study drug, whichever occurs later. After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

[c] For all serious infectious adverse events, CBC, differentials and platelets should be determined during the disease episode. Every effort should be made to collect appropriate specimens for serology, polymerase chain reaction, or culture to identify the infectious organism. The results of all laboratory assessments performed locally, except for CRP, should be reported on the eCRF.

[d] Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 4 weeks prior to screening until 8 weeks after the last dose of study drug or until completion of the last scheduled visit, whichever occurs later. *Patients who start other medications for systemic sclerosis (e.g., DMARDs) between treatment discontinuation and Week 48 may remain on these medications during the open-label period at the discretion of the investigator.*

[e] *Patients who enter the open-label period at Week 48 must complete the full Week 48 schedule of assessments in Appendix 1. If these patients discontinue after TCZ treatment in the open-label period they should undergo a second TD visit and complete the 4 and 8 week follow-up visits.*

Appendix 4
Work Productivity and Activity Impairment—General Health Questionnaire (Version 2.0)

The following questions ask about the effect of your health problems on your ability to work and perform regular activities. By health problems we mean any physical or emotional problem or symptom. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? ____ NO ____ YES
   If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of your health problems? *Include hours you missed on sick days, times you went in late, left early, etc., because of your health problems. Do not include time you missed to participate in this study.*

   _____HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS *(If "0", skip to question 6.)*

Appendix 4
Work Productivity and Activity Impairment—General Health Questionnaire (Version 2.0) (cont.)

5. During the past seven days, how much did your health problems affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If health problems affected your work only a little, choose a low number. Choose a high number if health problems affected your work a great deal.

Consider only how much health problems affected productivity while you were working.

Health problems had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Health problems completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did your health problems affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If health problems affected your activities only a little, choose a low number. Choose a high number if health problems affected your activities a great deal.

Consider only how much health problems affected your ability to do your regular daily activities, other than work at a job.

Health problems had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Health problems completely prevented me from doing my daily activities

CIRCLE A NUMBER

Appendix 5
Clinician's Global Assessment

On a scale of 0–100, where would you rate the overall effect systemic sclerosis has on your patient at this time?

PLACE A VERTICALMARK ON THE LINE TO INDICATE YOUR ANSWER.

_____

0 — Has no effect at all

100 — worst possible effect

Appendix 6
Health Assessment Questionnaire–Disability Index and Scleroderma-Specific Visual Analog Score Scales for 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?	_____	_____	_____	_____

Appendix 6
Health Assessment Questionnaire–Disability Index and Scleroderma-specific Visual Analog Score scales for Scleroderma Health Assessment Questionnaire (cont.)

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

_____ Cane

_____ Walker

_____ Crutches

_____ Wheelchair

_____ Devices used for dressing (button hook, zipper pull, long-handled shoe horn, etc.)

_____ Built up or special utensils

_____ Special or built up chair

_____ Other (Specify:_____)

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

_____ Dressing and Grooming

_____ Arising

_____ Eating

_____ Walking

Appendix 6
Health Assessment Questionnaire–Disability Index and Scleroderma-Specific Visual Analog Score Scales for Scleroderma Health Assessment Questionnaire (cont.)

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?	_____	_____	_____	_____

Appendix 6
Health Assessment Questionnaire–Disability Index and Scleroderma-Specific Visual Analog Score Scales for Scleroderma Health Assessment Questionnaire (cont.)

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

Appendix 6
Health Assessment Questionnaire–Disability Index and Scleroderma-Specific Visual Analog Score Scales for Scleroderma Health Assessment Questionnaire (cont.)

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's Global Assessment

On a scale of 0–100 where would you rate the overall effect your systemic sclerosis has on you at this time?

PLACE A <u>VERTICAL</u> MARK (I) ON THE LINE TO INDICATE YOUR ANSWER

_____

0 100
Has no effect at all worst possible effect

Appendix 8
Functional Assessment of Chronic Therapy–Fatigue

FACIT Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

Appendix 9
EQ-5D™

EQ-5D Health Questionnaire

(English version for the United States)

Appendix 9
EQ-5D™ (cont.)

