Clinical Trial Protocol

Clinical Trial Protocol Number	EMR200017-014
Title	A Phase II, randomized, double-blind, placebo-controlled, parallel-group, multicenter trial to evaluate the efficacy and safety of abituzumab in subjects with systemic sclerosis-associated interstitial lung disease (SSc-ILD)
Phase	II
IND Number	CCI
EudraCT Number	2015-005023-11
Coordinating Investigator	For all countries, except North America: PPD For sites in North America: PPD
Sponsor	For all countries, except the USA: Merck KGaA Frankfurter Strasse 250 64293 Darmstadt, Germany For sites in the USA: EMD Serono Research & Development Institute, Inc. 45A Middlesex Turnpike Billerica, MA 01821, USA Medical Responsible: PPD EMD Serono Research & Development Institute, Inc. 45A Middlesex Turnpike Billerica, MA, 01821 USA Telephone number: PPD Fax number: PPD
Clinical Trial Protocol Version	26 July 2017/Version 5.0 including Amendments 1 to 5
Replaces Version	14 September 2016/Version 4.0

[redacted]

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List of Abbreviations

ACR	American College of Rheumatology
ADA	Antidrug antibody
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
ANA	Antinuclear antibodies
ANCOVA	Analysis of covariance
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BDI	Baseline Dyspnea Index
BP	Blood pressure
C_{max}	Maximum observed concentration
C_{min}	Minimum observed concentration
CRISS	Combined Response Index for Systemic Sclerosis
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
dcSSc	Diffuse cutaneous systemic sclerosis
DLCO	Diffusion capacity of the lung for carbon monoxide
ECG	Electrocardiogram
eCRF	Electronic case report form
ERA	Endothelin receptor antagonist
EU	European Union
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
HBsAg	Hepatitis B surface antigen

HIV	Human immunodeficiency virus
HRCT	High-resolution computed tomography
HRQoL	Health-related quality of life
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgG2	Immunoglobulin G2
IgM	Immunoglobulin M
ILD	Interstitial lung disease
IMP	Investigational medicinal product
INR	International normalized ratio
IPF	Idiopathic pulmonary fibrosis
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intrauterine device
IUS	Intrauterine hormone releasing system
IVRS/IWRS	Interactive voice/web response system
KCO	Transfer coefficient of the lung for carbon monoxide
LTBI	Latent tuberculosis infection
MAR	Missing-at-random
mITT	Modified Intent-to-Treat
MMF	Mycophenolate mofetil
MPS	Sodium mycophenolate
mRNA	Messenger ribonucleic acid
mRSS	Modified Rodnan skin score
mSv	Millisieverts
NCI	National Cancer Institute
NT pro-BNP	N-terminal prohormone brain natriuretic peptide
NYHA	New York Heart Association
OMERACT	Outcome Measures in Rheumatology
PAH	Pulmonary arterial hypertension

PD	Pharmacodynamic(s)
PEF	Peak expiratory flow
PK	Pharmacokinetic(s)
PP	Per-Protocol
PRO	Patient-reported outcome
PTT	Partial thromboplastin time
QLF	Quantitative lung fibrosis
QoL	Quality of life
RNA	Ribonucleic acid
SAE	Serious adverse event
SGRQ	St. George Respiratory Questionnaire
SHAQ	Scleroderma Health Assessment Questionnaire
SLS	Scleroderma Lung Study
SOC	System organ class
SSc	Systemic sclerosis
SSc-ILD	Systemic sclerosis-associated interstitial lung disease
SUSAR	Suspected unexpected serious adverse reaction
TB	Tuberculosis
TDI	Transition Dyspnea Index
TEAE	Treatment-emergent adverse event
TGF	Transforming growth factor
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
VAS	Visual analogue scale
WOCF	Worst observation carried forward

1 Synopsis

Clinical Trial Protocol Number	EMR200017-014
Title	A Phase II, randomized, double-blind, placebo-controlled, parallel-group, multicenter trial to evaluate the efficacy and safety of abituzumab in subjects with systemic sclerosis-associated interstitial lung disease (SSc-ILD)
Trial Phase	II
IND Number	CCI
FDA covered trial	Yes
EudraCT Number	2015-005023-11
Coordinating Investigator	For all countries, except North America: PPD For sites in North America: PPD
Sponsor	For all countries, except the USA: Merck KGaA Frankfurter Strasse 250 64293 Darmstadt, Germany For sites in the USA: EMD Serono Research & Development Institute, Inc. 45A Middlesex Turnpike Billerica, MA 01821, USA
Trial centers/countries	This trial will be conducted at approximately 60 sites globally, including, but not limited to, North America and the European Union.
Planned trial period (first subject in-last subject out)	March 2016 to October 2020
Trial Registry	ClinicalTrials.gov and other clinical trial registries

Objectives:

Primary Objective

The primary objective of the trial is to demonstrate efficacy of abituzumab in improving lung function of subjects with systemic sclerosis (SSc) associated interstitial lung disease (SSc-ILD).

Secondary Objectives

The secondary objectives of the trial are:

- To characterize further the effect of abituzumab on subjects with SSc-ILD who are treated with a stable mycophenolate regimen;
- To characterize the safety, tolerability, and immunogenicity of abituzumab in subjects with SSc-ILD who are treated with a stable mycophenolate regimen;
- To evaluate the effect of abituzumab on SSc skin disease in subjects with diffuse skin involvement who are treated with a stable mycophenolate regimen;
- To evaluate health-related quality of life (HRQoL) outcomes of abituzumab in subjects with SSc-ILD who are treated with a stable mycophenolate regimen;
- To evaluate pharmacokinetic (PK) parameters of abituzumab in subjects with SSc-ILD who are treated with a stable mycophenolate regimen.

Exploratory Objectives

The exploratory objectives of the trial are:

- CCI [redacted]

Methodology: This is a Phase II, multicenter, double-blind, placebo-controlled, parallel-group trial to be conducted in adult subjects with SSc-ILD to evaluate the efficacy, safety, tolerability, and immunogenicity of multiple intravenous doses of abituzumab on top of background therapy. Subjects must be currently treated with the same mycophenolate regimen (stable dose) in a range of 1.5 to 3 g/day of mycophenolate mofetil (MMF) or 1080 to 2160 mg/day of sodium mycophenolate (MPS) for at least 2 months prior to the Screening Visit and continued through Day 1 of the Treatment Period.

The trial is composed of a Screening Period, a Double-blind Treatment Period, a Safety Follow-up Period, and Survival Follow-up as follows:

- Screening Period: duration of up to 6 weeks; however, subjects should have the Day 1 visit as soon as possible after eligibility for the trial has been confirmed.
- Double-blind Treatment Period: duration of 104 weeks (2 years) starting at randomization.

Subjects will be monitored at Weeks 2, 4, and every 4 weeks thereafter until Week 104.

- Safety Follow-up Period: duration of 12 weeks. During the Safety Follow-up Period, monitoring for adverse events (AEs), assessment of disease progression, and an assessment for antidrug antibodies (ADA) will be carried out.
- Survival Follow-up: each subject will be followed up by the site for survival status every 12 weeks (± 1 week) after the subject's last trial visit until death of the subject or end of the trial.

Approximately 175 subjects will be randomized in a 2:2:1 ratio to receive abituzumab 1500 mg, placebo, or abituzumab 500 mg, respectively, given as an intravenous infusion over 1 hour every 4 weeks with the last IMP administration at the Week 100 visit.

Subjects are to continue their previous stable mycophenolate therapy.

The effects of abituzumab on clinical status will be assessed through evaluations including pulmonary function tests, high-resolution computed tomography (HRCT), and patient-reported outcomes (PROs).

Subjects who meet the criteria for clinically meaningful progression during the Double-blind Treatment Period or Safety Follow-up Period should have a change in background therapy. With regard to progression of ILD, subjects taking less than the maximal specified dose of mycophenolate (3 g/day MMF or 2160 mg/day MPS) can have the mycophenolate dose increased while investigational medicinal product (IMP) is continued. Subjects taking the maximal specified dose of mycophenolate who have clinically meaningful progression should have the IMP discontinued and be treated according to local standard of care. If a nonbiologic immunosuppressant (such as cyclophosphamide [oral or intravenous]) is initiated, then mycophenolate must be discontinued.

With regard to progression of manifestations not including ILD, subjects should be considered for change in therapy according to local standard of care, at the discretion of the Investigator.

Subjects meeting 1 or both of the below criteria will be considered as having clinically meaningful disease progression:

1. SSc-ILD: one of the following (in the absence of other causative intercurrent illness) on at least 2 occasions within approximately 4 weeks apart (as per OMERACT criteria):

- Relative decrease from baseline in forced vital capacity (FVC) % predicted ≥ 10%;
- Relative decrease from baseline in FVC % predicted ≥ 5% to < 10% AND relative decrease from baseline in the diffusion capacity of the lung for carbon monoxide (DLCO) % predicted ≥ 15%.

2. SSc progression other than interstitial lung disease (ILD): new onset of one or more of the following:

- Scleroderma renal crisis;
- Left ventricular failure (defined as ejection fraction ≤ 45%);

- Pulmonary arterial hypertension requiring treatment.

If a subject discontinues IMP, then the subject should complete the early termination visit and then the remaining scheduled visits. At a minimum, the subject is expected to complete the trial visits at Weeks 12, 24, 36, 52, 64, 76, 88, and 104, as well as the Safety Follow-up period Week 12 visit. Subjects with discontinued IMP can come to the other scheduled visits during the trial period according to the Investigator's judgment.

Subjects who withdraw from the treatment period would have an early termination visit followed by entrance into the Safety Follow-up Period.

Subjects who withdraw from the trial (eg, withdraw consent, lost to follow up, or death) would not have any additional trial visits.

All subjects will be followed up by the site for survival from the subject's last trial visit until death or the end of the trial.

New onset or worsening of manifestations of scleroderma that are not captured by the pulmonary function tests, modified Rodnan skin score (mRSS), or digital ulcer count, should be reported as AEs.

If the ILD on HRCT worsens significantly according to the Investigator, then subjects can have the mycophenolate treatment increased to the protocol-specified maximal dose (ie, 3 g/day MMF or 2160 mg/day MPS).

During the conduct of the trial, an Independent Data Monitoring Committee (IDMC) will monitor safety data on a regular basis (to be specified in the IDMC charter). The IDMC will also review the results of the interim futility analysis conducted by an independent statistical center. Based on the prespecified stopping boundary of futility, and the totality of the information at interim, the IDMC will make a recommendation to the Sponsor on continuing or stopping the trial for futility. An independent panel of dermatologists will provide guidance for further investigation and interpretation of cutaneous AEs that are serious, are Grade 3 or higher, or are not responding to treatment, and advise the IDMC whether any actions to modify clinical trial conduct should be considered.

Planned number of subjects: Approximately 175 subjects are planned for trial randomization.

Primary endpoint: The primary endpoint of this trial is the annual rate of absolute FVC change in volume (mL).

Secondary efficacy endpoints:

The key secondary endpoints include the following:

- Change in dyspnea from baseline as measured by the Mahler Transition Dyspnea Index (TDI) at Week 52;
- Absolute change from baseline in St. George Respiratory Questionnaire (SGRQ) total score at Week 52;
- Absolute change from baseline in mRSS at Week 52 in subjects with diffuse cutaneous skin involvement at baseline;

- Absolute change from baseline in quantitative lung fibrosis (QLF) in the region of highest baseline severity at Week 52;
- Overall survival.

Other secondary efficacy endpoints include:

- Proportion of subjects with clinically meaningful progression of SSc by meeting clinically meaningful disease progression Criterion 1 (ILD) by Week 52 and by Week 104;
- Proportions of subjects with clinically meaningful progression of SSc by meeting clinically meaningful disease progression Criterion 2 (SSc progression other than ILD) by Week 52 and by Week 104;
- Proportion of subjects with clinically meaningful progression by Week 52 and by Week 104;
- Proportion of subjects with absolute decrease from baseline of FVC % predicted ≥ 10% on 2 or more consecutive occasions within approximately 4 weeks apart by Week 52 and by Week 104;
- Time to first clinically meaningful progression;
- Absolute change from baseline in FVC % predicted up to Week 104;
- Absolute change from baseline in DLCO % predicted up to Week 104;
- Absolute change from baseline in transfer coefficient of the lung for carbon monoxide (KCO) up to Week 104;
- Absolute change from baseline in QLF in the region of highest baseline severity at Week 104;
- Absolute change from baseline in quantitative HRCT analyses of extent of total ILD up to Week 104.

Safety endpoints:

- Nature, incidence, severity, relationship and outcome of AEs, serious AEs (SAEs), and AEs of special interest (AESIs) from screening up to Week 116;
- Number of subjects with treatment-emergent AEs, SAEs, and AESIs from baseline up to Week 116;
- Treatment-emergent changes in clinical laboratory measures, electrocardiogram (ECG) measures, and vital signs from baseline up to Week 116;
- Incidence of subjects with positive ADA titers from baseline up to Week 116.

Quality of life endpoints:

- Proportion of subjects with Mahler TDI worsening ≥ 2 up to Week 104;
- Proportion of subjects with Mahler TDI worsening ≥ 2 up to Week 104 for subjects with Mahler Baseline Dyspnea Index (BDI) ≥ 2;

- Change in dyspnea from baseline as measured by the Mahler TDI up to Week 104;
- Change in dyspnea from baseline as measured by the Mahler TDI up to Week 104 for subjects with Mahler BDI ≥ 2;
- Absolute change from baseline for each of the following HRQoL questionnaires up to Week 104:
  - Leicester Cough Index
  - SGRQ
  - Physician's Global Assessment
  - Patient's Global Assessment
  - Scleroderma Health Assessment Questionnaire (SHAQ)
  - EQ-5D.

Skin fibrosis endpoints:

- In subjects with diffuse cutaneous SSc (dcSSc):
  - Absolute change from baseline in mRSS up to Week 104;
  - Proportion of subjects with change from baseline in mRSS up to Week 104 according to the following categories:
    - Worsened (absolute increase of ≥ 5 points and relative increase ≥ 25%),
    - Improved (absolute decrease ≥ 5 points and relative decrease ≥ 25%), or
    - Stable (do not meet either Worsened or Improved category).
- In subjects with digital ulcers at baseline: absolute change from baseline in digital ulcer count up to Week 104.

Combined response endpoint:

- Proportion of responders as defined by the Combined Response Index for Systemic Sclerosis (CRISS) up to Week 104.

Pharmacokinetic endpoints:

Abituzumab concentrations and PK parameters (eg, C_{max} and C_{min}).

Other exploratory assessments:

- CCI [redacted]

[redacted]

- CCI [redacted]

[redacted]

Diagnosis and key inclusion and exclusion criteria:

Male or female subjects between 18 and 75 years of age who provide written consent and fulfill the 2013 American College of Rheumatology/European League Against Rheumatism criteria for classification of SSc, have been taking the same mycophenolate regimen (stable dose) in a range of 1.5 to 3 g/day of MMF or 1080 to 2160 mg/day of MPS for at least 2 months prior to the Screening Visit and continued through Day 1 of the Treatment Period, have at least 5% fibrosis of the lung on HRCT according to central reading, have a disease duration of < 7 years from the first non-Raynaud's symptom, DLCO ≥ 30% predicted, FVC 40% to 85% predicted, ratio of FVC to DLCO % predicted < 1.8, and agree to use a highly effective method of contraception for the duration of their participation in the trial meet the inclusion criteria.

Subjects must not have underlying conditions that constitute an inappropriate risk or contraindication for trial participation including, but not limited to: significant renal impairment, obstructive lung disease/emphysema, pulmonary arterial hypertension, another inflammatory connective tissue disease (apart from scleroderma-associated myopathy, fibromyalgia, and secondary Sjögren's syndrome, which are allowed), and/or tuberculosis. The use of agents other than mycophenolate (MPS or MMF) considered by the Investigator to have immunomodulating, immunosuppressive, or potential scleroderma disease-modifying properties within 2 months of the Screening Visit is not allowed (or 5 months prior to the Screening Visit for cyclophosphamide).

Investigational medicinal product: dose/mode of administration/dosing schedule: Abituzumab 1500 or 500 mg will be administered as an intravenous infusion over 1 hour once every 4 weeks. Close observation of the subject is recommended for a period of at least 1 hour after administration of the IMP. The last IMP administration is at the Week 100 visit (2 years).

Reference therapy: dose/mode of administration/dosing schedule: Placebo (citrate buffered saline) will be administered as an intravenous infusion over 1 hour once every 4 weeks. Close observation of the subject is recommended for a period of at least 1 hour after administration. The last administration of placebo is at the Week 100 visit (2 years).

Planned trial and treatment duration per subject: The planned total duration of the trial period with study visits is up to 122 weeks for each subject, including a 6-week Screening Period, a 104-week Double-blind Treatment Period, and a 12-week Safety Follow-up Period. All subjects will be followed up for survival from the last visit on trial until death or the end of trial.

Statistical methods:

Sample size:

CCI [redacted]

CCI [redacted]

Statistical analysis:

The interim futility analysis will be performed by an independent third party statistician when approximately 88 subjects have either completed 52 weeks of treatment or prematurely discontinued from the trial. The results of the interim analysis will be reviewed confidentially by the IDMC. The primary endpoint will be analyzed using all observed FVC data for these subjects by the interim analysis cut-off date and compared to the prespecified futility stopping boundary between the abituzumab 1500 mg arm and the placebo arm. The futility boundary is non-binding. Additional analysis of the primary and secondary endpoints is allowed at the IDMC's discretion and supported by the independent third-party statistician. Based on the totality of the information at interim, the IDMC will make a recommendation to the Sponsor on continuing or stopping the trial for futility.

The primary analysis will be performed by the Sponsor/Contract Research Organization staff when all subjects have either completed 52 weeks of treatment or prematurely discontinued from the trial. The primary endpoint and other efficacy endpoints will be analyzed using all observed data for all subjects by the primary analysis cut-off date. Results will be generated on the aggregate group level and reviewed by a restricted group to limit initial dissemination. The access of individual treatment information will be controlled to maintain the integrity of trial conduct.

The sites and subjects remain blinded until the end of the trial. The trial will continue as planned and a final treatment analysis will be performed when all subjects have either completed 104 weeks of treatment or prematurely discontinued from the trial.

The final database will be locked after all subjects have completed the 12 weeks of safety follow-up or prematurely discontinued from the trial. A final follow-up analysis will be performed to update the results with any remaining data collected from the Safety Follow-up Period.

The primary endpoint will be analyzed using a random coefficients linear regression model with absolute change from baseline in observed FVC volume (mL) as the outcome variable. The change in FVC volume is assumed to be linear within each subject over the course of the trial. The model will include random coefficients for intercept and time, fixed-effect terms for

treatment and time, treatment-by-time as the interaction term, and adjusting for baseline FVC, duration of prior mycophenolate use at baseline, age, sex, and height. Missing data will be assumed to be missing-at-random. The analysis of the primary endpoint and other efficacy endpoints will be conducted to include all the data collected during the trial for all subjects regardless of their adherence to treatment or use of rescue therapies. Sensitivity analysis will be performed to evaluate the potential effect of missing data on the robustness of the efficacy results, including tipping point analyses to assess the different assumptions about the missing outcomes and to explore the plausibility of missing data assumptions under which the conclusions change.

Table 1 Schedule of Assessments – Screening through Week 52

Trial Period	Screening	Weeks During Double-blind Treatment Period (Visit Window ±3 days)																	
Week		0			2	3	4	8	12	16	20	24	28	32	36	40	44	48	52
Trial Day	-42 to -1	1	3	5	15	22	29	57	85	113	141	169	197	225	253	281	309	337	365
Informed consent	X																		
Inclusion/exclusion criteria	X	X[a]																	
CCI																			
CCI																			
Pharmacokinetic informed consent (Rich PK sampling only)	X																		
Demographic data	X																		
SSc-ILD and other medical history, medications, surgery/procedures	X																		
HRCT	X											X							X
12-lead ECG (locally read)	X											X							X
Tuberculosis assessment	X																		
Serum virology (HIV, HCV, HBV)	X																		
Serum pregnancy test [c]	X																		
PT, aPTT, TSH, and NT pro-BNP	X																		
Urine pregnancy test [c,d]		X					X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X			X[e]		X	X[e]	X[e]	X[e]	X[e]	X	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X

Trial Period	**Screening**	**Weeks During Double-blind Treatment Period (Visit Window ±3 days)**																	
Week		**0**			**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**
Trial Day	**-42 to -1**	**1**	**3**	**5**	**15**	**22**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**
Vital signs, weight, height [f]	X	X			X		X	X	X	X	X	X	X	X	X	X	X	X	X
Mahler BDI/TDI and SGRQ [g]		X							X			X			X				X
Patient's Global Assessment, Leicester Cough Index, SHAQ, EQ-5D, and Physician's Global Assessment [g]		X										X							X
Randomization		X																	
IMP administration		X					X	X	X	X	X	X	X	X	X	X	X	X	X
PK sampling [h]		X					X	X		X									
Rich PK sampling [i]			X	X	X	X													
Routine hematology, clinical chemistry, urinalysis dipstick [j]	X	X			X		X	X	X	X	X	X		X	X	X		X	X
Pulmonary function tests (FVC, DLCO) [k]	X	X							X			X			X				X
mRSS		X							X			X			X				X
Digital ulcer counts [l]		X							X			X			X				X
Serum for ADA		X										X							X
CCI		[redacted]										[redacted]							[redacted]

CCI [redacted]

Trial Period	Screening	Weeks During Double-blind Treatment Period (Visit Window ±3 days)																	
Week		0			2	3	4	8	12	16	20	24	28	32	36	40	44	48	52
Trial Day	-42 to -1	1	3	5	15	22	29	57	85	113	141	169	197	225	253	281	309	337	365
Concomitant medications/procedures	X	X			X		X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events [o]	X	X			X		X	X	X	X	X	X	X	X	X	X	X	X	X

ADA = antidrug antibodies; AE = adverse event; aPTT = activated partial thromboplastin time; BDI = Baseline Dyspnea Index; DLCO = diffusion capacity of the lung for carbon monoxide; ECG = electrocardiogram; FVC = forced vital capacity; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HRCT = high-resolution computed tomography; IMP = investigational medicinal product; mRSS = modified Rodnan skin score; PK = pharmacokinetic; PT = prothrombin time; SGRQ = St. George Respiratory Questionnaire; SHAQ = Scleroderma Health Assessment Questionnaire; SSc-ILC = systemic sclerosis-associated interstitial lung disease; TDI = Transition Dyspnea Index; TSH = thyroid-stimulating hormone; VAS = visual analog scale.

a Subject eligibility (based on screening assessments of the inclusion and exclusion criteria) must be checked again on Day 1 prior to randomization.

CCI [redacted]

c For women of childbearing potential or who are postmenopausal for less than 2 years. At Day 1, if the urine test is negative, the subject can be randomized and receive the first dose of IMP.

d Performed locally per local constraints and regulations.

e Focused physical examination only, according to standard of care.

f Vital signs include 10-minute seated arterial blood pressure, pulse rate, and body temperature. Height will be measured at Day 1 only. Weight will be measured at Weeks 0, 24, 52, 76, and 104. Body weight will be measured with a balance beam scale, if possible.

g Questionnaires should be completed before any other procedures are performed. Questionnaires should be performed in the following order: Patient's Global Assessment, SHAQ, Mahler BDI (at Day 1) followed by Mahler TDI at the subsequent visits, SGRQ, Leicester Cough Index, and EQ-5D. The Mahler BDI/TDI administrator must be blinded to other assessments. The Physician's Global Assessment (VAS) may be performed after other assessments at the visit are completed.

h For all subjects, samples will be collected predose and immediately after the end of IMP infusion at Weeks 0 (Day 1), 4, 8, and 16.

i For subjects who have provided informed consent for the rich PK sampling, additional samples will be collected on Days 3, 5, 15, and 22 (in addition to the pre- and postdose samples at Weeks 0, 4, 8, and 16; see footnote h).

j See Section 7.4.3 for list of routine laboratory assessments. Urine protein:creatinine ratio to be performed if dipstick urinalysis reveals at least 3+ protein. Microscopic urinalysis to be performed if blood is present.

k The DLCO measurements will be corrected for hemoglobin level, and spirometry assessments will be centrally adjudicated.

l Digital ulcers are those distal to the metacarpal phalangeal joints. New or worsening digital ulcers, or at any other site on the body, will be captured as AEs.

CCI [redacted]

CCI [redacted]

o Adverse events should also be assessed for occurrence during the periods between trial visits.

Table 2 Schedule of Assessments – Week 56 through Safety Follow-up

Trial Period	Weeks During Double-blind Treatment Period (Visit Window ±5 days)														Safety Follow-up Number weeks post last visit (±5 days)		Survival Follow-up Post Last Trial Visit
Week	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**	**ET[a]**	**4**	**12**	**Every 12 Weeks**
Trial Day	**393**	**421**	**449**	**477**	**505**	**533**	**561**	**589**	**617**	**645**	**673**	**701**	**729**				
HRCT													X	X			
12-lead ECG (locally read)						X							X	X		X	
Urine pregnancy test [b,c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical examination	X[d]	X[d]	X[d]	X[d]	X[d]	X	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X	X	X[d]	X	
Vital signs, weight [e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Mahler TDI and SGRQ [f]			X			X			X				X	X		X	
Patient's Global Assessment, Leicester Cough Index, SHAQ, EQ-5D, and Physician's Global Assessment [f]						X							X	X			
IMP administration	X	X	X	X	X	X	X	X	X	X	X	X					
Routine hematology, clinical chemistry, urinalysis [g]		X	X	X		X		X	X	X		X	X	X	X	X	
Pulmonary function tests (FVC, DLCO) [h]			X			X			X				X	X		X	
mRSS			X			X			X				X	X		X	
Digital ulcer counts [i]			X			X			X				X	X		X	
Serum for ADA						X							X	X	X	X	
CCI																	
Concomitant medications/procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Trial Period	Weeks During Double-blind Treatment Period (Visit Window ±5 days)														Safety Follow-up Number weeks post last visit (±5 days)		Survival Follow-up Post Last Trial Visit
Week	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**	**ET[a]**	**4**	**12**	**Every 12 Weeks**
Trial Day	**393**	**421**	**449**	**477**	**505**	**533**	**561**	**589**	**617**	**645**	**673**	**701**	**729**				
Adverse events [j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital status [k]																	X

ADA = antidrug antibodies; AE = adverse event; BDI = Baseline Dyspnea Index; DLCO = diffusion capacity of the lung for carbon monoxide; ECG = electrocardiogram; ET = early termination; FVC = forced vital capacity; HRCT = high resolution computed tomography; IMP = investigational medicinal product; mRSS = modified Rodnan skin score; SGRQ = St. George Respiratory Questionnaire; SHAQ = Scleroderma Health Assessment Questionnaire; TDI = Transition Dyspnea Index; VAS = visual analog scale.

a Subjects who discontinue IMP for any reason should complete the ET visit as soon as possible, but within 2 weeks of IMP discontinuation, and then the remaining scheduled trial visits. At a minimum, the subject is expected to complete the trial visits at Weeks 12, 24, 36, 52, 64, 76, 88, and 104, as well as the Safety Follow-up period Week 12 visit. Subjects with discontinued IMP can come to the other scheduled visits during the trial period according to the Investigator's judgment. Subjects who withdraw from the treatment period would have an early termination visit followed by entrance into the Safety Follow-up Period. Subjects who withdraw from the trial (eg, withdraw consent, lost to follow up, or death; see Section 5.5.2) would not have any additional trial visits. All subjects will be followed up by the site approximately every 12 weeks for survival from the subject's last trial visit until death or the end of the trial.

b For women of childbearing potential or who are postmenopausal for less than 2 years. Positive urine pregnancy tests should be confirmed with a serum test. If the serum pregnancy test is subsequently positive, the subject will be withdrawn from IMP.

c Performed locally per local constraints and regulations.

d Focused physical examination only, according to standard of care.

e Vital signs include 10-minute seated arterial blood pressure, pulse rate, and body temperature. Weight will be measured at Weeks 0, 24, 52, 76, and 104. Body weight will be measured with a balance beam scale, if possible.

f Questionnaires should be completed before any other procedures are performed. Questionnaires should be performed in the following order: Patient's Global Assessment, SHAQ, Mahler BDI (at Day 1) followed by Mahler TDI at the subsequent visits, SGRQ, Leicester Cough Index, and EQ-5D. The Mahler BDI/TDI administrator must be blinded to other assessments. The Physician's Global Assessment (VAS) may be performed after other assessments at the visit are completed.

g See Section 7.4.3 for list of routine laboratory assessments. Urine protein:creatinine ratio to be performed if dipstick urinalysis reveals at least 3+ protein. Microscopic urinalysis to be performed if blood is present.

h The DLCO measurements will be corrected for hemoglobin level, and spirometry assessments will be centrally adjudicated.

l Digital ulcers are those distal to the metacarpal phalangeal joints. New or worsening digital ulcers, or at any other site on the body, will be captured as AEs.

j Adverse events should also be assessed for occurrence during the periods between trial visits.

k Survival follow-up: All subjects will be assessed for survival every 12 weeks (± 1 week) from the last trial visit until death or end of the trial.

2 Sponsor, Investigators, and Trial Administrative Structure

This clinical trial will be sponsored by:

- EMD Serono Research & Development Institute, Inc., Billerica, Massachusetts, in the USA.
- Merck KGaA, Darmstadt, Germany in the countries outside the USA.

The trial will be conducted at approximately 60 sites globally, including, but not limited to, North America and the European Union (EU). Approximately 15 sites are planned in the USA.

The Coordinating Investigators (for all countries, except in North America: PPD ; for sites in North America: PPD), represent all Investigators for decisions and discussions regarding this trial, consistent with the International Council for Harmonisation (ICH) Topic E6 Good Clinical Practice (GCP; hereafter referred to as ICH GCP). The Coordinating Investigators will provide expert medical input and advice relating to trial design and execution and are responsible for the review and signoff of the clinical trial report.

Signature pages for the Protocol Lead and the Coordinating Investigators as well as a list of Sponsor responsible persons are in Appendix I.

The trial will appear in clinicaltrials.gov and other clinical trial registries.

The Sponsor will enlist the support of PPD, a contract research organization (CRO), to conduct the clinical part of the trial including trial set-up, coordination, monitoring, medical oversight, data capture, data management, statistical analysis, and clinical trial reporting. The Sponsor will also make use of the CRO's central laboratory for sample analyses, storage, and shipment to specialized bioanalytical laboratories. The Sponsor will supervise all outsourced activities.

Investigational medicinal product (IMP) will be supplied by the Clinical Trial Supply Department at Merck and packaged and labeled by PPD.

Spirometry data will be centrally read by PPD .

Details of structures and associated procedures will be defined in the instructions and/or flow charts provided by each of the third-party vendors participating in the EMR200017-014 trial.

An independent data monitoring committee (IDMC) will be established to review available safety and tolerability data on a regular basis as well as the results of the interim futility analyses. Based on the prespecified stopping boundary of futility, and the totality of the information at interim, the IDMC will make a recommendation to the Sponsor on continuing or stopping the trial for futility. The IDMC will consist of an odd number of members appropriate to the type of trial and expertise needed, including at least 2 clinicians and a biostatistician. The membership is limited to individuals who are free of conflicts of interest and should not be employees of the Sponsor. The full list of IDMC members and IDMC responsibilities will be included in the IDMC charter.

3 Background Information

Fibrosis is a key process involved in chronic organ injury and failure. It contributes to significant morbidity and mortality in lung, heart, liver, and kidney disease (Denton 2017). Although advances have been made in understanding the molecular pathogenesis of fibrosis, these conditions often progress and transplants remain the last and only option for patients with advanced fibrosis and organ failure.

In recent years, a number of emerging therapeutic approaches demonstrated clinical utility of slowing progression and functional decline in distinct fibrotic disorders such as idiopathic pulmonary fibrosis (IPF) by early intervention in patient groups at risk, although at best with modest success.

While most fibrotic disorders manifest predominantly in a single target organ, systemic sclerosis (SSc) is characterized by multiple tissue involvement with severely reduced quality of life (QoL) in patients (Friedman 2013, Balibar-Gurman 2012). In view of the pressing medical needs in SSc patients with lung involvement (mortality up to 50% by 10 years in patients with extensive disease), and the multiple tissues and organs that may be involved and thus assessed in an investigational drug trial, SSc-associated interstitial lung disease (SSc-ILD) was chosen as the first indication to study the antifibrotic effects of abituzumab.

Current therapies for SSc focus upon treatment of symptoms and of organ-based manifestations. Therapeutic advances include the use of angiotensin-converting enzyme inhibitors in scleroderma renal crisis, proton-pump inhibitors in gastrointestinal reflux, calcium channel blocker, and prostacyclin analogues in the treatment of Raynaud's phenomenon, endothelin receptor antagonists (ERA) in ischemic digital ulcers prevention as well as prostacyclin analogs and ERA in associated pulmonary arterial hypertension (PAH). Treatments targeting inflammation include corticosteroids and immunosuppressive agents (Bussone 2011). The duration of cyclophosphamide treatment is generally limited to 1 year because of toxicities, including the risk of bladder carcinoma. Mycophenolate is the preferred immunosuppressive agent of many physicians; however, because it has a more favorable safety profile than cyclophosphamide. Nevertheless, gastrointestinal symptoms may limit tolerability, especially at higher doses. Although immunosuppressive therapies may have disease-modifying activity, the effects observed in randomized, controlled trials have been limited (Tashkin 2006, Tashkin 2016).

Despite advances in early diagnosis of disease and effective treatment for some complications, SSc still remains characterized by high morbidity and mortality. Five- and 10-year survival rates range between 78% to 84% and 55% to 65%, respectively. A recent report estimated lung involvement (PAH and interstitial lung disease [ILD]) mortality to be approximately 33% and ILD to account for 16% of SSc-related deaths. The 10-year survival rates of SSc-ILD is approximately 75% and 30% in limited versus extensive ILD, respectively.

With only limited treatment effects observed to date with candidate therapies, there remains a critical need for additional therapies.

3.1 Abituzumab

Abituzumab, also known as EMD 525797 or DI17E6, is a humanized monoclonal immunoglobulin G2 (IgG2) antibody against the human αv-integrin subunit. Integrins are transmembrane proteins that exist as heterodimers of an alpha (α) and a beta (β) subunit. The binding of abituzumab to the αv subunit inhibits the binding of all αv integrins (ie, αvβx) to its extracellular matrix ligands (eg, latency associated protein of transforming growth factor [TGF]-β1, vitronectin, and fibronectin). This inhibition of αv integrin function is anticipated to lead to a reduction in the activation of TGF-β, a major mediator of fibrosis. Abituzumab thus has potential to have antifibrotic activity.

Abituzumab drug product is currently formulated for administration via intravenous infusion. The target indication of the development program is SSc-ILD. For this trial in subjects with SSc-ILD, abituzumab will be administered at doses of 500 or 1500 mg at 4-week intervals on a background of stable mycophenolate.

Refer to the Investigator's Brochure (IB) for further information about the nonclinical and clinical programs and Guidance for the Investigator.

This clinical trial will be conducted in compliance with the clinical trial protocol, ICH GCP, and any additional applicable regulatory requirements.

3.2 Trial Rationale

This is a Phase II, multicenter, double-blind, placebo-controlled, parallel-group trial investigating the efficacy, safety, tolerability, and immunogenicity of abituzumab at 2 dose levels in subjects with SSc-ILD who are treated with a stable mycophenolate regimen.

An interim futility analysis will be performed by an independent third party statistician when approximately 88 subjects have either completed 52 weeks of treatment or prematurely discontinued from the trial. The results of the interim futility analysis will be reviewed confidentially by the IDMC, who will make a recommendation to the Sponsor on continuing or stopping the trial for futility, based on predefined criteria in the IDMC charter. If the Sponsor follows an IDMC recommendation to stop the trial, then enrollment and treatment with IMP will be stopped and subjects will be required to complete the early termination visit and move into the Safety Follow-up Period.

The trial design takes into consideration an emerging trend in the treatment of SSc-ILD for use of mycophenolate as an alternative to cyclophosphamide, given the recent data regarding similar effects on pulmonary function but more favorable safety profile of the former and thus its potential for long-term use (Tashkin 2016, Volkman 2015). The potential antifibrotic effects of abituzumab could have complementary effects on the disease process to the immunosuppressive effects of mycophenolate. Therefore, this trial will evaluate whether abituzumab is associated with benefit when added to stable mycophenolate treatment.

3.3 Risk-Benefit Analysis

Available data from preclinical studies with cynomolgus monkeys showed a favorable toxicological safety profile for abituzumab. No potential safety issues emerged from these studies other than antidrug antibody (ADA) formation.

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CCI [redacted] the digital ulcer count will be also be assessed at scheduled visits (see Table 1 and Table 2). Only an increase in number or worsening of digital ulcers would be considered a safety issue since SSc itself can be associated with digital ulcer formation. Together, these data sets will provide monitoring for impaired wound healing or skin breakdown. All blistering or Grade ≥ 3 AEs in the skin and subcutaneous tissue disorders system organ class (SOC), will be designated as AEs of special interest (AESI). Any cutaneous reaction of Grade 1 or 2 that is not responding to specific treatment or is worsening will also be designated as an AESI. The occurrence of AESI or cutaneous serious AEs (SAEs) will be reviewed by an independent panel of dermatologists to provide guidance for further investigation and interpretation of these events, and advise the IDMC whether any actions to modify clinical trial conduct should be considered. An IDMC will review safety data to ensure safety of all subjects enrolled in the trial. If subjects have significant worsening of lung function, they may start rescue medication, as appropriate. No additional risk minimization measures are considered necessary at this time for studying the effects of abituzumab in subjects with SSc-ILD.

Based on the available nonclinical and clinical data to date, the conduct of the trial specified in this protocol is considered justifiable.

4 Trial Objectives

4.1 Primary Objective

The primary objective of the trial is to demonstrate efficacy of abituzumab in improving lung function of subjects with SSc-ILD.

4.2 Secondary Objectives

The secondary objectives of the trial are:

- To characterize further the effect of abituzumab on subjects with SSc-ILD who are treated with a stable mycophenolate regimen;
- To characterize the safety, tolerability, and immunogenicity of abituzumab in subjects with SSc-ILD who are treated with a stable mycophenolate regimen;
- To evaluate the effect of abituzumab on SSc skin disease in subjects with diffuse skin involvement who are treated with a stable mycophenolate regimen;
- To evaluate health-related quality of life (HRQoL) outcomes of abituzumab in subjects with SSc-ILD who are treated with a stable mycophenolate regimen;
- To evaluate pharmacokinetic (PK) parameters of abituzumab in subjects with SSc-ILD who are treated with a stable mycophenolate regimen.

4.3 Other Objectives

The exploratory objectives of the trial are:

- CCI [redacted]

5 Investigational Plan

5.1 Overall Trial Design and Plan

This is a Phase II, multicenter, double-blind, placebo-controlled, parallel-group trial to be conducted in adult male and female subjects with SSc-ILD who are treated with stable mycophenolate to explore the efficacy, safety, tolerability, and immunogenicity of multiple intravenous doses of abituzumab. Subjects must have received the same mycophenolate treatment (ie, stable dose) in a range of 1.5 to 3 g/day of mycophenolate mofetil (MMF) or 1080 to 2160 mg/day of sodium mycophenolate (MPS) for at least 2 months prior to the Screening Visit and continued through Day 1 of the Treatment Period. The trial will be conducted at approximately 60 sites globally.

The planned total duration of the trial is up to 122 weeks and is composed of a Screening Period, a Double-blind Treatment Period, and a Safety Follow-up Period. In addition, there is a Survival Follow-up Period. The trial periods are as follows:

- Screening Period: duration of up to 6 weeks; however, subjects should have the Day 1 visit as soon as possible after the eligibility for the trial has been confirmed.
- Double-blind Treatment Period: duration of 104 weeks (2 years) starting at randomization. Subjects will be monitored at Weeks 2, 4, and every 4 weeks thereafter until Week 104.
- Safety Follow-up Period: duration of 12 weeks. During the Safety Follow-up Period, monitoring for AEs, disease progression, and an assessment for ADA will be carried out.
- Survival Follow-up: Each subject will be followed up by the site for survival status every 12 weeks (± 1 week) after the last trial visit, until death of the subject or end of the trial.

Approximately 175 subjects will be randomized in a 2:2:1 ratio to receive abituzumab 1500 mg, placebo, or abituzumab 500 mg, respectively, given by intravenous infusion over 1 hour every 4 weeks with the last IMP administration at the Week 100 visit.

Subjects are to continue their previous stable mycophenolate regimen.

The effects of abituzumab on clinical status will be assessed through evaluations including pulmonary function tests, high-resolution computed tomography (HRCT), and patient-reported

outcomes (PROs). The diffusion capacity of the lung for carbon monoxide (DLCO) measurements will be corrected for hemoglobin level and spirometry assessments will be centrally adjudicated.

Subjects who meet the criteria for clinically meaningful progression of SSc-ILD (see Section 6.5.5) during the Double-blind Treatment Period or Follow-up Period should have a change in background therapy. Subjects taking less than the maximal specified dose of mycophenolate (3 g/day MMF or 2160 mg/day MPS) can have the mycophenolate dose increased while IMP is continued. Subjects taking the maximal specified dose of mycophenolate who have clinically meaningful progression should have the IMP discontinued and be treated according to the local standard of care. If a nonbiologic immunosuppressant (such as cyclophosphamide [oral or intravenous]) is initiated, then mycophenolate must be discontinued.

If a subject discontinues IMP, then the subject should complete the early termination visit and then the remaining scheduled visits. At a minimum, the subject is expected to complete the trial visits at Weeks 12, 24, 36, 52, 64, 76, 88, and 104, as well as the Safety Follow-up period Week 12 visit. Subjects with discontinued IMP can come to the other scheduled visits during the trial period according to the Investigator's judgment.

Subjects who withdraw from the treatment period would have an early termination visit followed by entrance into the Safety Follow-up Period.

Subjects who withdraw from the trial (eg, withdraw consent, lost to follow-up, or death; see Section 5.5.2) would not have any additional trial visits.

Regardless of treatment completion or not, all subjects will be followed up by the site for survival from the subject's last visit on the trial until death or end of the trial. Subjects who have clinically meaningful progression of SSc other than ILD should be treated according to the local standard of care.

During the Double-blind Treatment Period, efficacy assessments will include evaluations of pulmonary function (forced vital capacity [FVC] and DLCO), HRCT, and PRO questionnaires. Routine safety, HRQoL, CCI , and PK assessments will be performed as described in the Schedule of Assessments (Table 1 and Table 2).

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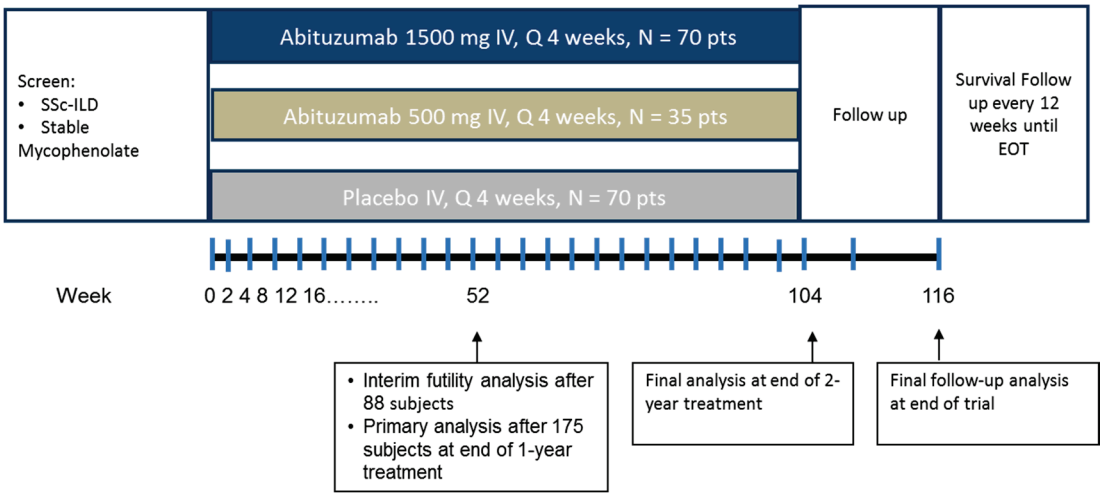
The trial design is displayed in Figure 1.

Figure 1 **Trial Design**



IV = intravenous; EOT = end of trial; pts = patients; Q4 weeks = every 4 weeks; SSc-ILD = systemic sclerosis-associated interstitial lung disease.

An interim futility analysis will be performed when approximately 88 subjects have either completed 52 weeks of treatment or prematurely discontinued from the trial. The primary analysis will be conducted when all subjects have either completed 52 weeks of treatment or prematurely discontinued from the trial. The primary analysis will use all the cumulative data at the time of the primary analysis cut-off date. The final treatment analysis will be conducted when all subjects have completed the 104-week treatment or prematurely discontinued from the trial. The final follow-up analysis will be conducted after all subjects have completed the 12-week Safety Follow-up Period or prematurely discontinued from the trial. All subjects will be followed up for survival until this point.

During the conduct of the trial, an IDMC will convene to monitor unblinded safety data on a regular basis, as specified in the IDMC charter, to ensure the safety of subjects in this trial. The IDMC will also review the results of the interim futility analysis and make a recommendation to the Sponsor on continuing or stopping the trial for futility, based on the criteria in the IDMC charter.

5.2 Discussion of Trial Design

5.2.1 Rationale for Trial Design

Given the expected rate of progression of SSc-ILD, a trial of 1-year duration is likely to be able to evaluate changes in FVC and other pulmonary function tests associated with the IMP. However, a 2-year treatment period is preferred because it will be important to evaluate the durability of the treatment effect, long-term safety, and whether treatment effect size increases during the second year of treatment (for instance, in case there is some lag time between initiation of IMP and significant changes in FVC). In the Scleroderma Lung Study (SLS) I trial (Tashkin 2006), in which the patients were treated for with oral cyclophosphamide/placebo for 1 year and then followed for an additional year without treatment, a benefit of cyclophosphamide

treatment as compared with placebo was observed up until approximately 18 months of treatment, but there was no notable benefit by 24 months of treatment.

Use of a placebo comparator arm is considered appropriate because subjects in this trial will continue to take their previous mycophenolate therapy, while placebo or abituzumab is added. In addition, there are clearly-defined criteria for clinically meaningful progression. Subjects who meet these criteria should have a change in therapy as outlined (either increase in mycophenolate dose or switch to local standard of care, such as cyclophosphamide, with discontinuation of mycophenolate and IMP).

Subjects with disease progression who are withdrawn from IMP will be encouraged to continue treatment period assessments through the Safety Follow-up Period to evaluate the clinical course after cessation of IMP and initiation of treatment under local standard care (eg, cyclophosphamide).

5.2.2 Selection of Doses

The relationship between target inhibition and clinical response remains to be determined in clinical trials. Two doses will be used to establish an exposure-response relationship. CCI

EOI = end of infusion; IV = intravenous.

5.2.3 Rationale for Inclusion and Exclusion Criteria

The 2013 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria are standard for use in clinical trials of subjects with SSc.

Subjects will have disease duration of less than 7 years from first non-Raynaud's sign or symptom in order to decrease the risk of recruiting subjects with disease that may be too far advanced, and thus associated with low likelihood to be able to demonstrate trial drug effect and increased safety risks (and thus drug treatment effect might not be shown).

Similarly, subjects will be required to have DLCO ≥ 30% predicted and FVC predicted 40% to 85%. The upper boundary specified for FVC selects subjects with clinically significant impairment for use of an interventional therapy. The lower boundaries for FVC and DLCO reduce risk of recruiting subjects with disease that is too far advanced to respond to medical intervention, and may also represent subjects at significantly increased risk of AEs. The inclusion of subjects with FVC/DLCO ratio < 1.8 decreases the likelihood of enrolling subjects with significant pulmonary hypertension (which is associated with poor prognosis and may confound interpretation of effects of abituzumab).

Fibrosis on HRCT (≥ 5% as defined in Inclusion Criterion 4) will be required in order to confirm that subjects have ILD, select for a population considered appropriate for treatment with a potentially antifibrotic therapy such as abituzumab, and possible improvement in fibrosis among all trial subjects. Computed tomography will only be done in subjects who meet the criteria for DLCO and FVC in order to reduce HRCT exposure in those subjects who would not be eligible for the trial.