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

I am moderately anxious or depressed ❑

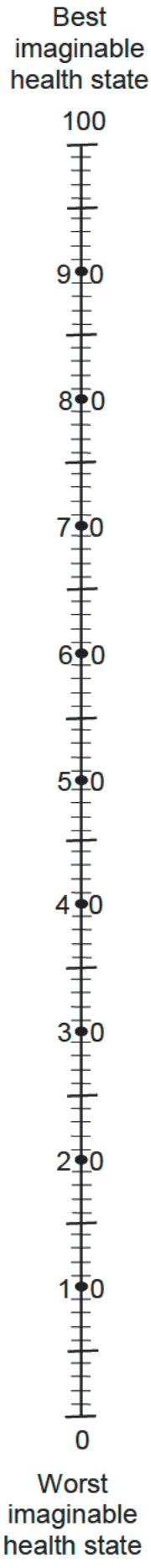
I am extremely anxious or depressed ❑

Appendix 9
EQ-5D™ (cont.)

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Appendix 10
Saint George's Respiratory Questionnaire

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE
ORIGINAL ENGLISH VERSION

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ)

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life. We are using it to find out which aspects of your illness cause you most problems, rather than what the doctors and nurses think your problems are.

Please read the instructions carefully and ask if you do not understand anything. Do not spend too long deciding about your answers.

Before completing the rest of the questionnaire:

Please tick in one box to show how you describe your current health:

Very good	Good	Fair	Poor	Very poor
☐	☐	☐	☐	☐

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continued…

St. George's Respiratory Questionnaire
PART 1

Questions about how much chest trouble you have had over the past 3 months.

Please tick (✓) *one box for each question*:

	most days a week	several days a week	a few days a month	only with chest infections	not at all
1. Over the past 3 months, I have coughed:	☐	☐	☐	☐	☐
2. Over the past 3 months, I have brought up phlegm (sputum):	☐	☐	☐	☐	☐
3. Over the past 3 months, I have had shortness of breath:	☐	☐	☐	☐	☐
4. Over the past 3 months, I have had attacks of wheezing:	☐	☐	☐	☐	☐

5. During the past 3 months how many severe or very unpleasant attacks of chest trouble have you had?

Please tick (✓) *one*:

- more than 3 attacks ☐
- 3 attacks ☐
- 2 attacks ☐
- 1 attack ☐
- no attacks ☐

6. How long did the worst attack of chest trouble last?
(Go to question 7 if you had no severe attacks)

Please tick (✓) *one*:

- a week or more ☐
- 3 or more days ☐
- 1 or 2 days ☐
- less than a day ☐

7. Over the past 3 months, in an average week, how many good days (with little chest trouble) have you had?

Please tick (✓) *one*:

- No good days ☐
- 1 or 2 good days ☐
- 3 or 4 good days ☐
- nearly every day is good ☐
- every day is good ☐

8. If you have a wheeze, is it worse in the morning?

Please tick (✓) *one:*

- No ☐
- Yes ☐

continued…

St. George's Respiratory Questionnaire
PART 2

Section 1

How would you describe your chest condition?

Please tick (✓) *one*:

- The most important problem I have ☐
- Causes me quite a lot of problems ☐
- Causes me a few problems ☐
- Causes no problem ☐

If you have ever had paid employment.

Please tick (✓) *one*:

- My chest trouble made me stop work altogether ☐
- My chest trouble interferes with my work or made me change my work ☐
- My chest trouble does not affect my work ☐

Section 2

Questions about what activities usually make you feel breathless <u>these days</u>.

	Please tick (✓) in ***each box*** that applies to you ***these days***: True	False
Sitting or lying still	☐	☐
Getting washed or dressed	☐	☐
Walking around the home	☐	☐
Walking outside on the level	☐	☐
Walking up a flight of stairs	☐	☐
Walking up hills	☐	☐
Playing sports or games	☐	☐

continued…

St. George's Respiratory Questionnaire
PART 2

Section 3

Some more questions about your cough and breathlessness <u>these days</u>.

	Please tick (✓) in ***each box*** that applies to you ***these days***: True	False
My cough hurts	☐	☐
My cough makes me tired	☐	☐
I am breathless when I talk	☐	☐
I am breathless when I bend over	☐	☐
My cough or breathing disturbs my sleep	☐	☐
I get exhausted easily	☐	☐

Section 4

Questions about other effects that your chest trouble may have on you <u>these days</u>.

	Please tick (✓) in ***each box*** that applies to you ***these days***: True	False
My cough or breathing is embarrassing in public	☐	☐
My chest trouble is a nuisance to my family, friends or neighbours	☐	☐
I get afraid or panic when I cannot get my breath	☐	☐
I feel that I am not in control of my chest problem	☐	☐
I do not expect my chest to get any better	☐	☐
I have become frail or an invalid because of my chest	☐	☐
Exercise is not safe for me	☐	☐
Everything seems too much of an effort	☐	☐

Section 5

Questions about your medication, if you are receiving no medication go straight to section 6.