In order to decrease confounding of trial results, subjects with concurrent conditions that may significantly impact safety and efficacy analyses will be excluded. Likewise, background mycophenolate should be stable in order to evaluate the effect of the addition of abituzumab compared with placebo (rather than the effect of changing mycophenolate dose). Immunosuppressant and other potentially disease-modifying treatment use within 2 months of the Screening Visit (or cyclophosphamide use within 5 months of the Screening Visit) is likewise excluded in order to decrease confounding trial results. Mycophenolate is chosen as the background medication for this trial as experience in the community has led to its increased use, and the results of the SLS II trial are expected to increase its use further.

5.2.4 Rationale for Primary Objective

Forced vital capacity is a clinically relevant surrogate endpoint for clinical benefit, as decreased FVC is associated with mortality (Steen 2000, Assassi 2009) and a decrease to < 70% FVC was associated with higher mortality than a decrease in which FVC remained ≥ 70% in SSc-ILD (Goh 2008, Moore 2013).

The primary endpoint of the trial is the annual rate of absolute FVC change in volume (mL). Forced vital capacity is robust, validated, sensitive to change, and doable in a setting of a clinical trial as shown in IPF (du Bois 2012). Decrease in FVC reflects decrease in lung function and has been associated with increased mortality. This measure was successfully used in SSc-ILD where

a significant difference between cyclophosphamide and placebo in FVC was observed in the SLS I trial (Tashkin 2006). The SLS I trial for cyclophosphamide versus placebo (without background immunosuppressive) showed a mean absolute improvement of FVC decline of 2.5% at 1 year and was considered clinically significant in the community. In addition, FVC is also the primary endpoint of the SLS II National Institutes of Health-sponsored trial.

A change of 2% to 6% in FVC % predicted is the minimally clinically important difference in IPF patients (du Bois 2011).

Change in FVC was the basis for the approvals of nintedanib and pirfenidone in IPF during 2014. These programs had primary endpoints of annual rate of decline in FVC (measured in milliliters per year) and change from baseline to Week 52 in the percentage of the predicted FVC, respectively (Richeldi 2014, King 2014). From 6 large independent placebo-controlled trials of pirfenidone and nintedanib in IPF, analysis showed an improvement of at least 100 mL in the annual rate of observed FVC decline in volume, equivalent to approximately 3% improvement in FVC % predicted at 1 year serving as the basis for approvals. The association between significant difference in FVC decline and numerical trend toward improvement in mortality in these IPF trials was also highlighted by FDA reviewers (Karimi-Shah 2015).

Pulmonary function tests will be performed according to the American Thoracic Society and European Respiratory Society recommendations. Detailed procedures for performing pulmonary function assessments are included in the Instructions for Use PPD and Procedural Manual for DLCO testing provided by PPD.

5.2.5 Rationale for Secondary Objectives

Efficacy

In addition to the primary efficacy endpoint, key secondary endpoints will include change in dyspnea as assessed by Mahler index, change in St. George Respiratory Questionnaire (SGRQ) total score, quantitative lung fibrosis (QLF), and overall survival. Effects on skin will be assessed using a standard index, the modified Rodnan skin score (mRSS). In addition to improving quality of life, including how patients with SSc-ILD feel and function, a critical goal of therapy is to prolong life. Overall survival will be evaluated as a key secondary endpoint. In addition, survival status will be followed for all subjects until the end of the trial in order to raise the potential to observe effects on survival.

The QLF change has been found to be a sensitive marker of change and can precede change in FVC (Kim 2010, Kim 2011, Tashkin 2014). Since QLF directly measures the treatment effect on lung fibrosis, the results are complementary to clinical data such as FVC and PROs. Quantitative lung fibrosis assessments will also be centrally read.

Forced vital capacity will also be assessed using categorical measures to define potential responders.

The DLCO is another standard measurement of lung function (MacIntyre 2005); it measures the diffusing capacity of the lung, reflecting vascular bed size/perfusion as well as the extent of

interstitial lung disease. However, it shows higher measurement variability compared to FVC. Measurements will be corrected for hemoglobin level and DLCO assessments will be centrally adjudicated with the other spirometry assessments.

An analysis of the proportion of subjects with clinically meaningful progression as defined by Outcome Measures in Rheumatology (OMERACT) for patients with ILD (Khanna 2015) will be performed. Abituzumab is expected to reduce the number of subjects with such progression of disease.

Several HRQoL parameters will be assessed in this trial. These will be administered based on availability of the respective validated questionnaires in local language.

The measures endorsed by the OMERACT working group as the 'inner core' measures for ILD (Khanna 2015) and included in this trial are the following: Leicester Cough Index, Patient's Global Assessment, and SGRQ, as well as 'functional status' (this will be assessed by the Scleroderma Health Assessment Questionnaire [SHAQ]), overall ILD on HRCT, FVC % predicted, and all-cause mortality. The assessments in this trial that are not part of the inner core include the Mahler index and the Physician's Global Assessment. The Mahler Dyspnea Index is advised to be included as this has been shown in the SLS I trial to show a statistically significant difference between the cyclophosphamide and placebo groups ($p < 0.001$). The Physician's Global Assessment is done rapidly via a visual analogue scale (VAS) and is standard in many trials for overall assessment of subjects.

The SHAQ is an adaptation of the HAQ-DI and has been validated in SSc (Steen 1997). In addition to the 8 domains of activity in the HAQ (dressing, arising, eating, walking, hygiene, reach, grip, and common daily activities), the SHAQ includes 5 additional scleroderma-specific VAS encompassing the domains of overall disease activity, Raynaud's phenomenon, finger ulcers, breathing, and intestinal problems. For each item in the HAQ, patients report the amount of difficulty experienced performing the activity. The 5 additional VAS in the SHAQ ask patients how much symptoms interfere with daily activities and are scored similarly to other VAS.

As dyspnea is a central feature of SSc-ILD and is an independent predictor of function and HRQoL, it will be assessed using 2 indices: the Mahler index and the SGRQ (Baron 2008). The Mahler Transition Dyspnea Index (TDI) fulfills OMERACT criteria for feasibility, reliability, and validity, and in moderate ILD, subject changes in Mahler TDI score were observed (Khanna 2009). The TDI is sensitive to change. The Baseline Dyspnea Index (BDI)-TDI measures changes in dyspnea severity from the baseline as established by the BDI. The computerized version appears to have eliminated earlier concerns regarding the role of the interviewer in influencing responses.

The SGRQ has been found to be useful in assessing patients with SSc-ILD (Beretta 2007, Wallace 2015).

Cough will be assessed using the Leicester Cough Index, which is a validated tool in chronic cough and chronic obstructive pulmonary disease (Birring 2003, Berkhof 2012). Nonproductive cough is a characteristic symptom of ILD in general, and SSc-ILD in particular. In the SLS I

trial, 73% of subjects reported cough at enrollment, representing the second most common non-Raynaud's symptom. This trial indicated that cough severity and frequency correlated with FVC % predicted, and cough frequency decreased significantly after a 12-month period of cyclophosphamide therapy compared with placebo. Of note, at baseline, compared to non-coughers, subjects with cough had lower DLCO and higher dyspnea and fibrosis score on HRCT (Theodore 2012).

The EQ-5D, measures health outcomes and is standardized for use across many indications and regions. It can be used for health outcomes including QoL and also economic analyses. Applicable to a wide range of health conditions and treatments, the EQ-5D health questionnaire provides a simple descriptive profile and a single-index value for health status.

Please note: Patient-reported Outcome questionnaires should be completed before any other procedures, as per the Schedules of Assessments (Table 1 and Table 2).

Questionnaires will be performed in the following order:

- Patient's Global Assessment
- SHAQ
- Mahler BDI (at Day 1) followed by Mahler TDI at the subsequent visits, by the request of the author of the Mahler TDI
- SGRQ
- Leicester Cough Index
- EQ-5D
- Physician's Global Assessment (VAS).

Since SSc is a multi-organ disease, it is critical to assess the overall disease activity of subjects. This is done routinely in clinical practice for a complete understanding of the clinical status. If efficacy is seen for abituzumab in the treatment of SSc-ILD, which is the manifestation associated with highest morbidity and mortality and thus unmet need, this will open the possibility to further investigate whether abituzumab could have benefit for other SSc manifestations. Assessment of manifestations of SSc other than ILD over time during the trial is also important to confirm that possible efficacy in SSc-ILD did not come at the expense of worsening in other organ systems. The expectation is that there will be trends towards improvement in the overall SSc severity (assessed by the Combined Response Index for Systemic Sclerosis [CRISS]) and specifically the skin scores (assessed by mRSS and ulcer count) which will be assessed only in those subjects with diffuse cutaneous SSc (dcSSc) at baseline.

The mRSS instrument is a validated tool and has been shown to be feasible, reliable, valid, and responsive to change in multicenter clinical trials (Khanna 2007). There was a significant change in the mRSS in the cyclophosphamide arm compared with the placebo arm in the SLS I trial.

The digital ulcer count is commonly included in trials of scleroderma skin disease.

The CRISS includes measures that assess change in skin and ILD, functional disability (as assessed by HAQ-DI), and Patient and Physician Global Assessments. In addition, the index captures clinically meaningful declines in internal organ involvement that indicate the subject has not improved during the clinical trial.

Safety

The safety profile of abituzumab remains to be established in subjects with SSc-ILD.

5.2.6 Rationale for Exploratory Objectives

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5.2.7 Inclusion of Special Populations

Not applicable.

5.3 Selection of Trial Population

Only persons meeting all inclusion criteria and no exclusion criteria may be enrolled into the trial as subjects. Prior to performing any trial assessments not part of the subject's routine medical care, the Investigator will ensure that the subject has provided written informed consent following the procedure described in Section 9.2.

5.3.1 Inclusion Criteria

Subjects are eligible for this trial if they fulfill all of the following inclusion criteria:

1. Female or male subjects aged between 18 and 75 years of age who provide informed written consent.

2. Subjects fulfilling the 2013 ACR/EULAR criteria for classification of SSc (van den Hoogen 2013; see Appendix IV).

3. Disease duration of < 7 years from first non-Raynaud's symptom.

4. According to central readings: DLCO ≥ 30% predicted, FVC 40% to 85% predicted[1], and ratio of FVC % predicted to DLCO % predicted < 1.8. A ratio of FVC % predicted to DLCO % predicted ≥ 1.8 is acceptable if right heart catheterization within 3 months of Screening revealed no pulmonary hypertension. If these criteria are met, then HRCT of lungs will be performed, and must show at least 5% fibrosis for subjects to be eligible.

   [1] The FVC % predicted that is reported by central reading will be rounded to the nearest whole number. If the number that follows the decimal point is ≤ 4, the FVC % predicted will be rounded down to the next whole number; if it is ≥ 5, the FVC % predicted will be rounded up to the next whole number.

5. Use of the same mycophenolate regimen (ie, stable dose) in a range of 1.5 to 3 g/day of MMF or 1080 to 2160 mg/day of MPS, for at least 2 months prior to the Screening Visit and continued through Day 1 of the Treatment Period.

6. 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 two effective methods of contraception, including at least one highly effective method that can achieve a failure rate of < 1% per year, when used consistently and correctly, and one other reliable method during the treatment period and for at least 90 days after the last dose of study treatment.

   Examples of contraceptive methods with a failure rate of < 1% per year (highly effective contraceptive methods) include:

   - combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation[1] (oral, intravaginal, transdermal)
   - progesterone-only hormonal contraception associated with inhibition of ovulation[1] (oral, injectable, implantable[2])
   - intrauterine device (IUD)[2]
   - intrauterine hormone-releasing system (IUS)[2]
   - bilateral tubal occlusion[2]
   - vasectomized partner[2,3]

- sexual abstinence[4]

[1] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.

[2] Contraception methods in the context of this guidance are considered to have low user dependency.

[3] Vasectomized partner is a highly effective birth control method provided that the partner is the sole sexual partner of the woman of childbearing potential trial participant and that the vasectomized partner has received medical assessment of the surgical success.

[4] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Barrier methods supplemented with the use of a spermicide could be considered as a reliable method.

For men (including those who have undergone a vasectomy): agreement to remain abstinent or use a condom during the treatment period and for at least 12 months after the last dose of study treatment and agreement to refrain from donating sperm during this same period.

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

In addition to male contraception, agreement to advise female partners of childbearing potential to use highly effective contraception during the study and for at least 12 months after the last dose of study treatment.

Upon termination of participation in this clinical study, patients continuing on MMF must continue effective contraception as required by the SPC.

5.3.2 Exclusion Criteria

Subjects are not eligible for this trial if they fulfill any of the following exclusion criteria:

1. Any condition that in the Investigator's opinion constitutes an inappropriate risk or a contraindication for participation in the trial or that could interfere with the trial objectives, conduct, or evaluation.

2. Renal impairment (glomerular filtration rate [GFR] < 45 mL/min/1.73 m^2 as calculated by the Modification of Diet in Renal Disease equation) calculated by the central laboratory as follows:

GFR (mL/min per 1.73 m^2) = 175 × standardized serum creatinine $^{-1.154}$ × age $^{-0.203}$ × 1.212 (if black) × 0.742 (if female)

3. Urine dipstick with ≥ 3+ protein and urine protein:creatinine ratio > 2 mg/mg. Urine protein:creatinine ratio will be determined only if urine dipstick indicates ≥ 3+ protein.

4. Known diagnosis of obstructive lung disease/emphysema as defined by forced expiratory volume in 1 second (FEV_1)/FVC ratio < 0.65 and/or significant emphysematous change on screening HRCT according to the central reader.

5. Other clinically significant abnormalities on HRCT not attributable to scleroderma or emphysema as defined above, which in the Investigator's opinion make enrollment in the trial inappropriate.

6. Known diagnosis of other significant respiratory disorders in the opinion of the Investigator.

7. Pulmonary hypertension that fulfills at least one of the following:

   - Currently being treated with systemic therapy targeted to PAH or pulmonary hypertension;
   - Considered by the Investigator to require initiation of systemic targeted PAH therapy;
   - History of transthoracic echocardiography showing at least one of the following (unless right heart catheterization subsequent to these measures did not reveal pulmonary hypertension): tricuspid regurgitation jet > 2.8 m/sec, right atrial enlargement (major dimension > 53 mm), right ventricular enlargement (mid cavity dimension > 35 mm), moderate to severe left ventricular dysfunction;
   - At screening, N-terminal prohormone brain natriuretic peptide (NT pro-BNP) > 3 × the upper limit of normal (ULN), unless, for example, right heart catheterization performed within 3 months of the Screening Visit did not reveal pulmonary hypertension.

8. Current clinical diagnosis of another inflammatory connective tissue disease (eg, systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, or dermato/polymyositis); concomitant scleroderma-associated myopathy, fibromyalgia, and secondary Sjögren's syndrome are allowed.

9. Clinical suspicion of or recent evidence of significant aspiration within the previous 6 months, such as chemical induced pneumonitis or aspiration pneumonia.

10. Active clinically significant viral, bacterial, or fungal infection, or any major episode of infection requiring hospitalization or treatment with parenteral anti-infectives within 4 weeks prior to screening or during the Screening Period, or completion of oral anti-infectives within 2 weeks before screening or use of oral anti-infectives during the Screening Period. Vaginal candidiasis, onychomycosis, and chronically suppressed oral

herpes simplex virus would not be exclusionary. Prophylaxis for *Pneumocystis jiroveci* pneumonia according to local guidelines will be permitted.

11. History of or positive human immunodeficiency virus (HIV), hepatitis C antibody and/or polymerase chain reaction or hepatitis B surface antigen (HBsAg) and/or hepatitis B core antibody (total and/or immunoglobulin M [IgM]) antibody at screening.

12. History of or current diagnosis of active tuberculosis (TB), or untreated latent TB infection (LTBI), determined by a TB skin test with purified protein derivative as evidenced by induration ≥ 5 mm or a positive QuantiFERON-TB or positive or borderline T-SPOT (Elispot) test performed locally, or centrally as needed, either at screening or documented with results within 3 months of the Screening Visit. Subjects who have previously completed appropriate and documented LTBI treatment or who are undergoing current treatment for LTBI will not be required to be tested.

    If the subject is undergoing current treatment for LTBI, they must have received at least 4 continuous weeks of an appropriate LTBI treatment prior to the Screening Visit (ie, start of trial treatment) without evidence of re-exposure. If on LTBI treatment at the Screening Visit, the subject will be expected to complete an appropriate LTBI treatment regimen to remain in the trial:

    - Subjects with current household contacts with active TB will also be excluded unless treated and evidence of household contacts being treated;

    - Indeterminate QuantiFERON-TB or T-SPOT tests may be repeated once, and will be considered positive if retest results are positive or indeterminate.

13. Presence of uncontrolled or New York Heart Association (NYHA) Class 3 or 4 congestive heart failure (refer to Appendix III).

14. History of cancer, except adequately treated (ie, no evidence of recurrence within 5 years prior to screening) basal cell or squamous cell carcinomas of the skin (no more than 3 total in lifetime) or carcinoma in situ of the cervix.

15. Known hypersensitivity to abituzumab or any component of the formulated abituzumab.

16. Current smoker (including e-cigarettes) or smoking within 4 weeks of screening.

17. Use of agents other than mycophenolate (MPS or MMF) considered by the Investigator to have immunomodulating, immunosuppressive, or potential scleroderma disease-modifying properties within 2 months of the Screening Visit. Examples of these agents include, but are not limited to, pirfenidone, nintedanib, methotrexate, azathioprine, leflunomide, calcineurin inhibitors, D-penicillamine, Potaba, and AIMSPRO. The use of cyclophosphamide within 5 months of the Screening Visit is not permitted. Hydroxychloroquine or chloroquine are permitted if dose has been stable for at least 4 weeks before the Screening Visit.

18. Use of systemic corticosteroids above 10 mg/day prednisone equivalent within 4 weeks of screening, during the Screening Period, or expected during the treatment period. Inhaled corticosteroids are not considered systemic and are permitted. Topical corticosteroids are permitted.

19. Use of any biologic agent within 12 weeks or 5 half-lives, whichever is longer, of screening.

20. History of anti-CD20 B-cell depleting therapy, eg, rituximab or ocrelizumab, within 6 months prior to the Screening Visit.

21. Use of any anticoagulant or antiplatelet agent (aspirin ≤ 350 mg daily is permitted).

22. Clinically significant or predefined abnormalities in laboratory tests:

    - Aspartate aminotransferase (AST), alanine aminotransferase (ALT), or alkaline phosphatase (AP) level > 2.5× ULN;
    - Total bilirubin > 1.5× ULN (other than that due to known Gilbert's disease);
    - Hemoglobin < 5.0 mmol/L (9 g/dL), white blood cell count < 2.5 $\times 10^9$/L, or platelets < 100 $\times 10^9$/L);
    - International normalized ratio (INR) or partial thromboplastin time (PTT) > 2.0× ULN;
    - Thyroid-stimulating hormone (TSH) < 0.01 or ≥ 7.1 mIU/L.

23. Individuals who cannot receive intravenous infusions (ie, difficult venous access).

24. History of alcohol or drug abuse for 1 year prior to screening in the opinion of the Investigator.

25. Pregnancy (documented by serum pregnancy test at screening or urine pregnancy test on Day 1) and/or breastfeeding/lactation within 3 months of the Screening Visit.

26. Subjects with a past medical history of thrombotic, thromboembolic, or abnormal bleeding events including concomitant antiphospholipid antibody syndrome (per Sydney classification criteria (Gomez-Puerta 2014, Miyakis 2006). Subjects should be questioned specifically for thrombosis, phlebitis, embolism, etc. at screening to establish negative history. Subjects with known lupus anticoagulant and/or anticardiolipin and/or anti-b2 glycoprotein antibodies alone should not be excluded.

27. Legal incapacity or limited legal capacity.

28. Receipt of a live/attenuated vaccine within 12 weeks prior to the Screening Visit or subjects who are expecting to receive any live virus or bacterial vaccinations during the trial, or up to 3 months after the last dose of study drug, are not permitted. Seasonal influenza vaccination is permitted if the inactivated vaccine formulation is administered.

29. Major surgery requiring hospitalization within 4 weeks prior to the Screening Visit and any planned major surgery for the duration of the trial. Subjects with a history of lung resection.

30. Have a history of a major organ transplant (eg, heart, lung, kidney, or liver) or hematopoietic stem cell/marrow transplant or are due to receive transplantation.

31. Severe gastrointestinal disease requiring parenteral nutrition.

5.4 Criteria for Initiation of Trial Treatment

All subjects who meet the inclusion and none of the exclusion criteria are eligible for randomization to one of the treatment groups.

5.5 Criteria for Subject Withdrawal

5.5.1 Withdrawal from Trial Therapy

A subject must be withdrawn from IMP if any of the following occur:

- Enrollment despite violation of an inclusion and/or exclusion criterion which, in the Investigator's and/or Sponsor's opinion, makes discontinuation of the subject necessary.
- Participation in any other interventional trial during the duration of this trial for which the Investigator or Sponsor considers discontinuation of the IMP necessary.
- Occurrence of pregnancy.
- Anaphylaxis, anaphylactoid, or other severe or life-threatening hypersensitivity reactions to IMP, based on Investigator judgment. Such cases should be discussed with the Medical Monitor.
- Occurrence of any other AE for which discontinuation of IMP is desired or considered necessary by the Investigator, Sponsor, and/or the subject.
- Noncompliance, judged as significant by the Investigator or Sponsor including noncompliance with the required trial considerations.
- Discontinuation of LTBI therapy before complete, if present at the Screening Visit.
- Surgery considered by the Investigator or Sponsor to be major.
- Occurrence of any other clinical condition or circumstances for which discontinuation is considered necessary by the Investigator and/or the Sponsor/designee.
- Significant disease progression which in the Investigator's opinion requires initiation of rescue therapy, such as cyclophosphamide or other local standard of care treatment (see Section 6.5.5) or other new treatment considered to have immunosuppressive or immunomodulating properties.

If a subject discontinues IMP, then the subject should complete the early termination visit and then the remaining scheduled visits. At a minimum, the subject is expected to complete the trial

visits at Weeks 12, 24, 36, 52, 64, 76, 88, and 104, as well as the Safety Follow-up period Week 12 visit. Subjects with discontinued IMP can come to the other scheduled visits during the trial period according to the Investigator's judgment.

Subjects who withdraw from the treatment period would have an early termination visit followed by entrance into the Safety Follow-up Period.

Subjects who withdraw from the trial (eg, withdraw consent, lost to follow-up, or death; see Section 5.5.2) would not have any additional trial visits.

It is important for site investigators to retain each subject through the end of the trial for prevention of missing data. Systematic and consistent attempts are needed to contact subjects who fail to actively maintain contact with the site Investigator. The nature, method, and frequency of such contact should be recorded in the source documents, including number of telephone calls, day of week, and time of such calls and source of information.

5.5.2 Withdrawal from the Trial

Subjects may withdraw from the trial at any time without giving a reason. Withdrawal of consent will be considered withdrawal from the trial. Subjects wishing to withdraw from the trial should be asked to complete the early termination visit, if not already performed.

A subject must be withdrawn if any of the following occur during the trial:

- Withdrawal of the subject's consent
- Death of subject
- Subject lost to follow up.

5.6 Premature Termination of the Trial

The clinical trial may be terminated prematurely or suspended at the request of Health Authorities or if new safety or efficacy information leads to an unfavorable risk-benefit judgment for IMP. The Sponsor may discontinue the trial if it becomes unjustifiable for medical or ethical reasons, for poor enrollment, or because of discontinuation of clinical development of abituzumab.

Health Authorities and Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) will be informed about the discontinuation of the trial in accordance with applicable regulations.

5.7 Definition of End of Trial

A clinical trial protocol may not be considered closed as long as:

- Any subject is still receiving any IMP;
- Visits specified by the protocol are still taking place;

- Procedures or interventions according to the protocol are still being undertaken in any subject;
- The post-treatment safety follow up period, defined in the clinical trial protocol as being part of the trial, has not yet been completed for any subject.

The Survival follow up period will end with the end of trial.

6 Investigational Medicinal Product and Other Drugs Used in the Trial

The term "Investigational Medicinal Product" refers to the active substance or placebo being tested or used in a clinical trial.

6.1 Description of the Investigational Medicinal Product

The active pharmaceutical ingredient in abituzumab drug product is a recombinant, de-immunized monoclonal antibody of the IgG2 subclass that is thought to block ligand binding to human αv-integrins.

CCI [redacted]

6.2 Dosage and Administration

In the Double-blind Treatment Period, subjects will be randomized in a 2:2:1 ratio to receive one of the following treatments: abituzumab 1500 mg, placebo, or abituzumab 500 mg, respectively. Treatment will be given as an intravenous infusion over approximately 1 hour every 4 weeks. The infusion time should not be less than 1 hour. Close observation of the subject is recommended for a period of at least 1 hour after administration of IMP. The last IMP/placebo administration will be at the Week 100 visit.

If administration of IMP or placebo cannot be performed within the specified protocol visit window, the decision to administer IMP or placebo outside of the window will be determined on a case-by-case basis after a discussion with the Medical Monitor and the Sponsor's Medical Director.

6.3 Assignment to Treatment Groups

After completion of all screening evaluations, all eligible subjects will be randomly allocated in a 2:2:1 randomization ratio to 1 of the 3 treatment groups: abituzumab 1500 mg, placebo, or abituzumab 500 mg, respectively. Randomization in permuted blocks will be conducted by a

central interactive voice/web response system (IVRS/IWRS) provider. Randomization will be stratified by baseline FVC % predicted (< 70% versus ≥ 70%) and by duration of mycophenolate use at baseline (< 6 months versus ≥ 6 months).

PPD

6.4 Noninvestigational Medicinal Products to be Used

Not applicable.

6.5 Concomitant Medications and Therapies

All concomitant medications taken by the subject during the trial, from the date of signature of the informed consent are to be recorded in the appropriate section of the electronic case report form (eCRF), noting the name, dose, duration, and indication of each drug. Nondrug interventions and any changes to a concomitant medication or other intervention should also be recorded in the eCRF.

6.5.1 Permitted Medicines

Any medications, other than those excluded or listed as prohibited, that are considered necessary for the subject's welfare, and that do not interfere with the trial conduct or assessment, may be given at the Investigator's judgment. The Investigator will record all concomitant medications and procedures throughout the trial.

Seasonal influenza vaccination is permitted if the inactivated vaccine formulation is administered. Prophylaxis for *Pneumocystis jiroveci* pneumonia according to local guidelines will be permitted.

Standard of Care in SSc

Treatment for SSc-ILD, including proton pump inhibitors, prokinetic drugs, antibiotics, medications for systemic blood pressure control and/or Raynaud's symptoms, topical nitroglycerin, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, selective serotonin reuptake inhibitors, and nonsteroidal anti-inflammatory drugs can be used or initiated during the trial. Oral corticosteroids up to 10 mg/day prednisone equivalent is permitted during the trial (doses given are for a total daily dose of prednisone; corticosteroids other than prednisone may be used instead at the equivalent doses; see Appendix II).

Dosing of mycophenolate must be kept stable during the Double-blind Treatment Period, unless a change in dose is warranted by clinically meaningful disease progression (see Section 6.5.5). Hydroxychloroquine or chloroquine are permitted if dose has been stable for at least 4 weeks prior to the Screening Visit.

Low-dose aspirin (< 350 mg/day) for cardiovascular prophylaxis is permitted during the trial. Paracetamol (acetaminophen) up to 3 g/day may be initiated for pain control of SSc symptoms during the trial. Any change, either in existing dosing or initiation of new therapy, should be recorded.

The criteria for clinically meaningful disease progression and associated changes in SSc therapy are described in Section 6.5.5.

6.5.2 Prohibited Medicines

Medications for treatment of PAH are not permitted during the Screening or Double-blind Treatment Periods. These medications include, but are not limited to, phosphodiesterase-5 inhibitors (eg, sildenafil), ERAs (eg, bosentan), prostanoids (epoprostenol, treprostinil), and riociguat. These medications can be used for treatment of conditions other than PAH, such as Raynaud's symptoms. If subjects meet criteria for rescue medication (see Section 6.5.5), then such therapy can be initiated.

The use of agents other than mycophenolate (MPS or MMF) considered by the Investigator to have immunomodulating, immunosuppressive, or potential scleroderma disease-modifying properties within 2 months of the Screening Visit is not permitted. The use of cyclophosphamide within 5 months of the Screening Visit is not permitted.

Receipt of a live/attenuated vaccine within 12 weeks prior to the Screening Visit is not permitted. Live virus or bacterial vaccinations during the trial, or up to 3 months after the last dose of study drug are not permitted.

6.5.3 Other Interventions

Not applicable.

6.5.4 Special Precautions

Abituzumab may have adverse effects common to monoclonal antibodies as well as compounds with anti-integrin activity and antiangiogenic potential.

CCI [redacted]

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 two effective methods of contraception, including at least one highly effective method that can achieve a failure rate of < 1% per year, when used consistently and correctly, and one other reliable method during the treatment period and for at least 90 days after the last dose of study treatment.

Examples of contraceptive methods with a failure rate of < 1% per year (highly effective contraceptive methods) include:

- combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation[1] (oral, intravaginal, transdermal)
- progesterone-only hormonal contraception associated with inhibition of ovulation[1] (oral, injectable, implantable[2])
- IUD[2]
- IUS[2]
- bilateral tubal occlusion[2]
- vasectomized partner[2,3]
- sexual abstinence[4]

[1] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.

[2] Contraception methods in the context of this guidance are considered to have low user dependency.

[3] Vasectomized partner is a highly effective birth control method provided that the partner is the sole sexual partner of the woman of childbearing potential trial participant and that the vasectomized partner has received medical assessment of the surgical success.

[4] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Barrier methods supplemented with the use of a spermicide could be considered as a reliable method.

For men (including those who have undergone a vasectomy): agreement to remain abstinent or use a condom during the treatment period and for at least 12 months after the last dose of study treatment and agreement to refrain from donating sperm during this same period.

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

In addition to male contraception, agreement to advise female partners of childbearing potential to use highly effective contraception during the study and for at least 12 months after the last dose of study treatment.

Upon termination of participation in this clinical study, patients continuing on MMF must continue effective contraception as required by the SPC.

6.5.5 Management of Specific Adverse Events or Adverse Drug Reactions

Subjects with cutaneous AESI thought to be related to IMP and Grade ≥ 3 in severity should have the IMP withheld. If subsequently the event has sufficiently resolved, re-initiation of IMP at half of the original dose may be considered by the Investigator after discussion with the CRO Medical Monitor.

Clinically Meaningful Disease Progression

Subjects meeting one or both of the below criteria will be considered as having clinically meaningful disease progression**:**

1. **SSc-ILD**: one of the following (in the absence of causative intercurrent illness) on at least 2 occasions within approximately 4 weeks (per OMERACT criteria):
   - Relative decrease from baseline in FVC % predicted ≥ 10%;
   - Relative decrease from baseline in FVC % predicted of ≥ 5% to < 10% and relative decrease from baseline in DLCO % predicted ≥ 15%.
2. **SSc progression other than ILD**: new onset of one or more of the following:
   - Scleroderma renal crisis;
   - Left ventricular failure (defined as ejection fraction ≤ 45%);
   - Pulmonary arterial hypertension requiring treatment.

Subjects with clinically meaningful disease progression of SSc-ILD should be considered for change in therapy according to the guidance below:

- Subjects taking submaximal doses of mycophenolate (MMF < 3 g/day or MPS < 2160 mg/day should have an increase to 3 g/day or 2160 mg/day, respectively, as tolerated. The IMP should be continued (unless meeting criteria for withdrawal from IMP, refer to Section 5.5.1).
- Subjects taking maximal doses of mycophenolate should have the IMP discontinued and be treated according to the local standard of care. If a nonbiologic immunosuppressant (such as cyclophosphamide [intravenous or oral]) is initiated, then mycophenolate must be discontinued. Subjects withdrawn from IMP should complete the early termination visit.

After the change in therapy as described above for progression of SSc-ILD, subjects would fulfill criteria for further disease progression if meeting 1 of the 2 specified criteria based on change in FVC and DLCO (ie, using the clinical data from the time of change in therapy as the new 'baseline'). Such subjects should be switched from mycophenolate to other local standard of care with discontinuation of IMP.

Subjects with clinically meaningful progression of SSc other than ILD should be treated according to the local standard of care, at the discretion of the Investigator.

If a subject discontinues IMP, then the subject should complete the early termination visit and then the remaining scheduled visits (refer to Table 1 and Table 2). All subjects will be followed up by the site for survival from the last visit on trial until death or end of the trial. New onset or worsening of manifestations of scleroderma that are not captured by the pulmonary function tests, mRSS, or digital ulcer score, should be reported as AEs. On the eCRF AE page, such events should be marked as 'yes' in response to the question "Is this a manifestation of worsening scleroderma?".

If the ILD on HRCT worsens significantly according to the Investigator, then subjects can have the mycophenolate treatment increased to the protocol-specified maximal dose (i.e., 3 g/day MMF or 2160 mg/day MPS).

6.6 Packaging and Labeling of the Investigational Medicinal Product

All IMPs will be packaged and labeled in accordance with all applicable regulatory requirements and Good Manufacturing Practice Guidelines.

Six vials will be packed in white cartons with foam inserts and a single panel/booklet label attached to the vial and carton.

6.7 Preparation, Handling, and Storage of the Investigational Medicinal Product

CCI [redacted] Detailed information on infusion bags and medical devices to be used for the preparation of the dilutions and subsequent administration will be provided in the manual of preparation. To prepare the dilutions, preparation steps must be accomplished by adequately trained personnel using aseptic techniques.

CCI [redacted] However, from a microbiological point of view, the diluted solution should be used just after and is not intended to be stored unless reconstitution and dilution has taken place in controlled and validated aseptic conditions. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

CCI [redacted]

The IMP must be stored at the Investigator's site safely and separately from other drugs under locked conditions. Only a pharmacist or a person designated by him/her will have access to the IMP and will prepare the IMP infusions. A detailed description of the preparation procedure will be provided prior to trial start in a separate Manual of Preparation.

6.8 Investigational Medicinal Product Accountability

The Investigator is responsible for ensuring IMP accountability, including reconciliation of drugs and maintenance of records.

- Upon receipt of IMP, the responsible person will check for accurate delivery and acknowledge receipt by signing or initialing and dating the appropriate documentation and returning it to the location specified. A copy will be archived for the Investigator Site File.
- Dispensing of IMP will be recorded on the appropriate drug accountability forms so that accurate records will be available for verification at each monitoring visit.
- Trial center IMP accountability records will include the following:
  - Confirmation of IMP receipt, in good condition and in the defined temperature range;
  - The inventory of IMP provided for the clinical trial and prepared at the site;
  - The volume administered to each subject;
  - The disposition (including return, if applicable) of any unused IMP;
  - Dates, quantities, kit numbers, expiry dates, and the individual subject trial numbers.

The Investigator site should maintain records, which adequately document that subjects were provided the volume specified in this protocol, and all IMPs provided were fully reconciled.

Unused IMP must not be discarded or used for any purpose other than the present trial. No IMP that is dispensed to a subject may be redispensed to a different subject.

A trial monitor will periodically collect the IMP accountability forms.

6.9 Assessment of Investigational Medicinal Product Compliance

The IMP will be administered by intravenous infusion by the Investigator or delegate. The Investigator or designee will record the date and time of the start and end of each infusion in the subject's medical records and in the eCRF.

The exact volumes of IMP given at each infusion will also be documented in the eCRF. If treatment is interrupted during infusion, the clinical staff will estimate the volume received by the subject and document this in the eCRF.

Any reasons for noncompliance must be documented, including, but not limited to:

- Missed visits
- Interruptions in the schedule of administration.

6.10 Blinding

This trial will be double-blinded.

Packaging and labeling will be prepared to protect the blinded status of the trial. Each kit will be labeled by the manufacturer with a unique kit number. Blinding will be maintained throughout the trial duration, unless an emergency unblinding occurs.

All breaks of the trial blind must be adequately documented.

Prior to the start of the trial, an IDMC will be formed to monitor interim safety data on a regular basis to ensure the safety of subjects in this trial. The IDMC will review the results of interim futility analysis and make a recommendation to the Sponsor on continuing or stopping the trial for futility, based on the criteria in the IDMC charter.

An independent statistical center will support the IDMC for safety analysis and the interim futility analysis.

A team from the Sponsor, independent of the CRO trial team, will be tasked with review of the unblinded interim analysis results. Details will be provided in the Firewall Charter.

The primary analysis will be performed by the Sponsor/CRO staff while the trial is ongoing for subjects who are still under trial treatment during the second year. To ensure the integrity of the trial conduct, results of primary analysis will be generated on the aggregate group level and reviewed by a restricted group to limit initial dissemination. The access of individual treatment information will be controlled so as not to impact the trial conduct. The sites and subjects remain blinded until the end of the trial.

The bioanalytical laboratory(ies) responsible for the analysis of the PK samples will be allowed to be unblinded to treatment so as not to analyze the samples from the placebo-treated subjects. The subject identifiers will be masked from any results of the PK analyses transferred to the Sponsor before the final database lock.

It is acknowledged that in the case of safety events, certain subject treatment information may be unintentionally revealed in the aggregate output of the primary analysis. The Sponsor considers it is a small risk and can be mitigated by using a restricted results review team to limit initial dissemination.

The Sponsor may decide to continue or terminate the trial following the primary analysis. The IDMC will be informed of the outcome of the primary analysis and will remain in place for monitoring subject safety until the end of the trial.

6.11 Emergency Unblinding

The trial blind may be broken for an individual only if knowledge of the IMP is essential for clinical management of the subject. The Investigator must promptly explain the reason for any unblinding of an IMP to the Sponsor without revealing the result to any Sponsor employee except the designated Drug Safety representative (using the Emergency Unblinding Notification Form). The Investigator must record the date of unblinding and the reason in the eCRF. Contact information for breaking the blind in an emergency is given on the subject emergency card provided to each subject (see Section 9.4).

If IMP is unblinded by the Investigator, the subject will be discontinued from treatment and followed up as appropriate.

Under certain circumstances, Drug Safety may be required to unblind the treatment assignment for an individual subject following an SAE or other serious event; for example, if an expedited regulatory report is required. See Section 7.4 for further details on expedited reporting and SAEs.

6.12 Treatment of Overdose

An overdose is defined as any amount of IMP greater than the assigned dose for an individual subject enrolled in the trial. Even if it does not meet other criteria for an SAE, any overdose must be recorded in the Trial Medication section of the eCRF and reported to Drug Safety in an expedited manner using the SAE Report Form, and following the procedure in Section 7.4. As the Investigator is blinded to the treatment group, it should be assumed that the subject received abituzumab 1500 mg and the overdose should be reported in a blinded manner, eg, without previous unblinding of the subject.

As no antidote or nondrug therapy is available, the Investigator should use clinical judgment when treating an overdose of the IMP.

6.13 Medical Care of Subjects after End of Trial

The Sponsor will not provide any additional care to subjects after they leave the trial period because such care should not differ from what is normally expected for patients with SSc-ILD. During the survival follow up period, subjects will be treated according to the local standard of care.

7 Trial Procedures and Assessments

7.1 Schedule of Assessments

Prior to performing any trial assessments that are not part of routine medical care for the subject, the Investigator will obtain written informed consent as described in Section 9.2.

Each subject's participation in the trial consists of a Screening Period, a Double-blind Treatment Period, and a Safety Follow-up Period. Details for the procedures and the Schedules of Assessments are provided in Table 1 and Table 2.

7.1.1 Screening Period

The subject's eligibility will be assessed at a Screening Visit that will occur within 42 days prior to Day 1. After providing written informed consent, the assessments described in Table 1 will be performed.

If at screening, the subject meets all of the protocol inclusion and none of the exclusion criteria (including complete history of immunosuppressive, immunomodulating, and potential scleroderma disease-modifying medications as well as history of other medications in the previous year), the subject will be considered as eligible and will be enrolled in the trial and randomized. Subjects who fail to meet the protocol-specified criteria for randomization or dosing, or withdraw their consent before randomization, are considered screening failures. If the Investigator feels a particular screening assessment is aberrant and retesting could confirm eligibility, these may be repeated under the same subject number, provided the retest is performed within the same screening period. A subject who was considered a screen failure may be re-screened (only once per subject). Re-screening is not encouraged. However, on a case-by-case basis with permission of the Medical Monitor and the Sponsor's Medical Director, a subject who has not met all of the eligibility criteria within the original screening period may be permitted to be re-screened one time. An HRCT would not need to be repeated if completed within 2 months of the re-screening visit. Any TB test, including negative TB skin test with purified protein derivative, QuantiFERON-TB, or T-SPOT, would not need to be repeated if completed within 3 months of the re-screening visit. Each subject must be re-consented before re-screening occurs. A new subject number will be assigned and all screening assessments have to be repeated.

The following information, as a minimum should be collected for screen failure subjects: informed consent, demographics, reason for screen failure, AEs from the date of informed consent until subject is considered screen failure by the Investigator, and the Investigator`s signature.

7.1.2 Double-blind Treatment Period

All subjects will return to the trial center on Days 1, 15, and 29, then every 4 weeks through Week 104. Visit windows of ±3 days through Week 52 and ±5 days for Weeks 56 through 104 are permitted. Beginning on Day 1, subjects will receive their assigned dose of IMP as an intravenous infusion every 4 weeks with the last IMP administration at the Week 100 visit. Efficacy, safety, HRQoL, PK, and CCI assessments will be performed as described in Table 1 and Table 2.

All visit dates up to Week 104 and the end of the Safety Follow-up Period will be calculated based on Day 1. Any assessments specified on the schedules of assessments may be performed at an unscheduled visit and, if performed, should be documented on the eCRF.

7.1.3 Safety Follow-up Period

Subjects who complete the 104-week treatment period will return to the trial center 4 and 12 weeks (±5 days) after the Week 104 visit for the Safety Follow-up Visits.

Subjects who are withdrawn from IMP should complete the early termination visit as soon as possible, but within 2 weeks of IMP discontinuation, and then the remaining scheduled visits. At a minimum, the subject is expected to complete the trial visits at Weeks 12, 24, 36, 52, 64, 76, 88, and 104, as well as the Safety Follow-up period Week 12 visit. Subjects with discontinued IMP can come to the other scheduled visits during the trial period according to the Investigator's judgment.

Subjects who withdraw from the treatment period would have an early termination visit followed by entrance into the Safety Follow-up Period.

Subjects who withdraw from the trial (eg, withdraw consent, lost to follow-up, or death; see Section 5.5.2) would not have any additional trial visits.

Assessments will be performed as described in Table 2.

7.1.4 Survival Follow-up

All subjects will be assessed for survival by the site every 12 weeks (± 1 week) from the last visit on the trial until death or end of the trial. Each subject's vital status, and date of death if known, will be recorded in the eCRF. Systematic and consistent attempts will be made to contact subjects who fail to actively maintain contact with the site Investigator (see Section 5.5.1).

7.2 Demographic and Other Baseline Characteristics

At screening, the following demographic data will be collected: date of birth, sex (gender), height, weight, race, and ethnicity. In addition, a complete medical history (including a history of SSc-ILD), medication history (including complete history of immunosuppressive, immunomodulating, and potential scleroderma disease-modifying medications, as well as history of other medications in the previous year), and history of surgical procedures will be collected. Other baseline measurements such as clinical laboratory parameters, ECG, vital signs, and physical examination will also be assessed.

7.3 Efficacy Assessments

Efficacy assessments include evaluation of lung function (FVC and DLCO) and lung abnormalities on HRCT. Assessments will be performed as described in Table 1 and Table 2.

Relative change is defined as percentage change from baseline FVC percent predicted (eg, change from FVC 80% predicted to FVC 70% predicted corresponds to an absolute change of 10% and a relative change of 12.5%).

In this trial, full volume HRCT of the chest will be performed at Sponsor-qualified imaging centers per guidelines outlined in an imaging manual. High resolution computer tomography will be performed on all trial subjects during the Screening Period and at Months 6, 12, and 24 (Weeks 24, 52, and 104; or early termination, if applicable). To ensure comparability, the same scan, equipment, method, and technique used during the baseline HRCT scan should be used for all the subsequent HRCT scans. For all subjects, HRCT scans will be performed with no contrast agent administration, reconstructed every 0.6 to 2 mm, using a low-dose protocol.

The HRCT images will be analyzed by computer-based quantitative scoring system and also by visual review by a central imaging review panel. The HRCT analysis will focus on changes visual and CAD scores for lobar lung fibrosis evaluation. Changes in the lung fibrosis scores from the Screening Period HRCT will be used to evaluate the treatment responses.

Detailed imaging procedures of HRCT will be defined in a separate imaging manual, and detailed image analysis procedures of HRCT will be defined in an imaging review charter.

Radiation Dose

The radiation dose that results from the entire scan can be described as having a whole body effective dose of 2.1 milliSieverts (mSv). Thus, for the 4 scans given over the 104 weeks (2 years) in this trial, the estimated total body effective dose would be 8.4 mSv. The average annual exposure from natural sources of radiation in the USA, for example, is approximately 3.0 mSv per year, and a radiation worker (such as a radiologic technologist or a radiologist) is allowed 50 mSv per year, for a total of 6.0 and 100 mSv, respectively, over 2 years. Therefore, this trial delivers the equivalent of approximately 1.4 times the expected natural radiation exposure and 8.4% of what a radiation worker is allowed over a 2-year period. This is considered acceptable, given the potential utility of the derived data.

7.4 Assessment of Safety

The safety profile of the IMP will be assessed through the recording, reporting, and analysis of baseline medical conditions, AEs, physical examination findings including vital signs and laboratory tests.

Comprehensive assessment of any apparent toxicity experienced by each subject will be performed from the time of giving informed consent and throughout the trial. The Investigator will report any AEs, whether observed by the Investigator or reported by the subject (see Section 7.4.1.2). The reporting period for AEs is described in Section 7.4.1.3.

7.4.1 Adverse Events

7.4.1.1 Adverse Event Definitions

Adverse Event

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, regardless of causal relationship with this treatment. An

AE can therefore be 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 IMP.

A TEAE is defined as any event not present prior to the initiation of the IMP or any event already present that worsens in either severity or frequency following exposure to the IMP.

For surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

The Investigator is required to grade the severity or toxicity of each AE.

Investigators will reference the National Cancer Institute (NCI) - CTCAE, Version 4.03 (publication date: 14 June 2010), a descriptive terminology that can be used for AE reporting.

A general grading (severity/intensity; hereafter referred to as severity) scale is provided at the beginning of the above referenced document, and specific event grades are also provided.

If a particular AE's severity is not specifically graded by the guidance document, the Investigator is to use the general NCI-CTCAE definitions of Grade 1 through Grade 5 following his or her best medical judgment.

The 5 general grades are:

- Grade 1 or Mild
- Grade 2 or Moderate
- Grade 3 or Severe
- Grade 4 or Life-threatening
- Grade 5 or Death.

According to Sponsor convention, any clinical AE with severity of Grade 4 or 5 must also be reported as an SAE. However, a laboratory abnormality of Grade 4, such as anemia or neutropenia, is considered serious only if the condition meets one of the serious criteria described below.

If death occurs, the primary cause of death or event leading to death should be recorded and reported as an SAE. "Fatal" will be recorded as the outcome of this specific event and death will not be recorded as separate event. Only, if no cause of death can be reported (for example, sudden death or unexplained death), the death per se might then be reported as an SAE.

Investigators must also systematically assess the causal relationship of AEs to IMP (including any other non-IMPs, radiation therapy, etc.) using the following definitions. Decisive factors for the assessment of causal relationship of an AE to the IMP include, but may not be limited to, temporal relationship between the AE and the IMP, known side effects of IMP, medical history, concomitant medication, course of the underlying disease, or trial procedures.

Unrelated: Not reasonably related to the IMP. The AE could not medically (pharmacologically/clinically) be attributed to the IMP under study in this clinical trial protocol. A reasonable alternative explanation must be available.

Related: Reasonably related to the IMP. The AE could medically (pharmacologically/clinically) be attributed to the IMP under study in this clinical trial protocol.

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Abnormal laboratory findings and other abnormal investigational findings (for example, on an ECG trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to treatment discontinuation or are considered otherwise medically important by the Investigator. If a laboratory abnormality fulfills these criteria, the identified medical condition (for example, anemia or increased ALT) must be reported as the AE rather than the abnormal value itself.

Serious Adverse Events

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

- Results in death.
- Is life-threatening. (Note: The term "life-threatening" refers to an event in which the subject is at risk of death at the time of the event, not an event that hypothetically might have caused death if it was more severe.)
- Requires inpatient hospitalization or prolongs an existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is otherwise considered to be medically important. (Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.)