	Please tick (✓) in ***each box*** that applies to you ***these days***: True	False
My medication does not help me very much	☐	☐
I get embarrassed using my medication in public	☐	☐
I have unpleasant side effects from my medication	☐	☐
My medication interferes with my life a lot	☐	☐

continued…

St. George's Respiratory Questionnaire
PART 2

Section 6

These are questions about how your activities might be affected by your breathing.

Please tick (✓) in ***each box*** that applies to you ***because of your breathing***:

	True	False
I take a long time to get washed or dressed	☐	☐
I cannot take a bath or shower, or I take a long time	☐	☐
I walk slower than other people, or I stop for rests	☐	☐
Jobs such as housework take a long time, or I have to stop for rests	☐	☐
If I walk up one flight of stairs, I have to go slowly or stop	☐	☐
If I hurry or walk fast, I have to stop or slow down	☐	☐
My breathing makes it difficult to do things such as walk up hills, carrying things up stairs, light gardening such as weeding, dance, play bowls or play golf	☐	☐
My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk at 5 miles per hour, play tennis or swim	☐	☐
My breathing makes it difficult to do things such as very heavy manual work, run, cycle, swim fast or play competitive sports	☐	☐

Section 7

We would like to know how your chest <u>usually</u> affects your daily life.

Please tick (✓) in ***each box*** that applies to you ***because of your chest trouble***:

	True	False
I cannot play sports or games	☐	☐
I cannot go out for entertainment or recreation	☐	☐
I cannot go out of the house to do the shopping	☐	☐
I cannot do housework	☐	☐
I cannot move far from my bed or chair	☐	☐

continued…

St. George's Respiratory Questionnaire

Here is a list of other activities that your chest trouble may prevent you doing. (You do not have to tick these, they are just to remind you of ways in which your breathlessness may affect you):

Going for walks or wa king the dog

Doing things at home or in the garden

Sexual intercourse

Going out to church, pub, club or place of entertainment

Going out in bad weather or into smoky rooms

Visiting family or friends or playing with children

Please write in any other important activities that your chest trouble may stop you doing:

. . . . . .

. . . . . .

. . . . . .

. . . . . .

Now would you tick in the box (one only) which you think best describes how your chest affects you:

It does not stop me doing anything I would like to do ☐

It stops me doing one or two things I would like to do ☐

It stops me doing most of the things I would like to do ☐

It stops me doing everything I would like to do ☐

Thank you for filling in this questionnaire. Before you finish would you please check to see that you have answered all the questions.

Appendix 11
Scleroderma Skin Patient-Reported Outcome Questionnaire

We would like to know how scleroderma affects **your SKIN** and how these skin problems has affected the way you feel and do things. Please try to think back to your SKIN as you answer these questions.

Note that **ulcers on your hands or fingers or Raynaud's symptoms are NOT** the focus of this questionnaire, as they are more related to how scleroderma affects the blood vessels.

Some questions may have different meanings for different people, please answer according to whatever you feel the question means for you.

Over the PAST 4 WEEKS:	Not at all ↓						Very Much ↓
1. How **tight** has your skin felt?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
2. How **swollen** have your hands been?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
3. How **dry** has your skin been?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
4. How much has your skin been **tingling** or **burning**?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
5. How **painful** has your skin been?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
6. How **hard** has your skin felt?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
7. How **discolored** has your skin been?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
8. How **itchy** has your skin felt?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
9. How **self-conscious** have you been because of your skin?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
10. How **worried** have you been about your skin?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
11. How **depressed** have you been about your skin?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
12. How much have you **not felt like your true self** because of the way your skin is?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
13. How **frustrated** have you been about your skin?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
14. How much have you felt like you **lack control over** your skin's condition?	☐0	☐1	☐2	☐3	☐4	☐5	☐6

Date Prepared: 18-Jun-2014

Over the PAST 4 WEEKS:	Not at all ↓						Very Much ↓
15. How much difficulty have you had **doing things with your hands** because of skin tightness?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
16. How much difficulty have you had with **opening or closing your mouth** because of skin tightness?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
17. How much difficulty have you had with **moving parts of your body** because of skin tightness?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
18. How much has your skin's condition interfered with your **daily activities** (examples: work, study, leisure activities)?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
19. How much has your skin **prevented you from going out to socialize**?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
20. How much has your skin interfered with your **interactions with people**?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
21. How much has your skin affected the **clothes** you wear?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
22. How much has your skin interfered with your **sex life**? (please answer "Not at all" if this does not apply to you)	☐0	☐1	☐2	☐3	☐4	☐5	☐6