For the purposes of reporting, any suspected transmission of an infectious agent via an IMP is also considered an SAE, as described in Section 7.4.1.4.

Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify trial treatment or trial procedures (for example, an overnight stay to facilitate chemotherapy and related hydration therapy application) are not considered SAEs. However, all events leading to unplanned hospitalizations or unplanned

prolongation of an elective hospitalization (for example, undesirable effects of any administered treatment) must be documented and reported as SAEs.

Events Not to Be Considered as AEs/SAEs

Medical conditions present at the initial trial visit that do not worsen in severity or frequency during the trial are defined as Baseline Medical Conditions, and are not to be considered AEs.

However, if adverse signs or symptoms occur in association with disease progression then these should be recorded as AEs.

Adverse Events of Special Interest

All blistering or Grade ≥ 3 AEs in the skin and subcutaneous tissue disorders SOC will be designated as AESI. Any cutaneous reaction of Grade 1 or 2 that is not responding to specific treatment or is worsening will also be designated as an AESI. The occurrence of cutaneous AESI or SAEs will be reviewed by an independent panel of dermatologists to provide guidance for further investigation and interpretation of these events, and advise the IDMC whether any actions to modify clinical trial conduct should be considered.

7.4.1.2 Methods of Recording and Assessing Adverse Events

At each trial visit, the subject will be queried on changes in his or her condition. During the reporting period, any unfavorable changes in the subject's condition will be recorded as AEs, whether reported by the subject or observed by the Investigator.

Complete, accurate, and consistent data on all AEs experienced for the duration of the reporting period (defined below) will be reported on an ongoing basis in the appropriate section of the eCRF. All SAEs must be additionally documented and reported using the appropriate report form as described in Section 7.4.1.4.

It is important that each AE report include a description of the event, its duration (onset and resolution dates and times when it is important to assess the time of AE onset relative to the recorded treatment administration time), its severity, its causal relationship with the trial treatment, any other potential causal factors, any treatment given or other action taken, including dose modification or discontinuation of the IMP, and its outcome. In addition, serious cases should be identified and the appropriate seriousness criteria documented.

For suspected anaphylactic events, including infusion-related reactions, Investigators should utilize the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network criteria (Sampson 2006).

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

   AND AT LEAST ONE OF THE FOLLOWING

a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow (PEF), hypoxemia)

b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that subject (minutes to several hours):

a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)

b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)

d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

3. Reduced BP after exposure to known allergen for that subject (minutes to several hours):

a. Adults: systolic BP of less than 90 mmHg or greater than 30% decrease from that person's baseline

Adapted from Sampson 2006

Specific guidance can be found in the eCRF Completion and Monitoring Conventions provided by the Sponsor.

7.4.1.3 Definition of the Adverse Event Reporting Period

The AE reporting period for safety surveillance begins when the subject is initially included in the trial (date of first signature of first informed consent) and continues through the post-treatment Safety Follow-up Period.

Any SAE assessed as related to IMP must be reported whenever it occurs, irrespective of the time elapsed since the last administration of IMP.

7.4.1.4 Procedure for Reporting Serious Adverse Events

In the event of any new SAE occurring during the reporting period, the Investigator must immediately (within a maximum of 24 HOURS after becoming aware of the event) inform the Sponsor or its designee in writing. All written reports should be transmitted using the SAE Report Form, which must be completed by the Investigator following specific completion instructions.

In exceptional circumstances, an SAE (or follow-up information) may be reported by telephone; in these cases, an SAE report form must be provided immediately thereafter.

Relevant pages from the eCRF may be provided in parallel (for example, medical history and concomitant drugs). Additional documents may be provided by the Investigator, if available (for example, laboratory results, hospital report, and autopsy report). In all cases, the information provided on the SAE Report Form must be consistent with the data about the event recorded in the eCRF.

The Investigator must respond to any request for follow-up information (for example, additional information, outcome, final evaluation, and other records where needed) or to any question the Sponsor/designee may have on the AE within the same timelines as those noted above for initial reports. This is necessary to ensure prompt assessment of the event by the Sponsor or designee and (as applicable) to allow the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

Requests for follow-up will usually be made via the responsible Monitor, although in exceptional circumstances the Global Drug Safety department may contact the Investigator directly to obtain further information or to discuss the event.

Any AESI will be reported according to the procedure for SAEs described above.

7.4.1.5 Safety Reporting to Health Authorities, Independent Ethics Committees/Institutional Review Boards, and Investigators

The Sponsor will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations.

The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (particularly deaths) involving trial subjects to the IEC/IRB that approved the trial.

In accordance with ICH GCP, the Sponsor/designee will inform the Investigator of "findings that could adversely affect the safety of subjects, impact the conduct of the trial or alter the IEC's/IRB's approval/favorable opinion to continue the trial." In particular and in line with respective regulations, the Sponsor/designee will inform the Investigator of AEs that are both serious and unexpected and are considered to be related to the administered product ("suspected unexpected serious adverse reactions" or SUSARs). The Investigator should place copies of Safety Reports in the Investigator Site File. National regulations with regard to Safety Report notifications to Investigators will be taken into account.

When specifically required by regulations and guidelines, the Sponsor/designee will provide appropriate Safety Reports directly to the concerned lead IEC/IRB and will maintain records of these notifications. When direct reporting is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC/IRB of any Safety Reports provided by the Sponsor/designee and of filing copies of all related correspondence in the Investigator Site File.

For trials covered by the European Directive 2001/20/EC, the Sponsor's responsibilities regarding the reporting of SAEs/SUSARs/Safety Issues will be carried out in accordance with that Directive and with the related Detailed Guidance documents.

7.4.1.6 Monitoring of Subjects with Adverse Events

Adverse events are recorded and assessed continuously throughout the trial (see Section 7.4.1.3) and are assessed for final outcome at the Safety Follow-up Visits. All SAEs ongoing at the Safety Follow-up Visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the subject is documented as "lost to follow-up". Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

7.4.2 Pregnancy and In Utero Drug Exposure

Only pregnancies considered by the Investigator to be related to trial treatment (for example, resulting from a drug interaction with a contraceptive medication) are considered to be AEs. However, all pregnancies with an estimated conception date during the period defined in Section 7.4.1.3 must be recorded by convention in the AE page/section of the eCRF. The same rule applies to pregnancies in female subjects and to pregnancies in female partners of male subjects. The Investigator must notify the Sponsor/designee in an expedited manner of any pregnancy using the Pregnancy Report Form, which must be transmitted according to the same process as described for SAE reporting in Section 7.4.1.4.

Investigators must actively follow up, document, and report on the outcome of all these pregnancies, even if the subjects are withdrawn from the trial.

The Investigator must notify the Sponsor/designee of these outcomes using the Pregnancy Report Form. If an abnormal outcome occurs, the SAE Report Form will be used if the subject sustains an event and the Parent-Child/Fetus Adverse Event Report Form if the child/fetus sustains an event.

Any abnormal outcome must be reported in an expedited manner as described in Section 7.4.1.4, while normal outcomes must be reported within 45 days after delivery.

In the event of a pregnancy in a subject occurring during the course of the trial, the subject must be discontinued from IMP immediately. The Sponsor/designee must be notified without delay and the subject must be followed as mentioned above.

7.4.3 Clinical Laboratory Assessments

The Sponsor should receive a list of laboratory normal ranges before shipment of IMP. Any change in laboratory normal ranges during the trial should be forwarded to the Sponsor and PPD .

Blood and urine samples will be collected for the clinical laboratory tests in Table 4, following the timing noted in the Schedule of Assessments (Table 1 and Table 2). All samples should be clearly identified. Samples will be collected, processed, and stored in accordance with the directions provided in the PPD Flow Chart. Urine pregnancy tests analyses are to be performed locally. All other parameters will be analyzed at the central laboratories.

Table 4 Clinical Laboratory Testing

Clinical Chemistry	Routine Hematology	Urinalysis (dipstick)
Gamma glutamyl transferase	Hematocrit	pH
ALT	Hemoglobin	Specific gravity
Albumin	Mean cellular hemoglobin	Leukocytes
AP	Mean cellular hemoglobin concentration	Nitrite
AST		Glucose
Bilirubin – direct (only if total bilirubin is outside the normal range)	Mean cellular volume	Ketones
	Platelet count	Protein
Bilirubin – total	Red blood cell count	Blood
Calcium	Red cell distribution width	
Chloride	White blood cell count and differential	**Additional Urinalysis**
Bicarbonate		Urine protein:creatinine ratio (performed if dipstick urinalysis reveals at least 3+ protein)
Serum creatinine		
Glucose	**Coagulation (at screening only)**	Microscopy if blood present
Potassium	Prothrombin time	
Protein – total	Activated partial thromboplastin time	**Immunogenicity**
Sodium		Anti-abituzumab antibodies
Urea		
Uric acid		
C-reactive protein		
TSH (at screening only)		
NT pro-BNP (at screening only)		

ALT = alanine aminotransferase, AP = alkaline phosphatase, AST = aspartate aminotransferase,
NT pro-BNP = N-terminal prohormone brain natriuretic peptide, TSH = thyroid-stimulating hormone.

Other laboratory assessments include the following:

- Serum pregnancy test in female subjects of childbearing potential;
- Urine pregnancy test in female subjects of childbearing potential, to be performed locally;
- HIV, hepatitis C, and hepatitis B (HBsAg, hepatitis B core antibody [IgM and total]) serologies;
- $HbA1_c$ may be evaluated for subjects with diabetes, at the discretion of the Investigator, and by forwarding a prior request to the Medical Monitor and notification to the Sponsor's

Medical Director. Samples may be collected at any time point judged appropriate by the Investigator with Medical Monitor approval. Testing will be conducted by a local laboratory.

- Tuberculosis testing as requested by Investigator.

7.4.4 Vital Signs, Physical Examinations, and Other Assessments

Vital signs, physical examinations, and locally read 12-lead ECGs will be performed and documented throughout the trial at the time points specified in the Schedule of Assessments (Table 1 and Table 2). Blood pressure and pulse rate should be measured after the subject has been in the sitting position for at least 10 minutes. The ECGs will be read in accordance with local practice.

7.5 Pharmacokinetics

Serum samples for the determination of abituzumab concentrations will be collected from all subjects at the time points given in Table 1. In a subset of subjects who give separate consent to provide additional PK samples (rich PK sampling), additional samples will be collected at the time points given in Table 1 (see footnote i).

For the PK evaluation, serum levels of abituzumab will be analyzed by the bioanalytical laboratory using an appropriate validated method.

The actual date and time of sample collection will be recorded.

Instructions for the collection, storage, handling, and shipping of PK samples will provided in the PPD Flow Chart.

CCI [redacted]

CCI [redacted]

8 Statistics

8.1 Sample Size

Based on reference data from randomized clinical trials in SSc-ILD and IPF, an expected improvement of 150 mL in the annual rate of absolute FVC change (mL) is assumed for abituzumab 1500 mg versus placebo with a common standard deviation of 300 mL. CCI [redacted] The inclusion of abituzumab 500 mg in conjunction with abituzumab 1500 mg will support abituzumab exposure-response analysis for dosing optimization.

A blinded sample size review is planned after at least 50% of the subjects complete their first year on treatment. The review will either lead to an increase in the total sample size or to a continuation of the trial with the original sample size. Following Kieser 2003, the estimated one-sample variance will be adjusted for bias. If the adjusted standard deviation is more than 10% larger than the hypothesized standard deviation (ie, 330 mL or more), then the sample size may be increased by up to 40 subjects. Details will be provided in the Statistical Analysis Plan.

Hypothesis Testing

The primary endpoint is the annual rate of absolute FVC change in volume (mL).

- The null hypothesis is:

  H0: There is no improvement in annual rate of absolute FVC change for the abituzumab 1500 mg arm compared with the placebo arm on top of stable mycophenolate.

- The alternative hypothesis is:

  H1: There is an improvement in annual rate of absolute FVC change for the abituzumab 1500 mg arm compared with the placebo arm on top of stable mycophenolate.

8.2 Randomization

Once all eligibility criteria have been met, subjects will be randomly assigned to 1 of the 3 treatment groups of the trial: abituzumab 1500 mg, placebo, or abituzumab 500 mg in a ratio of 2:2:1, respectively.

Randomization will be conducted in permuted blocks by a central IVRS/IWRS provider and stratified by baseline FVC % predicted (< 70% versus ≥ 70%) and by duration of mycophenolate use at baseline (< 6 months versus ≥ 6 months).

8.3 Endpoints

8.3.1 Primary Endpoint

The primary endpoint for the trial is annual rate of absolute FVC change in volume (mL). This endpoint will be assessed after all subjects have either completed 52 weeks of treatment or prematurely discontinued from the trial. The primary efficacy analysis will be conducted on all observed FVC data during the trial for all subjects regardless of their adherence to treatment or use of rescue therapies. The primary efficacy analysis will be performed using the modified Intent-to-Treat (mITT) population.

8.3.2 Secondary Endpoints

The key secondary efficacy endpoints for the trial include the following:

- Change in dyspnea from baseline as measured by the Mahler TDI at Week 52;
- Absolute change from baseline in SGRQ total score at Week 52;
- Absolute change from baseline in mRSS at Week 52 in subjects with diffuse cutaneous skin involvement at baseline;
- Absolute change from baseline in QLF in the region of highest severity at Week 52;
- Overall survival.

Other secondary efficacy endpoints for the trial include:

- Proportion of subjects with clinically meaningful progression of SSc by meeting Criterion 1 (ILD) by Week 52 and by Week 104 (refer to Section 6.5.5 for the definition of clinically meaningful progression);
- Proportion of subjects with clinically meaningful progression of SSc by meeting Criterion 2 (SSc progression other than ILD) by Week 52 and by Week 104;
- Proportion of subjects with clinically meaningful progression by Week 52 and by Week 104;
- Proportion of subjects with absolute decrease from baseline of FVC % predicted ≥ 10% on 2 or more consecutive occasions at least 4 weeks apart by Week 52 and by Week 104;
- Time to first clinically meaningful progression;
- Absolute change from baseline in FVC % predicted up to Week 104;
- Absolute change from baseline in DLCO % predicted up to Week 104;
- Absolute change from baseline in transfer coefficient of the lung for carbon monoxide (KCO) at Week 104;

- Absolute change from baseline in QLF in the region of highest severity at Week 104;
- Absolute change from baseline in quantitative HRCT analyses of extent of total ILD up to Week 104.

8.3.3 Safety Endpoints

Safety endpoints in this trial include the following:

- The nature, incidence, severity, relationship, and outcome of AEs, SAEs, and AESIs from screening up to Week 116;
- Number of subjects with treatment-emergent AEs, SAEs, and AESIs from baseline up to Week 116;
- Treatment-emergent changes in clinical laboratory measures, ECGs, and vital signs from baseline up to Week 116;
- Incidence of subjects with positive ADA titers from baseline up to Week 116.

8.3.4 Other Endpoints

Quality of Life endpoints in this trial include the following:

- Proportion of subjects with Mahler TDI worsening ≥ 2 up to Week 104;
- Proportion of subjects with Mahler TDI worsening ≥ 2 up to Week 104 for subjects with Mahler BDI of ≥ 2;
- Change in dyspnea from baseline as measured by the Mahler TDI up to Week 104;
- Change in dyspnea from baseline as measured by the Mahler TDI up to Week 104 for subjects with Mahler BDI ≥ 2;
- Absolute change from baseline for each of the following HRQoL questionnaires up to Week 104:
  - Leicester Cough Index
  - SGRQ
  - Physician's Global Assessment
  - Patient's Global Assessment
  - SHAQ
  - EQ-5D.

Skin fibrosis endpoints include the following:

- In subjects with dcSSc:
  a. Absolute change from baseline in mRSS up to Week 104,
  b. Proportion of subjects with change from baseline in mRSS up to Week 104 according to the following categories:

  - Worsened (absolute increase of ≥ 5 points and relative increase ≥ 25%)
  - Improved (absolute decrease ≥ 5 points and relative decrease ≥ 25%)
  - Stable (do not meet either Worsened or Improved category)
- In subjects with digital ulcers at baseline: absolute change from baseline in digital ulcer count up to Week 104.

Combined response endpoints include the following:

- Proportion of responders as defined by CRISS up to Week 104.

8.3.5 Pharmacokinetic Endpoints

Pharmacokinetic endpoints include the following:

- Abituzumab concentrations;
- PK parameters (eg, C_{max} and C_{min}). Further PK parameters will be derived by population PK.

8.3.6 Other Exploratory Assessments

CCI

- CCI

8.4 Analysis Sets

8.4.1 Modified Intent-to-Treat

The mITT Population is defined as all randomized subjects who receive at least 1 dose of IMP (including placebo). Subjects will be analyzed according to their randomized treatment. All endpoint analyses other than safety will be performed using the mITT population.

8.4.2 Intent-to-Treat

The Intent-To-Treat (ITT) Population will consist of all randomized subjects. Subjects will be analyzed according to their randomized treatment.

8.4.3 Per-Protocol

The Per-Protocol (PP) Population will consist of all randomized and treated subjects who do not have any clinically important protocol deviations. Subjects will be analyzed according to their randomized treatment.

The following are criteria for inclusion in the PP Population:

- Compliance with all entry criteria;
- Absence of clinically important clinical trial protocol violations with respect to factors likely to affect the efficacy of treatment;
- Adequate compliance with and sufficient exposure to IMP.

The criteria will be defined in detail in the Statistical Analysis Plan, and clinically important protocol violators to be excluded from the PP Population will be identified prior the database lock for the primary analysis.

The analysis of the primary endpoint and the key secondary endpoints will be repeated using the PP Population as an additional sensitivity analysis.

8.4.4 Safety

The Safety Population will consist of all randomized subjects who receive at least 1 dose of IMP (including placebo) and have at least 1 postdose safety assessment. All safety analyses will be performed using this population. Subjects in the Safety Population will be analyzed according to the actual treatment received during the trial.

8.5 Description of Statistical Analyses

8.5.1 General Considerations

An outline of key statistical analyses is provided below. Full details of planned analyses will be provided in the Statistical Analysis Plan, to be finalized and approved prior to the interim futility analysis.

It is the intention of this trial that all subjects will adhere to the same visit schedule regardless of whether they have discontinued IMP prematurely. In addition, subjects who discontinue early from IMP will undergo an early termination visit to perform the same assessments scheduled for the Week 104 visit.

Multiple Comparisons/Multiplicity

During the primary analysis, hypothesis testing of the primary endpoint and key secondary endpoints will be formally performed for the abituzumab 1500 mg versus placebo under the family-wise Type I error rate following a hierarchical testing procedure to control for multiplicity. For these endpoints, statistical significance will be met at one-sided $p < 0.025$ and the corresponding two-sided 95% confidence intervals will be provided. CCI [redacted]

CCI [redacted]

Subgroups

The primary and key secondary endpoints and key safety data will be analyzed by subgroup. The subgroups of interest will be prespecified in the Statistical Analysis Plan, including the stratification factors of baseline FVC % predicted (< 70% versus ≥ 70%) and duration of prior mycophenolate use (< 6 months versus ≥ 6 months).

8.5.2 Analysis of Primary Endpoints

The primary endpoint will be analyzed using a random coefficients linear regression model with absolute change from baseline in observed FVC volume (mL) as the outcome variable. The change in FVC volume is assumed to be linear within each subject over the course of the trial. The model will include random coefficients for intercept and time, fixed-effect terms for treatment and time, treatment-by-time as the interaction term, and adjusting for baseline FVC, duration of prior mycophenolate use at baseline, age, sex, and height. Time is the duration (in years) between each postbaseline FVC assessment and baseline assessment. Missing data will be assumed to be missing-at-random (MAR). The analysis of the primary endpoint and other efficacy endpoints will be conducted to include all the data collected during the trial for all subjects regardless of their adherence to treatment or use of rescue therapies.

Sensitivity analysis will be performed to evaluate the potential effect of missing data on the robustness of the efficacy results, including tipping point analyses to assess the different assumptions about the missing outcomes and to explore the plausibility of missing data assumptions under which the conclusions change. The tipping point analysis will allow assumptions about the missing outcomes on the treatment arms to vary independently and will also include scenarios where dropouts on abituzumab arm have worse outcomes than dropouts on placebo arm. Details will be described in the Statistical Analysis Plan.

The linearity assumption for the absolute FVC change in volume over time will be examined. The time course of trends in absolute FVC over time will be presented using observed data collected at multiple time points for each subject. The mean value of absolute FVC and the treatment effect on mean change from baseline in absolute FVC will be presented for each treatment arm over time.

Supportive analysis will be performed to analyze the difference in annual rates using the absolute change from baseline in FVC% predicted. The absolute change in FVC% predicted at Week 52 and at Week 104 will be also analyzed using a ranked analysis of covariance (ANCOVA) model. Missing outcome due to reasons other than death will be replaced with imputed values based on the worst outcome carried forward (WOCF) during the trial. Missing outcome due to death will be ranked worse than others and ordered according to the time from randomization to death, with the shortest time to death as the worst rank.

A continuous responder analysis will be performed using absolute change in FVC% predicted at Week 52 and at Week 104. Missing data will be imputed by WOCF for reasons other than death. Missing data due to death are considered non responders and imputed by the observed highest decline in FVC% predicted among all subjects. A continuous responder curve will be plotted for each treatment arm in a graph to display the relative benefit of abituzumab across the entire range of response. The x-axis shows the absolute change from baseline in FVC% predicted at Week 52. The y-axis shows the corresponding percentage of subjects achieving that level of FVC% predicted decline or greater. A positive treatment effect is demonstrated by consistent separation of the curves across different level of response. A cut-off point of at least 10% decline in FVC% predicted will be performed for a binary responder analysis.

8.5.3 Analysis of Secondary Endpoints

Analysis of Key Secondary Efficacy Endpoints

The key secondary endpoints will be tested for abituzumab 1500 mg versus placebo, using data for subjects on trial treatment, in the following order after the primary endpoint is met.

1. The Mahler TDI at Week 52 will be analyzed using a mixed-effects model adjusting for baseline FVC% predicted, duration of prior mycophenolate use at baseline, and Mahler BDI.

2. The absolute change in SGRQ total score at Week 52 will be analyzed using a mixed-effects model adjusting for baseline FVC% predicted, duration of prior mycophenolate use at baseline, and baseline SGRQ score.

3. The absolute change from baseline in mRSS at Week 52 in subjects with dcSSc at baseline will be analyzed using a mixed-effects model adjusting for baseline FVC% predicted, duration of prior mycophenolate use at baseline, and baseline mRSS.

4. The absolute change from baseline in QLF in the region of highest severity at Week 52 will be analyzed using an ANCOVA model adjusting for baseline FVC% predicted, duration of prior mycophenolate use at baseline, and baseline QLF.

5. Overall survival will be analyzed using a stratified log-rank test and presented by Kaplan-Meier estimates and 95% confidence interval, including the survival data available up to the analysis cut-off date. A Cox proportional hazards regression model will be used to obtain hazard ratios and 95% confidence intervals adjusting for baseline FVC% predicted and duration of prior mycophenolate use at baseline.

The mixed-effects model will include random intercept, treatment, and visit as fixed effect terms, treatment-by-visit as the interaction term, adjusting for baseline covariates. An unstructured covariance matrix will be used as the default option. Missing data is assumed MAR.

Missing data for binary endpoint will be imputed as non-responders.

Analysis of Other Secondary Efficacy Endpoints

CCI [redacted]

Analysis of Safety Endpoints

Adverse events will be summarized by treatment group, by severity, and by relationship to IMP. Serious AEs, AEs leading to treatment discontinuation, and AESI will be summarized by treatment group.

Summary statistics will be used to present changes from baseline in continuous laboratory and vital sign data. Shift tables will be used to present changes in categorical laboratory parameters. Figures may be generated to assist safety evaluation.

Analysis of Quality of Life Endpoints

Quality of life endpoints will be summarized according to their scoring instructions. Continuous variable will be analyzed using ANCOVA unless otherwise specified. Categorical variable will be analyzed using categorical methods. Details will be specified in the Statistical Analysis Plan.

Pharmacokinetic Analyses

A Population PK model will be developed. The influence of covariates on PK parameters will be assessed. From the final Population PK model, individual estimates of the PK parameters and exposure parameters (AUC, C_{max}, and C_{min}) will be derived. The exposure parameters may be used for further exposure-response assessment.

CCI [redacted]

8.6 Interim and Additional Planned Analyses

The interim futility analysis on the primary endpoint will be performed by an independent third party statistician when approximately 88 subjects have either completed 52 weeks of treatment or prematurely discontinued from the trial. The results of interim analysis will be reviewed confidentially by IDMC. The futility boundary is non-binding (to be specified in the IDMC charter). Additional analysis of the primary and secondary endpoints is allowed at the IDMC's discretion and supported by the independent third-party statistician. Based on the totality of the information at interim, the IDMC will make a recommendation to the Sponsor on continuing or stopping the trial for futility. There is no prespecified boundary for efficacy, therefore there is no alpha spending for the interim analysis.

The primary analysis will be performed by the Sponsor/Contract Research Organization staff when all subjects have either completed 52 weeks of treatment or prematurely discontinued from the trial. Results will be generated on the aggregate group level and reviewed by a restricted group to limit initial dissemination. The access of individual treatment information will be controlled to not impact the trial conduct.

The sites and subjects remain blinded until the end of the trial. The trial will continue as planned and a final treatment analysis will be performed when all subjects have either completed 104 weeks of treatment or prematurely discontinued from the trial.

The final database will be locked after all subjects have completed the 12 weeks of safety follow-up or prematurely discontinued from the trial. A final follow-up analysis will be performed after the final database lock.

9 Ethical and Regulatory Aspects

9.1 Responsibilities of the Investigator

The Investigator is responsible for the conduct of the trial at the site and will ensure that the trial is performed in accordance with this protocol, the ethical principles outlined in the Declaration of Helsinki, ICH GCP, and any other applicable regulations. The Investigator must ensure that only subjects who have given informed consent are included in the trial.

According to United States Code of Federal Regulations Part 54.2 (e), for trials conducted in any country that could result in a product submission to the United States Food and Drug Administration (FDA) for marketing approval and could contribute significantly to the demonstration of efficacy and safety of an IMP (which are considered "covered clinical trials" by the FDA), the Investigator and all subinvestigators are obliged to disclose any financial interest which they, their spouses, or their dependent children may have in the Sponsor or the Sponsor's product under study. This information is required during the trial and for 12 months following completion of the trial.

9.2 Subject Information and Informed Consent

An unconditional prerequisite for each subject prior to participation in the trial is written informed consent, which must be given before any trial-related activities are carried out. Adequate information must therefore be given to the subject by the Investigator or an appropriate designee (if local regulations permit) before informed consent is obtained.

A subject information sheet must be prepared in the local language in accordance with ICH GCP and will be provided by the Sponsor for the purpose of obtaining informed consent. In addition to providing this written information to a potential subject, the Investigator or a designee will inform the subject verbally of all pertinent aspects of the trial, using language chosen so that the information can be fully and readily understood by laypersons. The subject will be given sufficient time to read the information and the opportunity to ask questions and to request additional information and clarification.

If permitted by national regulations, a person other than the Investigator may inform the subject about the trial and sign the Informed Consent Form, as above.

After the information is provided by the Investigator, the Informed Consent Form must be signed and dated by the subject and the Investigator.

The signed and dated declaration of informed consent will remain at the Investigator's site, and must be safely archived so that the forms can be retrieved at any time for monitoring, auditing, and inspection purposes. A copy of the signed and dated information and Informed Consent Form should be provided to the subject prior to participation.

Whenever important new information becomes available that may be relevant to informed consent, the Investigator will revise the subject information sheet and any other written information to be provided to the subjects and submit them to the IRB for review and opinion. Using the approved revised subject information sheet and other written information, the Investigator will explain the changes to the previous version to each trial subject and obtain new written consent for continued participation in the trial. The subject will be given sufficient time to read the information and the opportunity to ask questions and to request additional information and clarification about the changes.

Rich Pharmacokinetic Sampling Informed Consent

All subjects who are enrolled in the trial will be eligible to participate in the optional rich PK analysis. As participation is optional, the subjects willing to participate will need to sign a specific PK Informed Consent Form.

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

9.3 Subject Identification and Privacy

A unique number will be assigned to each subject, immediately after informed consent has been obtained. This number will serve as the subject's identifier in the trial as well as in the clinical trial database. All subject data collected in the trial will be stored under the appropriate subject number. Only the Investigator will be able to link trial data to an individual subject via an identification list kept at the site. For each subject, original medical data will be accessible for the purposes of source data verification by the Monitor, audits, and regulatory inspections, but subject confidentiality will be strictly maintained.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing subject data. Subjects will be informed accordingly, and will be requested to give their consent on data handling procedures in accordance with national regulations.

Storage and analyses of samples will be handled according to the specifications as described in the Informed Consent Form.

9.4 Emergency Medical Support and Subject Card

Subjects will be provided with Emergency Medical Support cards supplied by the Sponsor for use during trial participation in order to provide clinical trial subjects with a way of identifying themselves as participating in a clinical trial and to give health care providers access to any information about this participation that may be needed to determine the course of medical treatment for the subject. The information provided on the Emergency Medical Support card will include the process for emergency unblinding.

The first point of contact for all emergencies will be the clinical trial Investigator caring for the affected subject. The Investigator agrees to provide his or her emergency contact information on the card for this purpose. If the Investigator is available when an event occurs, he/she will answer any questions. Any subsequent action (for example, unblinding) will follow the standard process established for Investigators.

In cases where the Investigator is not available, the Sponsor provides the appropriate means to contact a Sponsor physician. This includes the provision of a 24-hour contact number at a call center, whereby the health care providers will be given access to the appropriate Sponsor physician to assist with the medical emergency and to provide support for the potential unblinding of the subject concerned.

9.5 Clinical Trial Insurance and Compensation to Subjects

Insurance coverage will be provided for each country participating in the trial. Insurance conditions shall meet good local standards, as applicable.

9.6 Independent Ethics Committee or Institutional Review Board

Prior to commencement of the trial at a given site, this clinical trial protocol will be submitted together with its associated documents (subject information sheet and Informed Consent Forms) to the responsible IEC/IRB for its favorable opinion or approval, which will be filed in the Investigator Site File. A copy will be filed in the Sponsor Trial Master File at PPD .

The IEC/IRB will be asked to document the date of the meeting at which the favorable opinion or approval was given and the members and voting members present. Written evidence of favorable opinion or approval that clearly identifies the trial, the clinical trial protocol version and the Subject Information and Informed Consent Form version reviewed should be provided. Where possible, copies of the meeting minutes should be obtained.

Amendments to this clinical trial protocol will also be submitted to the concerned IEC/IRB, before implementation of substantial changes (see Section 10.5). Relevant safety information will be submitted to the IEC/IRB during the course of the trial in accordance with national regulations and requirements.

9.7 Health Authorities

The clinical trial protocol and any applicable documentation (for example, Investigational Medicinal Product Dossier, Subject Information and Informed Consent Form) will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

10 Trial Management

10.1 Case Report Form Handling

Refer to the eCRF Completion Guidelines for eCRF handling instructions.

The main purpose of the eCRF is to obtain data required by the clinical trial protocol in a complete, accurate, legible, and timely fashion. The data in the eCRF should be consistent with the relevant source documents.

The Investigator or designee is responsible for ensuring that the data collected in the course of this trial are accurate and documented appropriately on all applicable forms or eCRF. They will then be processed, evaluated, and stored in anonymous form in accordance with applicable data protection regulations. The Investigator must ensure that the eCRFs and any other associated

documents forwarded to Sponsor or its designated organization contain no mention of any subject names.

For patient-reported outcome data, such as HRQoL, electronic patient reported outcome will be used.

The data will be entered into a validated database. PPD Data Management will be responsible for data processing, in accordance with PPD ' standard operating procedures. Database lock will occur once quality control and quality assurance procedures have been completed. Portable document format files of the eCRFs will be provided to the Investigators at the completion of the trial.

The Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) standards, required by the FDA for the submission of trial data, are followed by Merck Serono. Merck Serono General Data Standards and, if applicable, Therapeutic Area Data Standards, as well as Merck Serono SDTM Guidelines, will be used in all clinical trials as predefined in the applicable Merck Serono SOP, Working Instructions, and Guidelines, to create the Case Report Forms (CRFs), the SDTM delivery package (SDTM domains, define.xml, Reviewer's Guide, SDTM annotated CRF), and the operational database; any exemptions need to be discussed and decided by the Project Team. In addition it is intended to convert non-SDTM trial data from legacy trials, and possibly ongoing trials not conducted by Merck Serono, into an FDA submission compliant CDISC-SDTM format. Individual trial data and documents will be migrated into the ICMS (Integrated CDISC-based Data Model and System, a cross-functional platform designed to maintain the data of all current and future projects). These measures will facilitate the integration of data across multiple trials and projects so that more comprehensive data pools can be generated. If significant non-SDTM format data already exists for a drug, trials may not be converted to, or delivered in, SDTM format, if decided by the Project Team and agreed by Senior Management. The Program Data Manager ensures that data standards are harmonized across all trials within this development program.

10.2 Source Data and Subject Files

Source data are defined as all data in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial that are necessary for the reconstruction and evaluation of the trial.

The Investigator must keep a file (medical file and original medical records) on paper or electronically for every subject in the trial. It must be possible to identify each subject by using this subject file. This file will contain the demographic and medical information for the subject listed below and should be as complete as possible.

- Subject's full name, date of birth, sex, height, and weight;
- Medical history and concomitant diseases;
- Prior and concomitant therapies (including changes during the trial);
- Trial identification, that is, the Sponsor trial number for this clinical trial, and subject number;

- Dates for entry into the trial (informed consent) and visits to the site;
- Any medical examinations and clinical findings predefined in this clinical trial protocol;
- All AEs;
- Date that the subject left the trial including any reason for early withdrawal from the trial or IMP (if applicable).

All documents containing source data must be filed, including, but not limited to: HRCT, CT, or magnetic resonance imaging scan images, lung function test results, ECG recordings, and laboratory results. Such documents must bear the subject number and the date of the procedure. If possible, this information should be printed by the instrument used to perform the assessment or measurement. As necessary, medical evaluation of such records should be performed; all evaluations should be documented, signed, and dated by the Investigator.

Electronic subject files will be printed whenever the Monitor performs source data verification. Printouts must be signed and dated by the Investigator, countersigned by the Monitor and kept in a safe place at the site.

10.3 Investigator Site File and Archiving

Upon initiation of the trial, the Investigator will be provided with an Investigator Site File containing all necessary trial documents, which will be completed throughout the trial and updated as necessary. The file must be available for review by the Monitor, during Sponsor audits and for inspection by Health Authorities during and after the trial, and must be safely archived for at least 15 years (or longer, per local requirements or as otherwise notified by the Sponsor) after the end of the trial. The documents to be archived include the Subject Identification List and the signed subject Informed Consent Forms. If archiving of the Investigator Site File is no longer possible at the site, the Investigator must notify the Sponsor/designee.

All original subject files (medical records) must be stored at the site (hospital, research institute, or practice) for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. In any case, the Investigator should ensure that no destruction of medical records is performed without the written approval of the Sponsor.

10.4 Monitoring, Quality Assurance, and Inspection by Health Authorities

This trial will be monitored in accordance with the ICH GCP, and any other applicable regulations. The site Monitor will perform visits to the trial center at regular intervals. The trial will be monitored using a risk-based approach and the details of the model will be described in the Clinical Operational Plan.

The clinical trial protocol, each step of the data capture procedure, and the handling of the data, including the final clinical trial report, will be subject to independent Quality Assurance activities. Audits may be conducted at any time during or after the trial to ensure the validity and

integrity of the trial data. Representatives of the Quality Assurance unit from the Sponsor or a designated organization, as well as Health Authorities, must be permitted to access all trial documents and other materials at the site, including the Investigator Site File, the completed eCRFs, all IMP and IMP accountability records, and the original medical records or files for each subject.

10.5 Changes to the Clinical Trial Protocol

Changes to the clinical trial protocol will be documented in writing. Substantive amendments will usually require submission to the Health Authorities and to the relevant IEC/IRB for approval or favorable opinion. In such cases, the amendment will be implemented only after approval or favorable opinion has been obtained.

Minor (nonsubstantial) protocol amendments, including administrative changes, will be filed by the Sponsor and at the site. They will be submitted to the relevant IEC/IRB or to Health Authorities only where requested by pertinent regulations. Any amendment that could affect the subject's agreement to participate in the trial requires additional informed consent prior to implementation following the process as described in Section 9.2.

10.6 Clinical Trial Report and Publication Policy

10.6.1 Clinical Trial Report

After completion of the trial, a clinical trial report will be written by the Sponsor in consultation with the CRO and any other relevant committees or groups, following the guidance in ICH Topic E3.

10.6.2 Publication

The first publication will include the results of the analysis of the primary endpoints and will include data from all trial centers. The Investigator will inform the Sponsor in advance about any plans to publish or present data from the trial. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc.), either in whole or in part, by Investigators or their representatives will require review by the Sponsor before submission. The Sponsor will not suppress publication, but maintains the right to delay publication in order to protect intellectual property rights.

Posting of data on clinicaltrials.gov is planned and will occur 12 months after the last clinic visit of the final trial subject or another appropriate date to meet applicable requirements.

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12 Appendices

Appendix I: Signature Pages and Responsible Persons for the Trial

Signature Page – Protocol Lead

Trial Title:	A Phase II, randomized, double-blind, placebo-controlled, parallel-group, multicenter trial to evaluate the efficacy and safety of abituzumab in subjects with systemic sclerosis-associated interstitial lung disease (SSc-ILD)
IND Number:	CCI
EudraCT Number:	2015-005023-11
Clinical Trial Protocol Date / Version:	26 July 2017/Version 5.0

Protocol Lead:

I approve the design of the clinical trial:

_____ _____

Signature Date of Signature

Name, academic degree: PPD

Function / Title: PPD

Institution: EMD Serono Research & Development Institute, Inc.

Address: 45A Middlesex Turnpike
Billerica, MA 01821 USA

Telephone number: PPD

Fax number: PPD

E-mail address: PPD

Signature Page –Coordinating Investigator

Trial Title	A Phase II, randomized, double-blind, placebo-controlled, parallel-group, multicenter trial to evaluate the efficacy and safety of abituzumab in subjects with systemic sclerosis-associated interstitial lung disease (SSc-ILD)
IND Number	CCI
EudraCT Number	2015-005023-11
Clinical Trial Protocol Date / Version	26 July 2017/Version 5.0

I approve the design of the clinical trial and I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, International Council for Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

_____ _____

Signature Date of Signature

Name, academic degree: PPD

Function / Title: Coordinating Investigator for all countries, except in North America

Institution: PPD

Address: PPD

Telephone number: PPD

Fax number: PPD

E-mail address: PPD

Signature Page –Coordinating Investigator

Trial Title	A Phase II, randomized, double-blind, placebo-controlled, parallel-group, multicenter trial to evaluate the efficacy and safety of abituzumab in subjects with systemic sclerosis-associated interstitial lung disease (SSc-ILD)
IND Number	CCI
EudraCT Number	2015-005023-11
Clinical Trial Protocol Date / Version	26 July 2017/Version 5.0

I approve the design of the clinical trial and I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, International Council for Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

_____ _____

Signature Date of Signature

Name, academic degree: PPD

Function / Title: Coordinating Investigator for sites in North America

Institution: PPD

Address: PPD

Telephone number: PPD

Fax number: PPD

E-mail address: PPD

Signature Page – Principal Investigator

Trial Title	A Phase II, randomized, double-blind, placebo-controlled, parallel-group, multicenter trial to evaluate the efficacy and safety of abituzumab in subjects with systemic sclerosis-associated interstitial lung disease (SSc-ILD)
IND Number	CCI [redacted]
EudraCT Number	2015-005023-11
Clinical Trial Protocol Date / Version	26 July 2017/Version 5.0
Center Number	
Principal Investigator	

I, the undersigned, am responsible for the conduct of the trial at this site and affirm that I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, International Council for Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

I also affirm that I understand that Health Authorities may require the Sponsors of clinical trials to obtain and supply details about ownership interests in the Sponsor or Investigational Medicinal Product and any other financial ties with the Sponsor. The Sponsor will use any such information solely for the purpose of complying with the regulatory requirements. I therefore agree to supply the Sponsor with any necessary information regarding ownership interest and financial ties including those of my spouse and dependent children, and to provide updates as necessary to meet Health Authority requirements.

_____ _____

Signature Date of Signature

Name, academic degree:

Function / Title:

Institution:

Address:

Telephone number:

Fax number:

E-mail address:

Sponsor Responsible Persons not Named on the Cover Page

Name, academic degree:	PPD
Function / Title:	PPD
Institution:	EMD Serono Research and Development Institute, Inc.
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Function / Title:	PPD
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Appendix II: Prednisone Equivalence Calculation

Medication	Equivalent (mg) to 1 mg of Prednisone
Betamethasone	0.15
Cortisone	5
Dexamethasone	0.15
Hydrocortisone	4
Prednisolone	1
Methylprednisone	0.8
Triamcinolone	0.8

Appendix III: New York Heart Association (NYHA) Criteria

NYHA Class 1: Cardiac disease, but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.

NYHA Class 2: Cardiac disease resulting in slight limitation of physical activity. Subjects are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.

NYHA Class 3: Cardiac disease resulting in marked limitation of physical activity. Subjects are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.

NYHA Class 4: Cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Appendix IV: Criteria for the Classification of Systemic Sclerosis

Table A1 The American College of Rheumatology/European League Against Rheumatism criteria for the classification of systemic sclerosis*

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

SSc, systemic sclerosis.

* These criteria are applicable to any patient considered for inclusion in a systemic sclerosis study. The criteria are not applicable to patients with skin thickening sparing the fingers or to patients who have a scleroderma-like disorder that better explains their manifestations (eg, nephrogenic sclerosing fibrosis, generalised morphea, eosinophilic fasciitis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft-versus-host disease, diabetic cheiroarthropathy).

† The total score is determined by adding the maximum weight (score) in each category. Patients with a total score of ≥ 9 are classified as having definite systemic sclerosis.

Reproduced from van den Hoogen, et al (2013).

Table A2 Definitions of items/sub-items in the American College of Rheumatology/European League Against Rheumatism criteria for the classification of systemic sclerosis

Item	Definition
Skin thickening	Skin thickening or hardening not due to scarring after injury, trauma, etc.
Puffy fingers	Swollen digits - a diffuse, usually nonpitting increase in soft tissue mass of the digits extending beyond the normal confines of the joint capsule. Normal digits are tapered distally with the tissues following the contours of the digital bone and joint structures. Swelling of the digits obliterates these contours. Not due to other causes such as inflammatory dactylitis.
Fingertip ulcers or pitting scars	Ulcers or scars distal to or at the proximal interphalangeal joint not thought to be due to trauma. Digital pitting scars are depressed areas at digital tips as a result of ischaemia, rather than trauma or exogenous causes.
Telangiectasia	Telangiectasiae are visible macular dilated superficial blood vessels, which collapse upon pressure and fill slowly when pressure is released. Telangiectasiae in a scleroderma-like pattern are round and well demarcated and found on hands, lips, inside of the mouth, and/or are large mat-like telangiectasiae. Distinguishable from rapidly filling spider angiomas with central arteriole and from dilated superficial vessels.
Abnormal nailfold capillary pattern consistent with systemic sclerosis	Enlarged capillaries and/or capillary loss with or without pericapillary haemorrhages at the nailfold. May also be seen on the cuticle.
Pulmonary arterial hypertension	Pulmonary arterial hypertension diagnosed by right-sided heart catheterisation according to standard definitions.
Interstitial lung disease	Pulmonary fibrosis seen on high-resolution CT or chest radiography, most pronounced in the basilar portions of the lungs, or occurrence of 'Velcro' crackles on auscultation, not due to another cause such as congestive heart failure.
Raynaud's phenomenon	Self-reported or reported by a physician, with at least a 2-phase colour change in finger(s) and often toe(s) consisting of pallor, cyanosis, and/or reactive hyperemia in response to cold exposure or emotion; usually one phase is pallor.
SSc-related auto antibodies	Anticentromere antibody or centromere pattern seen on antinuclear antibody testing, anti–topoisomerase I antibody (also known as anti-Scl-70 antibody), or anti-RNA polymerase III antibody. Positive according to local laboratory standards.

SSc, systemic sclerosis.
Reproduced from van den Hoogen, et al (2013).

Appendix V: Protocol Amendments and List of Changes

Previous Protocol Amendments

Table of Amendments

Amendment Number	Substantial (Y/N)	Date	Region or Country	Included in the current document (Y/N)
1	Y	02 Feb 2016	Global	Y
2	Y	16 May 2016	Global (except in the USA, Argentina, Australia, Israel, and Turkey)[a]	Y
3	Y	14 September 2016	Global (except in the USA, Argentina, Australia, Israel, and Turkey)	Y
4	Y	27 September 2016	Local (USA, Argentina, Australia, Israel, and Turkey) [a]	N

a Protocol Amendment 4 is applicable or submitted only to sites in the USA, Argentina, Australia, Israel, and Turkey. For this reason, details of this amendment are not included in the current document. Protocol Amendment 3 (Protocol Version 4.0) was the last applicable version in all other countries prior to the current document.

Amendment 1

Rationale

The purpose of this protocol amendment is:

- To remove the Dyspnea-12 index assessment;
- To decrease the frequency of select quality of life assessments;
- To specify the required visits following discontinuation of Investigational Medicinal Product (IMP);
- To update the number of planned sites;
- To include criteria for the classification of systemic sclerosis to the protocol appendices;
- To include minor corrections and clarifications to the clinical trial protocol.

The changes to be made to the clinical trial protocol and the rationale for the changes are described below.

Major Scientific Changes

Removal of the Dyspnea-12 Index

The Dyspnea-12 index has been removed because the symptom of dyspnea is considered to be adequately assessed through the Mahler index as well as components of the St. George Respiratory Questionnaire (SGRQ). The Mahler index was used in the scleroderma lung study (SLS I) and was associated with a significant difference between active drug (cyclophosphamide) and placebo. The SGRQ has been used to reveal treatment effects in multiple pulmonary diseases, including restrictive disease such as idiopathic pulmonary fibrosis (IPF).

Decrease in Frequency of Select Quality of Life Assessments

The frequency of assessment for the Scleroderma Health Assessment Questionnaire (SHAQ), Leicester Cough Index, Patient Global Assessment, EQ-5D, and Physician Global Assessment is decreased from approximately every 12 weeks to approximately every 24 weeks. This reduction maintains the ability of the trial to meet its objectives, while also affording a lower burden on subjects and trial site staff.

Required Visits Following Discontinuation of IMP

The Sponsor recognizes that assessment of all randomized subjects through the complete trial period is important for interpretation of the trial results and treatment responses. To meet this objective, the protocol will require all subjects to complete the trial visits in which the efficacy and safety assessments are done. These assessments include the pulmonary function tests, high-resolution computed tomography (HRCT), and subject questionnaires as well as the safety laboratories and assessments of adverse events. In order to promote subject retention for completion of the trial visits even after discontinuation of IMP, subjects will not be required to return to the clinic for trial visits every 4 weeks (as done for those continuing to receive IMP). All of the trial visits are available for the subject to attend, however, at the Investigator's discretion if follow-up every 4 weeks is considered appropriate.

Update of number of planned sites

The number of planned sites is increased from 50 to 60 sites globally to reflect the current enrollment strategy.

Addition of criteria for classification of systemic sclerosis

Detailed criteria for the classification of systemic sclerosis are added to Appendix IV for use by the Investigators.

Administrative and Editorial Changes

The Schedule of Assessments has been revised to present the Week 104 and Early Termination visits in separate columns to facilitate data collection for subjects who discontinue IMP; to

clarify the rich pharmacokinetic samples are collected at Weeks 8 and 16; and to make minor editorial changes for clarity.

Analysis of the diffusion capacity of the lung for carbon monoxide (DLCO) was not always noted to refer to the DLCO % predicted. This has been clarified.

Notation is added that the method of performance of the pulmonary function tests will be specified in the manual of procedures.

Text has been revised to clarify the last IMP administration will occur at the Week 100 visit.

Text has been updated to remove area under the concentration-time curve (AUC) from the planned pharmacokinetic parameters and to indicate further parameters will be derived by population pharmacokinetics.

Standard language describing Clinical Data Interchange Standards Consortium (CDISC) standards has been added.

The clinical team has been changed from PPD .

The address and telephone number for PPD .

List of Changes

Changes to the clinical trial protocol text are presented in the table below. Additions and amended text are shown in bold. If the original clinical trial protocol text was already bold, changes are shown in bold and underlined, deletions are marked using strike-through.

Comparison with Clinical Trial Protocol Version 1.0, 04 Dec 2015

Change	Section	Page	Previous Wording	New Wording
Update of date and version number	Throughout		04 Dec 2015/Version 1.0	2 Feb 2016/Version 2.0
Update organization name	List of Abbreviations	9	ICH International Conference on Harmonization	ICH International ~~Conference on~~ **Council for** Harmonization
Update number of planned sites	Synopsis, Trial Centers/countries	11	This trial will be conducted at approximately 50 sites globally, including, but not limited to, North America and the European Union.	This trial will be conducted at approximately ~~50~~**60** sites globally, including, but not limited to, North America and the European Union.
Clarify last dose of IMP	Synopsis, Methodology	13	Approximately 175 subjects will be randomized in a 2:2:1 ratio to receive abituzumab 1500 mg, placebo, or abituzumab 500 mg, respectively, given as an intravenous infusion over 1 hour every 4 weeks for 104 weeks**.**	Approximately 175 subjects will be randomized in a 2:2:1 ratio to receive abituzumab 1500 mg, placebo, or abituzumab 500 mg, respectively, given as an intravenous infusion over 1 hour every 4 weeks ~~for 104 weeks~~ **with the last IMP administration at the Week 100 visit.**
Clarification of DLCO measurement	Synopsis, Methodology	13	• Relative decrease from baseline in FVC % predicted ≥5% to <10% AND relative decrease from baseline in the diffusion capacity of the lung for carbon monoxide (DLCO) ≥15%.	• Relative decrease from baseline in FVC % predicted ≥5% to <10% AND relative decrease from baseline in the diffusion capacity of the lung for carbon monoxide (DLCO) **% predicted** ≥15%.
Specify required visits after IMP discontinuation	Synopsis, Methodology	13-14	Subjects who discontinue IMP for any reason will complete the early termination visit. Even if IMP is discontinued, subjects will complete the remainder of the scheduled trial visits, including the Safety Follow-up Visits, unless the subject is withdrawn from the trial. All subjects will be followed up by the site for survival from the subject's last trial visit until death or the end of the trial.	**If a subject discontinues IMP, then the subject should complete the early termination visit and then the remaining scheduled visits. At a minimum, the subject is expected to complete the trial visits at Weeks 12, 24, 36, 52, 64, 76, 88, and 104, as well as the Safety Follow-up period Week 12 visit. Subjects with discontinued IMP can come to the other scheduled visits during the trial period according to the Investigator's judgment.** **Subjects who withdraw from the treatment period would have an early termination visit followed by entrance into the Safety Follow-up Period.** **Subjects who withdraw from the trial (eg, withdraw consent, lost to follow up, or death) would not have any additional study visits.** ~~Subjects who discontinue IMP for any reason will complete the early termination visit. Even if IMP is~~

Change	Section	Page	Previous Wording	New Wording
				~~discontinued, subjects will complete the remainder of the scheduled trial visits, including the Safety Follow-up Visits, unless the subject is withdrawn from the trial.~~ All subjects will be followed up by the site for survival from the subject's last trial visit until death or the end of the trial.
Remove Dyspnea-12 index	Synopsis, Quality of life endpoints	15-16	• Absolute change from baseline for each of the following HRQoL questionnaires up to Week 104: • Leicester Cough Index • SGRQ • Physician's Global Assessment • Patient's Global Assessment • Dyspnea-12 • Scleroderma Health Assessment Questionnaire (SHAQ) • EQ-5D.	• Absolute change from baseline for each of the following HRQoL questionnaires up to Week 104: • Leicester Cough Index • SGRQ • Physician's Global Assessment • Patient's Global Assessment ~~• Dyspnea-12~~ • Scleroderma Health Assessment Questionnaire (SHAQ) • EQ-5D.
Update planned pharmacokinetic parameters	Synopsis, Pharmacokinetic endpoints	16	Abituzumab concentrations and PK parameters (eg, AUC, C_{max}, and C_{min}).	Abituzumab concentrations and PK parameters (eg, ~~AUC,~~ C_{max}~~,~~ and C_{min}).
Clarify last dose of IMP	Synopsis, Investigational medicinal product: dose/mode of administration/dosing schedule	17	Abituzumab 1500 or 500 mg will be administered as an intravenous infusion over 1 hour once every 4 weeks up to Week 104 (2 years) on top of background therapy.	Abituzumab 1500 or 500 mg will be administered as an intravenous infusion over 1 hour once every 4 weeks **with the last IMP administration at the Week 100 visit** ~~up to Week 104~~ (2 years) on top of background therapy.
Clarify last dose of IMP	Synopsis, Reference therapy: dose/mode of administration/ dosing schedule	17	Placebo (citrate buffered saline) will be administered as an intravenous infusion over 1 hour once every 4 weeks up to Week 104 (2 years) on top of background therapy.	Placebo (citrate buffered saline) will be administered as an intravenous infusion over 1 hour once every 4 weeks **with the last administration at the Week 100 visit**~~up to Week 104~~ (2 years) on top of background therapy.

Change	Section	Page	Previous Wording	New Wording
Remove Dyspnea-12 index; Decrease frequency of select quality of life assessments; minor clarifications	Schedules of Assessments	19-23	Refer to Amendment 1 - Tables 1 and 2, below.	Refer to Amendment 1 - Tables 1 and 2, below.
Update number of planned sites	Section 2	24	The trial will be conducted at approximately 50 sites globally, including, but not limited to, North America and the European Union (EU). Approximately 15 sites are planned in the USA.	The trial will be conducted at approximately ~~50~~ **60** sites globally, including, but not limited to, North America and the European Union (EU). Approximately 15 sites are planned in the USA.
Update organization name	Section 2	24	The Coordinating Investigators (for all countries, except in North America: PPD , PPD ; for sites in PPD : PPD , represent all Investigators for decisions and discussions regarding this trial, consistent with the International Conference on Harmonisation (ICH) Topic E6 Good Clinical Practice (GCP; hereafter referred to as ICH GCP). The Coordinating Investigators will provide expert medical input and advice relating to trial design and execution and are responsible for the review and signoff of the clinical trial report.	The Coordinating Investigators (for all countries, except in North America: PPD ; for sites in PPD : PPD , represent all Investigators for decisions and discussions regarding this trial, consistent with the International ~~Conference on~~**Council for** Harmonisation (ICH) Topic E6 Good Clinical Practice (GCP; hereafter referred to as ICH GCP). The Coordinating Investigators will provide expert medical input and advice relating to trial design and execution and are responsible for the review and signoff of the clinical trial report.
Clarify last dose of IMP	Section 5.1	30	Approximately 175 subjects will be randomized in a 2:2:1 ratio to receive abituzumab 1500 mg, placebo, or abituzumab 500 mg, respectively, given by intravenous infusion over 1 hour every 4 weeks for 104 weeks.	Approximately 175 subjects will be randomized in a 2:2:1 ratio to receive abituzumab 1500 mg, placebo, or abituzumab 500 mg, respectively, given by intravenous infusion over 1 hour every 4 weeks **with the last IMP administration at the Week 100 visit**~~for 104 weeks~~.
Specify required visits after IMP discontinuation	Section 5.1	31	Subjects who meet the criteria for clinically meaningful progression of SSc-ILD (see Section 6.5.5) during the Double-blind Treatment Period or Follow up Period should have a change in background therapy. Subjects taking less than the maximal specified dose of mycophenolate (3 g/day MMF or 2160 mg/day MPS) can have the mycophenolate dose increased while IMP is continued. Subjects taking the maximal specified	Subjects who meet the criteria for clinically meaningful progression of SSc-ILD (see Section 6.5.5) during the Double-blind Treatment Period or Follow up Period should have a change in background therapy. Subjects taking less than the maximal specified dose of mycophenolate (3 g/day MMF or 2160 mg/day MPS) can have the mycophenolate dose increased while IMP is continued. Subjects taking the maximal specified

Change	Section	Page	Previous Wording	New Wording
			dose of mycophenolate who have clinically meaningful progression should have the IMP discontinued and be treated according to the local standard of care. If an immunosuppressant (such as cyclophosphamide [oral or intravenous]) is initiated, then mycophenolate must be discontinued. Subjects who discontinue IMP for any reason should complete the early termination visit. Even if IMP is discontinued, subjects will complete the remainder of the scheduled trial visits, including the Safety Follow-up Visits, unless the subject is withdrawn from the trial. Regardless of treatment completion or not, all subjects will be followed up by site for survival from the subject's last visit on the trial until death or end of the trial. Subjects who have clinically meaningful progression of SSc other than ILD should be treated according to the local standard of care.	dose of mycophenolate who have clinically meaningful progression should have the IMP discontinued and be treated according to the local standard of care. If an immunosuppressant (such as cyclophosphamide [oral or intravenous]) is initiated, then mycophenolate must be discontinued. ~~Subjects who discontinue IMP for any reason should complete the early termination visit. Even if IMP is discontinued, subjects will complete the remainder of the scheduled trial visits, including the Safety Follow-up Visits, unless the subject is withdrawn from the trial.~~ **If a subject discontinues IMP, then the subject should complete the early termination visit and then the remaining scheduled visits. At a minimum, the subject is expected to complete the trial visits at Weeks 12, 24, 36, 52, 64, 76, 88, and 104, as well as the Safety Follow-up period Week 12 visit. Subjects with discontinued IMP can come to the other scheduled visits during the trial period according to the Investigator's judgment.** **Subjects who withdraw from the treatment period would have an early termination visit followed by entrance into the Safety Follow-up Period.** **Subjects who withdraw from the trial (eg, withdraw consent, lost to follow-up, or death; see Section 5.5.2) would not have any additional trial visits.** Regardless of treatment completion or not, all subjects will be followed up by site for survival from the subject's last visit on the trial until death or end of the trial. Subjects who have clinically meaningful progression of SSc other than ILD should be treated according to the local standard of care.
Indicate pulmonary function tests will be described separately	Section 5.2.4	35	Not applicable.	**Pulmonary function tests will be performed according to the American Thoracic Society and European Respiratory Society recommendations. Detailed procedures for performing pulmonary function assessments**

Change	Section	Page	Previous Wording	New Wording
				are included in a separate manual of procedures.
Remove Dyspnea-12 index and clarify endpoints	Section 5.2.5	35-36	The measures endorsed by the OMERACT working group as the 'inner core' measures for ILD (Khanna 2015) include the following: Leicester Cough Index, Patient's Global Assessment, Medical Outcomes Study Short Form (SF-36), Medical Research Council chronic dyspnea scale, Dyspnea-12, and SGRQ, as well as 'functional status' (this will be assessed by the Scleroderma Health Assessment Questionnaire [SHAQ]), overall ILD on HRCT, FVC % predicted, and all-cause mortality. For this trial, the SF-36 is not considered necessary because the other measures are considered adequate to assess the SSc disease-specific manifestations of this population, and thus SF-36 is not included in this trial. The assessments in this trial that are not part of the inner core include the Mahler index and the Physician's Global Assessment. The Mahler Dyspnea Index is advised to be included as this has been shown in the SLS I trial to show a statistically significant difference between the cyclophosphamide and placebo groups (p <0.001). The Physician's Global Assessment is done rapidly via a visual analogue scale (VAS) and is standard in many trials for overall assessment of subjects.	The measures endorsed by the OMERACT working group as the 'inner core' measures for ILD (Khanna 2015) ~~include~~ **and included in this trial are** the following: Leicester Cough Index, Patient's Global Assessment, ~~Medical Outcomes Study Short Form (SF-36), Medical Research Council chronic dyspnea scale, Dyspnea-12,~~ and SGRQ, as well as 'functional status' (this will be assessed by the Scleroderma Health Assessment Questionnaire [SHAQ]), overall ILD on HRCT, FVC % predicted, and all-cause mortality. ~~For this trial, the SF-36 is not considered necessary because the other measures are considered adequate to assess the SSc disease-specific manifestations of this population, and thus SF-36 is not included in this trial.~~ The assessments in this trial that are not part of the inner core include the Mahler index and the Physician's Global Assessment. The Mahler Dyspnea Index is advised to be included as this has been shown in the SLS I trial to show a statistically significant difference between the cyclophosphamide and placebo groups (p <0.001). The Physician's Global Assessment is done rapidly via a visual analogue scale (VAS) and is standard in many trials for overall assessment of subjects.
Remove Dyspnea-12 index	Section 5.2.5	36	As dyspnea is a central feature of SSc-ILD and is an independent predictor of function and HRQoL, it will be assessed using 3 indices: the Mahler index, the Dyspnea-12, and the SGRQ (Baron 2008). The Mahler Transition Dyspnea Index (TDI) fulfills OMERACT criteria for feasibility, reliability, and validity, and in moderate ILD, subject changes in Mahler TDI score were observed (Khanna 2009). The TDI is sensitive to change. The Baseline Dyspnea Index (BDI)-TDI measures changes in dyspnea severity from the baseline as established by the BDI. The computerized version appears to have eliminated earlier concerns regarding the role of the interviewer in influencing responses.	As dyspnea is a central feature of SSc-ILD and is an independent predictor of function and HRQoL, it will be assessed using **2**~~3~~ indices: the Mahler index~~, the Dyspnea-12,~~ and the SGRQ (Baron 2008). The Mahler Transition Dyspnea Index (TDI) fulfills OMERACT criteria for feasibility, reliability, and validity, and in moderate ILD, subject changes in Mahler TDI score were observed (Khanna 2009). The TDI is sensitive to change. The Baseline Dyspnea Index (BDI)-TDI measures changes in dyspnea severity from the baseline as established by the BDI. The computerized version appears to have eliminated earlier concerns regarding the role of the interviewer in influencing responses.

Change	Section	Page	Previous Wording	New Wording
Remove Dyspnea-12 index	Section 5.2.5	36	Dypspnea-12 has been found to be a valid and reliable measure of dyspnea in patients with ILD (Yorke 2011). The SGRQ has also been found to be useful in assessing patients with SSc-ILD (Beretta 2007, Wallace 2015).	~~Dypspnea-12 has been found to be a valid and reliable measure of dyspnea in patients with ILD (Yorke 2011).~~ The SGRQ has ~~also~~ been found to be useful in assessing patients with SSc-ILD (Beretta 2007, Wallace 2015).
Add reference to classification criteria	Section 5.3.1	38	2. Subjects fulfilling the 2013 ACR/European League Against Rheumatism criteria for classification of SSc.	2. Subjects fulfilling the 2013 ACR/European League Against Rheumatism criteria for classification of SSc **(van den Hoogen 2013; see Appendix IV)**.
Specify required visits after IMP discontinuation	Section 5.5.1	42	If subjects are withdrawn from IMP, they will be expected to complete an early termination visit followed by continuation of all scheduled assessments through the end of the trial (ie, including through the Safety Follow-up Period). It is important for site investigators to retain each subject through the end of the trial for prevention of missing data. Systematic and consistent attempts are needed to contact subjects who fail to actively maintain contact with the site Investigator. The nature, method, and frequency of such contact should be recorded in the source documents, including number of telephone calls, day of week, and time of such calls and source of information.	**If a subject discontinues IMP, then the subject should complete the early termination visit and then the remaining scheduled visits. At a minimum, the subject is expected to complete the trial visits at Weeks 12, 24, 36, 52, 64, 76, 88, and 104, as well as the Safety Follow-up period Week 12 visit. Subjects with discontinued IMP can come to the other scheduled visits during the trial period according to the Investigator's judgment.** **Subjects who withdraw from the treatment period would have an early termination visit followed by entrance into the Safety Follow-up Period.** **Subjects who withdraw from the trial (eg, withdraw consent, lost to follow-up, or death; see Section 5.5.2) would not have any additional trial visits.**~~If subjects are withdrawn from IMP, they will be expected to complete an early termination visit followed by continuation of all scheduled assessments through the end of the trial (ie, including through the Safety Follow-up Period).~~ It is important for site investigators to retain each subject through the end of the trial for prevention of missing data. Systematic and consistent attempts are needed to contact subjects who fail to actively maintain contact with the site Investigator. The nature, method, and frequency of such contact should be recorded in the source documents, including number of telephone calls, day of week, and time of such calls and source of information.

Change	Section	Page	Previous Wording	New Wording
Clarify last dose of IMP	Section 6.2	44	In the Double-blind Treatment Period, subjects will be randomized in a 2:2:1 ratio to receive one of the following treatments: abituzumab 1500 mg, placebo, or abituzumab 500 mg, respectively. Treatment will be given as an intravenous infusion over approximately 1 hour every 4 weeks for 104 weeks. The infusion time should not be less than 1 hour.	In the Double-blind Treatment Period, subjects will be randomized in a 2:2:1 ratio to receive one of the following treatments: abituzumab 1500 mg, placebo, or abituzumab 500 mg, respectively. Treatment will be given as an intravenous infusion over approximately 1 hour every 4 weeks **with the last IMP administration at the Week 100 visit**~~for 104 weeks~~. The infusion time should not be less than 1 hour.
Clarification of DLCO measurement	Section 6.5.5	46	1. SSc-ILD: one of the following (in the absence of causative intercurrent illness) on at least 2 occasions within approximately 4 weeks (per OMERACT criteria): • Relative decrease from baseline in FVC % predicted ≥10%; • Relative decrease from baseline in FVC % predicted of ≥5% to <10% and relative decrease from baseline in DLCO ≥15%.	1. SSc-ILD: one of the following (in the absence of causative intercurrent illness) on at least 2 occasions within approximately 4 weeks (per OMERACT criteria): • Relative decrease from baseline in FVC % predicted ≥10%; • Relative decrease from baseline in FVC % predicted of ≥5% to <10% and relative decrease from baseline in DLCO **% predicted** ≥15%.
Specify required visits after IMP discontinuation	Section 6.5.5	47	Even if IMP is discontinued, subjects will complete the remainder of the scheduled trial visits, including the Safety Follow-up Visits, unless the subject is withdrawn from the trial. All subjects will be followed up by the site for survival from the last visit on trial until death or end of the trial. New onset or worsening of manifestations of scleroderma that are not captured by the pulmonary function tests, mRSS, or digital ulcer score, should be reported as AEs. On the eCRF AE page, such events should be marked as 'yes' in response to the question "Is this a manifestation of worsening scleroderma?".	**If a subject discontinues IMP, then the subject should complete the early termination visit and then the remaining scheduled visits (refer to Table 1 and Table 2)**~~Even if IMP is discontinued, subjects will complete the remainder of the scheduled trial visits, including the Safety Follow-up Visits, unless the subject is withdrawn from the trial~~. All subjects will be followed up by the site for survival from the last visit on trial until death or end of the trial. New onset or worsening of manifestations of scleroderma that are not captured by the pulmonary function tests, mRSS, or digital ulcer score, should be reported as AEs. On the eCRF AE page, such events should be marked as 'yes' in response to the question "Is this a manifestation of worsening scleroderma?".
Clarify last dose of IMP	Section 7.1.2	51	All subjects will return to the trial center on Days 1, 15, and 29, then every 4 weeks through Week 104. Visit windows of ± 3 days through Week 52 and ± 5 days for Weeks 56 through 104 are permitted. Beginning on Day 1, subjects will receive their assigned dose of IMP as an intravenous infusion	All subjects will return to the trial center on Days 1, 15, and 29, then every 4 weeks through Week 104. Visit windows of ± 3 days through Week 52 and ± 5 days for Weeks 56 through 104 are permitted. Beginning on Day 1, subjects will receive their assigned dose of IMP as an intravenous infusion

Change	Section	Page	Previous Wording	New Wording
			every 4 weeks up to Week 104. Efficacy, safety, HRQoL, PK, and CCI assessments will be performed as described in Table 1 and Table 2.	every 4 weeks **with the last IMP administration at the Week 100 visit** ~~up to Week 104~~. Efficacy, safety, HRQoL, PK, and CCI assessments will be performed as described in Table 1 and Table 2.
Minor clarification of text Specify required visits after IMP discontinuation	Section 7.1.3	51	Subjects who complete the 104 weeks of treatment will return to the trial center 4 and 12 weeks (± 5 days) after the Week 104 visit for the Safety Follow up Visits. Subjects who are withdrawn from IMP should complete the early termination visit. Unless the subject is withdrawn from the trial, subjects withdrawn from IMP should also be followed through the remainder of the scheduled trial visits, including the Safety Follow-up Visits.	Subjects who complete the 104-week~~s of~~ treatment **period** will return to the trial center 4 and 12 weeks (± 5 days) after the Week 104 visit for the Safety Follow up Visits. Subjects who are withdrawn from IMP should complete the early termination visit **as soon as possible, but within 2 weeks of IMP discontinuation, and then**~~. Unless the subject is withdrawn from the trial, subjects withdrawn from IMP should also be followed through the remainder of the scheduled trial visits, including the Safety Follow-up Visits.~~ **the remaining scheduled visits. At a minimum, the subject is expected to complete the trial visits at Weeks 12, 24, 36, 52, 64, 76, 88, and 104, as well as the Safety Follow-up period Week 12 visit. Subjects with discontinued IMP can come to the other scheduled visits during the trial period according to the Investigator's judgment.** **Subjects who withdraw from the treatment period would have an early termination visit followed by entrance into the Safety Follow-up Period.** **Subjects who withdraw from the trial (eg, withdraw consent, lost to follow-up, or death; see Section 5.5.2) would not have any additional trial visits.**
Minor text revision for clarity	Section 7.3	52	Efficacy assessments include evaluation of lung function using spirometry (FVC, DLCO, and TLC) and lung abnormalities on HRCT. Assessments will be performed as described in Table 1 and Table 2.	Efficacy assessments include evaluation of lung function ~~using spirometry~~ (FVC, DLCO, and TLC) and lung abnormalities on HRCT. Assessments will be performed as described in Table 1 and Table 2.

Remove Dyspnea-12 index	Section 8.3.4	64	• Absolute change from baseline for each of the following HRQoL questionnaires up to Week 104:
			  • Leicester Cough Index
				• Absolute change from baseline for each of the following HRQoL questionnaires up to Week 104:
				  • Leicester Cough Index

Change	Section	Page	Previous Wording	New Wording
			• SGRQ • Physician's Global Assessment • Patient's Global Assessment • Dyspnea-12 • Scleroderma Health Assessment Questionnaire (SHAQ) • EQ-5D.	• SGRQ • Physician's Global Assessment • Patient's Global Assessment ~~• Dyspnea-12~~ • Scleroderma Health Assessment Questionnaire (SHAQ) • EQ-5D.
Update planned pharmacokinetic parameters	Section 8.3.5	64	Pharmacokinetic endpoints include the following: • Abituzumab concentrations; • PK parameters (eg, AUC, C_{max}, and C_{min}).	Pharmacokinetic endpoints include the following: • Abituzumab concentrations; • PK parameters (eg, ~~AUC,~~ C_{max}~~,~~ and C_{min}). **Further PK parameters will be derived by population PK.**
Add standard text for CDISC standards	Section 10.1	73	Not applicable.	**The Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) standards, required by the FDA for the submission of trial data, are followed by Merck Serono. Merck Serono General Data Standards and, if applicable, Therapeutic Area Data Standards, as well as Merck Serono SDTM Guidelines, will be used in all clinical trials as predefined in the applicable Merck Serono SOP, Working Instructions, and Guidelines, to create the Case Report Forms (CRFs), the SDTM delivery package (SDTM domains, define.xml, Reviewer's Guide, SDTM annotated CRF), and the operational database; any exemptions need to be discussed and decided by the Project Team. In addition it is intended to convert non-SDTM trial data from legacy trials, and possibly ongoing trials not conducted by Merck Serono, into an FDA submission compliant CDISC-SDTM format. Individual trial data and documents will be migrated into the ICMS (Integrated CDISC-based Data Model and System, a cross-functional platform designed to maintain the data of all current and future projects). These measures will facilitate the integration of data across multiple trials and projects so that more comprehensive data pools can be generated. If significant non-SDTM**

Change	Section	Page	Previous Wording	New Wording
				format data already exists for a drug, trials may not be converted to, or delivered in, SDTM format, if decided by the Project Team and agreed by Senior Management. The Program Data Manager ensures that data standards are harmonized across all trials within this development program.
Add reference	Section 11	78	Not applicable	**van den Hoogen F, Khanna D, Fransen J, et al. 2013 Classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. Ann Rheum Dis. 2013;72:1747–55.**
Remove unneeded reference	Section 11	78	Yorke J, Swigris J, Russell AM, et al. Dyspnea-12 Is a Valid and Reliable Measure of Breathlessness in Patients With Interstitial Lung Disease. Chest. 2011;139(1):159-64.	~~Yorke J, Swigris J, Russell AM, et al. Dyspnea-12 Is a Valid and Reliable Measure of Breathlessness in Patients With Interstitial Lung Disease. Chest. 2011;139(1):159-64.~~
Update coordinating investigator contact information	Signature page – Coordinating Investigator	82	PPD	PPD
Update clinical team lead contact information	Sponsor Responsible Persons	86	PPD Merck KGaA Frankfurter Str. 250 Postcode: F135/302 64293 Darmstadt, Germany PPD PPD PPD	PPD PPD ~~Merck KGaA~~**EMD Serono Research and Development Institute, Inc.** ~~Frankfurter Str. 250~~ ~~Postcode: F135/302~~ ~~64293 Darmstadt, Germany~~ **45A Middlesex Turnpike** **Billerica, MA 01821** **USA** PPD PPD PPD

Change	Section	Page	Previous Wording	New Wording
Addition of criteria for classification of systemic sclerosis	Appendix IV	NA	NA	See copies of Tables A1 and A2, given below.

Amendment 1 - Table 1 Schedule of Assessments – Screening through Week 52

Trial Period	**Screening**	**Weeks During Double-blind Treatment Period (Visit Window ±3 days)**														
Week		**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**
Trial Day	**-28 to -1**	**1**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**
Informed consent	X															
Inclusion/exclusion criteria	X	X[a]														
CCI																
Pharmacokinetic informed consent (Rich PK sampling only)	X															
Demographic data	X															
SSc-ILD and other medical history, medications, surgery/procedures	X															
HRCT	X								X							X
12-lead ECG (locally read)	X								X							X
Tuberculosis assessment	X															
Serum virology (HIV, HCV, HBV)	X															
Serum pregnancy test [c]	X															
PT, aPTT, TSH, and NT pro-BNP	X															
Urine pregnancy test [c,d]		X		X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X	X[e]	X	X[e]	X[e]	X[e]	X[e]	X	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X
Vital signs, weight, height [f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
~~Questionnaires~~ **Mahler BDI/TDI and SGRQ**		X				X			X			X				X

Trial Period	Screening	Weeks During Double-blind Treatment Period (Visit Window ±3 days)														
Week		0	2	4	8	12	16	20	24	28	32	36	40	44	48	52
Trial Day	-28 to -1	1	15	29	57	85	113	141	169	197	225	253	281	309	337	365
[g]																
Patient's Global Assessment, Leicester Cough Index, SHAQ, EQ-5D, and Physician's Global Assessment [g]		**X**							**X**							**X**
Randomization		X														
IMP administration		X		X	X	X	X	X	X	X	X	X	X	X	X	X
PK sampling [h]		X		X	X		X									
Rich PK sampling [i]		X	X	X	**X**		**X**									
Routine hematology, clinical chemistry, urinalysis dipstick [j]	X	X	X	X	X	X	X	X	X		X		X		X	X
Pulmonary function tests (FVC, TLC) with DLCO [k]	X	X				X			X			X				X
mRSS		X				X			X			X				X
Digital ulcer counts [l]		X				X			X			X				X
Serum for ADA		X							X							X
Sample for autoantibodies		X							X							X
[redacted]																
Concomitant medications/procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events [n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

ADA = antidrug antibodies; AE = adverse event; aPTT = activated partial thromboplastin time; BDI = Baseline Dyspnea Index; DLCO = diffusion capacity of the lung for carbon monoxide; ECG = electrocardiogram; FVC = forced vital capacity; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HRCT = high-resolution computed tomography; IMP = investigational medicinal product; mRSS = modified Rodnan skin score; PK = pharmacokinetic; PT = prothrombin time; **SGRQ = St. George Respiratory Questionnaire;** SHAQ = Scleroderma Health Assessment Questionnaire; SSc-ILC = systemic sclerosis-associated interstitial lung disease; TDI = Transition Dyspnea Index; TLC = total lung capacity; TSH = thyroid-stimulating hormone; VAS = visual analog scale.

a Subject eligibility (based on screening assessments of the inclusion and exclusion criteria) must be checked again on Day 1 prior to randomization.

CCI

c For women of childbearing potential or who are postmenopausal for less than 2 years. At Day 1, if the urine test is negative, the subject can be randomized and receive the first dose of IMP.

d Performed locally per local constraints and regulations.

e Focused physical examination only, according to standard of care.

f Vital signs include 10-minute seated arterial blood pressure, pulse rate, and body temperature. Height will be measured at Day 1 only. Weight will be measured at Weeks 0, 24, 52, 76, and 104. Body weight will be measured with a balance beam scale, if possible.

g Questionnaires should be completed before any other procedures are performed. Questionnaires should be performed in the following order: Patient's Global Assessment, SHAQ, Mahler BDI (at Day 1) followed by Mahler TDI at the subsequent visits, ~~St. George Respiratory Questionnaire~~ **SGRQ**, ~~Dyspnea-12,~~ Leicester Cough Index, and EQ-5D. The Physician's Global Assessment (VAS) may be performed after other assessments at the visit are completed.

h For all subjects, samples will be collected predose and immediately after the end of IMP infusion at Weeks 0 (Day 1), 4, 8, and 16.

i For subjects who have provided ~~PK~~ informed consent for the rich PK sampling, additional samples will be collected on Days 3, 5, 15, and 22 **(in addition to the pre- and postdose samples at Weeks 0, 4, 8, and 16; see footnote h)**.

j See Section 7.4.3 for list of routine laboratory assessments. Urine protein:creatinine ratio to be performed if dipstick urinalysis reveals at least 3+ protein. Microscopic urinalysis to be performed if blood is present.

k The TLC should be performed at Weeks 0, 24, 52, 76, and 104. The DLCO measurements will be corrected for hemoglobin level, and spirometry assessment**s** will be centrally adjudicated.

l Digital ulcers are those distal to the metacarpal phalangeal joints. New or worsening digital ulcers, or at any other site on the body, will be captured as AEs.

CCI

n Adverse events should also be assessed for occurrence during the periods between trial visits.

Amendment 1 - Table 2 Schedule of Assessments – Week 56 through Safety Follow-up

Trial Period	Weeks During Double-blind Treatment Period (Visit Window ±5 days)														Safety Follow-up Number weeks post last dose (±5 days)		Survival Follow-up Post Last Trial Visit
Week	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104/ ~~ET~~[a]**	**ET[a]**	**4**	**12**	**Every 12 Weeks**
Trial Day	**393**	**421**	**449**	**477**	**505**	**533**	**561**	**589**	**617**	**645**	**673**	**701**	**729**				
HRCT													X	**X**			
12-lead ECG (locally read)						X							X	**X**		X	
Urine pregnancy test [b,c]	X	X	X	X	X	X	X	X	X	X	X	X	X	**X**	X	X	
Physical examination	X[d]	X[d]	X[d]	X[d]	X[d]	X	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X	**X**	X[d]	X	
Vital signs, weight [e]	X	X	X	X	X	X	X	X	X	X	X	X	X	**X**	X	X	
~~Questionnaires~~ **Mahler TDI and SGRQ** [f]			X			X			X				X	**X**		X	
Patient's Global Assessment, Leicester Cough Index, SHAQ, EQ-5D, and Physician's Global Assessment [f]						**X**							**X**	**X**			
IMP administration	X	X	X	X	X	X	X	X	X	X	X	X					
Routine hematology, clinical chemistry, urinalysis [g]		X		X		X		X		X		X	X	**X**	X	X	
Pulmonary function tests (FVC, TLC) with DLCO [h]			X			X			X				X	**X**		X	
mRSS			X			X			X				X	**X**		X	
Digital ulcer counts [i]			X			X			X				X	**X**		X	
Serum for ADA						X							X	**X**	X	X	
Sample for autoantibodies													X	**X**			
CCI																	
Concomitant	X	X	X	X	X	X	X	X	X	X	X	X	X	**X**	X	X	

Trial Period	Weeks During Double-blind Treatment Period (Visit Window ±5 days)														Safety Follow-up Number weeks post last dose (±5 days)		Survival Follow-up Post Last Trial Visit
Week	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104/ ~~ET~~[a]**	**ET[a]**	**4**	**12**	**Every 12 Weeks**
Trial Day	**393**	**421**	**449**	**477**	**505**	**533**	**561**	**589**	**617**	**645**	**673**	**701**	**729**				
medications/procedures																	
Adverse events[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	**X**	X	X	
Vital status[k]																	X

ADA = antidrug antibodies; AE = adverse event; BDI = Baseline Dyspnea Index; DLCO = diffusion capacity of the lung for carbon monoxide; ECG = electrocardiogram; ET = early termination; FVC = forced vital capacity; HRCT = high resolution computed tomography; IMP = investigational medicinal product; mRSS = modified Rodnan skin score; **SGRQ = St. George Respiratory Questionnaire;** SHAQ = Scleroderma Health Assessment Questionnaire; TDI = Transition Dyspnea Index; TLC = total lung capacity; VAS = visual analog scale.

a Subjects who discontinue IMP for any reason should complete the ET visit **as soon as possible, but within 2 weeks of IMP discontinuation,** ~~. Unless the subject is withdrawn from the trial, subjects should also complete~~ **and then** the ~~remainder~~ **remaining** ~~of the~~ scheduled trial visits~~, including the Safety Follow-up Visits, even if IMP is discontinued~~. **At a minimum, the subject is expected to complete the trial visits at Weeks 12, 24, 36, 52, 64, 76, 88, and 104, as well as the Safety Follow-up period Week 12 visit. Subjects with discontinued IMP can come to the other scheduled visits during the trial period according to the Investigator's judgment. Subjects who withdraw from the treatment period would have an early termination visit followed by entrance into the Safety Follow-up Period. Subjects who withdraw from the trial (eg, withdraw consent, lost to follow-up, or death; see Section 5.5.2) would not have any additional trial visits. All subjects will be followed up by the site approximately every 12 weeks for survival from the subject's last trial visit until death or the end of the trial.**

b For women of childbearing potential or who are postmenopausal for less than 2 years. Positive urine pregnancy tests should be confirmed with a serum test. If the serum pregnancy test is subsequently positive, the subject will be withdrawn from IMP.

c Performed locally per local constraints and regulations.

d Focused physical examination only, according to standard of care.

e Vital signs include 10-minute seated arterial blood pressure, pulse rate, and body temperature. Weight will be measured at Weeks 0, 24, 52, 76, and 104. Body weight will be measured with a balance beam scale, if possible.

f Questionnaires should be completed before any other procedures are performed. Questionnaires should be performed in the following order: Patient's Global Assessment, SHAQ, Mahler BDI (at Day 1) followed by Mahler TDI at the subsequent visits, ~~St. George Respiratory Questionnaire~~ **SGRQ**, ~~Dyspnea-12,~~ Leicester Cough Index, and EQ-5D. The Physician's Global Assessment (VAS) may be performed after other assessments at the visit are completed.

g See Section 7.4.3 for list of routine laboratory assessments. Urine protein:creatinine ratio to be performed if dipstick urinalysis reveals at least 3+ protein. Microscopic urinalysis to be performed if blood is present.

h The TLC should be performed at Weeks 0, 24, 52, 76, and 104. The DLCO measurements will be corrected for hemoglobin level, and spirometry assessments will be centrally adjudicated.

i Digital ulcers are those distal to the metacarpal phalangeal joints. New or worsening digital ulcers, or at any other site on the body, will be captured as AEs.

j Adverse events should also be assessed for occurrence during the periods between trial visits.

k Survival follow-up: All subjects will be assessed for survival every 12 weeks (± 1 week) from the last trial visit until death or end of the trial.

Appendix IV: Criteria for the Classification of Systemic Sclerosis

Copy of Table A1 The American College of Rheumatology/European League Against Rheumatism criteria for the classification of systemic sclerosis*

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

SSc, systemic sclerosis.

* These criteria are applicable to any patient considered for inclusion in a systemic sclerosis study. The criteria are not applicable to patients with skin thickening sparing the fingers or to patients who have a scleroderma-like disorder that better explains their manifestations (eg, nephrogenic sclerosing fibrosis, generalised morphea, eosinophilic fasciitis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft-versus-host disease, diabetic cheiroarthropathy).

† The total score is determined by adding the maximum weight (score) in each category. Patients with a total score of ≥9 are classified as having definite systemic sclerosis.

Reproduced from van den Hoogen, et al (2013).

Copy of Table A2 Definitions of items/sub-items in the American College of Rheumatology/European League Against Rheumatism criteria for the classification of systemic sclerosis

Item	Definition
Skin thickening	Skin thickening or hardening not due to scarring after injury, trauma, etc.
Puffy fingers	Swollen digits - a diffuse, usually nonpitting increase in soft tissue mass of the digits extending beyond the normal confines of the joint capsule. Normal digits are tapered distally with the tissues following the contours of the digital bone and joint structures. Swelling of the digits obliterates these contours. Not due to other causes such as inflammatory dactylitis.
Fingertip ulcers or pitting scars	Ulcers or scars distal to or at the proximal interphalangeal joint not thought to be due to trauma. Digital pitting scars are depressed areas at digital tips as a result of ischaemia, rather than trauma or exogenous causes.
Telangiectasia	Telangiectasiae are visible macular dilated superficial blood vessels, which collapse upon pressure and fill slowly when pressure is released. Telangiectasiae in a scleroderma-like pattern are round and well demarcated and found on hands, lips, inside of the mouth, and/or are large mat-like telangiectasiae. Distinguishable from rapidly filling spider angiomas with central arteriole and from dilated superficial vessels.
Abnormal nailfold capillary pattern consistent with systemic sclerosis	Enlarged capillaries and/or capillary loss with or without pericapillary haemorrhages at the nailfold. May also be seen on the cuticle.
Pulmonary arterial hypertension	Pulmonary arterial hypertension diagnosed by right-sided heart catheterisation according to standard definitions.
Interstitial lung disease	Pulmonary fibrosis seen on high-resolution CT or chest radiography, most pronounced in the basilar portions of the lungs, or occurrence of 'Velcro' crackles on auscultation, not due to another cause such as congestive heart failure.
Raynaud's phenomenon	Self-reported or reported by a physician, with at least a 2-phase colour change in finger(s) and often toe(s) consisting of pallor, cyanosis, and/or reactive hyperemia in response to cold exposure or emotion; usually one phase is pallor.
SSc-related auto antibodies	Anticentromere antibody or centromere pattern seen on antinuclear antibody testing, anti–topoisomerase I antibody (also known as anti-Scl-70 antibody), or anti-RNA polymerase III antibody. Positive according to local laboratory standards.

SSc, systemic sclerosis.
Reproduced from van den Hoogen, et al (2013).

Amendment 2

Rationale

The purpose of this protocol amendment is to revise the contraception requirements based on comments received from a Voluntary Harmonisation Procedure (VHP) review.

Major Scientific Changes

The contraception requirements for study inclusion were updated to more clearly define effective contraception for consistency with current Clinical Trial Facilitation Group guidelines and recommendations from the VHP.

Administrative and Editorial Changes

The Sponsor's Medical Responsible contact was changed from PPD to PPD. The date and version number of the protocol were changed throughout and new abbreviations were added to the list of abbreviations as needed.

List of Changes

Changes to the clinical trial protocol text are presented in the table below. Additions and amended text are shown in bold. If the original clinical trial protocol text was already bold, changes are shown in bold and underlined, deletions are marked using strike-through.

Comparison with Clinical Trial Protocol Version 2.0, 02 Feb 2016 (Amendment No. 1)

Change	Section	Page	Previous Wording	New Wording
Change in Sponsor's Responsible Medical	Title Page	1	Medical Responsible: PPD EMD Serono Research & Development Institute, Inc. 45A Middlesex Turnpike Billerica, MA, 01821 USA Telephone number: PPD Fax number: PPD	Medical Responsible: PPD EMD Serono Research & Development Institute, Inc. 45A Middlesex Turnpike Billerica, MA, 01821 USA Telephone number: PPD Fax number: PPD
More clearly define contraception methods allowed	5.3.1	39	6. Female subjects of childbearing potential must use a highly effective method of contraception to prevent pregnancy for 4 weeks before randomization and must agree to continue to practice adequate contraception for the duration of their participation in the trial (up to the last Safety Follow-Up Visit). For the purposes of this trial, women of childbearing potential are defined as "All female subjects after puberty unless they are post-menopausal for at least 2 years or are surgically sterile." Highly effective contraception is defined as 2 barrier methods (eg, female diaphragm and male condoms); or 1 barrier method with at least one of the following: spermicide, a hormonal method, or an intrauterine device. Note that because mycophenolate affects the metabolism of oral contraceptives and may reduce their effectiveness, women receiving mycophenolate who are using oral contraceptives for birth control should employ an additional contraceptive method (eg, male or female barrier method).	~~6. Female subjects of childbearing potential must use a highly effective method of contraception to prevent pregnancy for 4 weeks before randomization and must agree to continue to practice adequate contraception for the duration of their participation in the trial (up to the last Safety Follow-Up Visit). For the purposes of this trial, women of childbearing potential are defined as "All female subjects after puberty unless they are post-menopausal for at least 2 years or are surgically sterile." Highly effective contraception is defined as 2 barrier methods (eg, female diaphragm and male condoms); or 1 barrier method with at least one of the following: spermicide, a hormonal method, or an intrauterine device. Note that because mycophenolate affects the metabolism of oral contraceptives and may reduce their effectiveness, women receiving mycophenolate who are using oral contraceptives for birth control should employ an additional contraceptive method (eg, male or female barrier method).~~ **6. 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 two effective methods of contraception, including at least one highly effective method that can achieve a failure rate of < 1% per year, when used consistently and correctly, and one other reliable method during the treatment period and for at least 90 days after the last dose of study**

Change	Section	Page	Previous Wording	New Wording
				treatment. Examples of contraceptive methods with a failure rate of < 1% per year (highly effective contraceptive methods) include: • combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation[1] (oral, intravaginal, transdermal) • progesterone-only hormonal contraception associated with inhibition of ovulation[1] (oral, injectable, implantable[2]) • intrauterine device (IUD)[2] • intrauterine hormone-releasing system (IUS)[2] • bilateral tubal occlusion[2] • vasectomized partner[2,3] • sexual abstinence[4] [1] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method. [2] Contraception methods in the context of this guidance are considered to have low user dependency. [3] Vasectomized partner is a highly effective birth control method provided that the partner is the sole sexual partner of the woman of childbearing potential trial participant and that the vasectomized partner has received medical assessment of the surgical success. [4] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Barrier methods supplemented with the use of a spermicide could be considered as a reliable

Change	Section	Page	Previous Wording	New Wording
				method. **For men (including those who have undergone a vasectomy): agreement to remain abstinent or use a condom during the treatment period and for at least 12 months after the last dose of study treatment and agreement to refrain from donating sperm during this same period.** **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.** **In addition to male contraception, agreement to advise female partners of childbearing potential to use highly effective contraception during the study and for at least 12 months after the last dose of study treatment.** **Upon termination of participation in this clinical study, patients continuing on MMF must continue effective contraception as required by the SPC.**
More clearly define contraception methods allowed	6.5.4	46	Women of childbearing potential and men must use highly effective contraception, including 2 barrier methods or 1 barrier method in combination with a spermicide, hormonal method, or intrauterine device, until further availability of reproductive toxicity data.	~~Women of childbearing potential and men must use highly effective contraception, including 2 barrier methods or 1 barrier method in combination with a spermicide, hormonal method, or intrauterine device, until further availability of reproductive toxicity data.~~ **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 two effective methods of contraception, including at least one highly effective method that can achieve a failure rate of < 1% per year, when used consistently and correctly, and one other reliable method during the treatment period and for at least 90 days after the last dose of study treatment.** **Examples of contraceptive methods with a failure rate of < 1% per year (highly effective contraceptive methods) include:**

Change	Section	Page	Previous Wording	New Wording
				• combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation[1] (oral, intravaginal, transdermal) • progesterone-only hormonal contraception associated with inhibition of ovulation[1] (oral, injectable, implantable[2]) • intrauterine device (IUD)[2] • intrauterine hormone-releasing system (IUS)[2] • bilateral tubal occlusion[2] • vasectomized partner[2,3] • sexual abstinence[4] [1] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method. [2] Contraception methods in the context of this guidance are considered to have low user dependency. [3] Vasectomized partner is a highly effective birth control method provided that the partner is the sole sexual partner of the woman of childbearing potential trial participant and that the vasectomized partner has received medical assessment of the surgical success. [4] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Barrier methods supplemented with the use of a spermicide could be considered as a reliable method. For men (including those who have undergone a vasectomy): agreement to remain abstinent or use a condom during the treatment period and for at least 12 months after the last dose of study

Change	Section	Page	Previous Wording	New Wording
				treatment and agreement to refrain from donating sperm during this same period. **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.** **In addition to male contraception, agreement to advise female partners of childbearing potential to use highly effective contraception during the study and for at least 12 months after the last dose of study treatment.** **Upon termination of participation in this clinical study, patients continuing on MMF must continue effective contraception as required by the SPC.**

Amendment 3

This is a global amendment, effective 14 September 2016.

Rationale

The purpose of this protocol amendment is to:

- Clarify the role of the independent panel of dermatology experts
- Specify the period of observation after IMP administration in order to detect any delayed onset of sign/symptoms of infusion reactions
- Add additional hematology time points to align with DLCO assessments
- Provide further rationale for exploratory endpoints
- Revise exclusion criteria to allow subjects with secondary Sjögren's syndrome
- Allow prophylactic treatment for *Pneumocystis jiroveci* pneumonia
- Exclude the use of e-cigarettes
- Clarify allowable corticosteroid use
- Exclude the administration of vaccines from 12 weeks prior until 3 months after the study
- Exclude subjects with recent or planned major surgery or major organ transplant
- Clarify re-screening procedures
- Allow $HbA1_c$ testing in subjects with diabetes at the discretion of the Investigator and with Medical Monitor approval.

The changes to be made to the clinical trial protocol and the rationale for the key scientific changes are described below.

Major Scientific Changes

Sjögren's syndrome: Secondary Sjögren's syndrome is usually present in autoimmune diseases. Over 20% of patients with systemic sclerosis, and a few with localized scleroderma also have secondary Sjögren syndrome, and are usually permitted in trials for rheumatic diseases.

Pneumocystis jiroveci: Approximately 1% to 2% of patients with rheumatologic diseases develop *Pneumocystis jiroveci*, usually in the setting of immunosuppressive therapy and particularly in combined therapy, and are more likely to develop in subjects with interstitial pulmonary fibrosis.

Live vaccines: The use of live vaccines is contra-indicated in patients receiving immunosuppressive treatment or patients taking moderate or high doses of steroids. Inactivated vaccines can be administered safely to persons with altered immunocompetence whether the vaccine is a killed whole organism or a recombinant, subunit, toxoid, polysaccharide, or

polysaccharide protein-conjugate vaccine. Inactivated vaccines are indicated for persons with altered immunocompetence at the usual doses and schedules. In addition, seasonal inactivate influenza vaccine is recommended.

Corticosteroids: The protocol has been updated to provide further clarification with regards to the use of inhaled and topical corticosteroids. Corticosteroids using these routes are minimally systemically absorbed and may be beneficial in several cutaneous and respiratory diseases, including SSc complications.

Administrative and Editorial Changes

The Schedule of Assessments was updated as follows:

- A typographical error for the rich PK sampling time points was corrected.
- The timing of safety follow-up visits was clarified.
- Text clarifying the Mahler BDI/TDI administrator must be blinded to other assessments was added.

The name of the biostatistical expert has been revised to reflect a change in team membership. The date and version number of the protocol were changed throughout and minor typographical errors were corrected. Minor editorial revisions were made to enhance reader understanding.

List of Changes

Changes to the clinical trial protocol text are presented in the table below. Additions and amended text are shown in bold. If the original clinical trial protocol text was already bold, changes are shown in bold and underlined; deletions are marked using strike-through.

Comparison with Clinical Trial Protocol Version 3.0, 16 May 2016 (Amendment No. 2)

Change	Section	Page	Previous Wording	New Wording
To clarify role of the independent panel of dermatology experts	Synopsis; Methodology, last paragraph	14	During the conduct of the trial, an Independent Data Monitoring Committee (IDMC) will monitor safety data on a regular basis (to be specified in the IDMC charter). The IDMC will also review the results of the interim futility analysis conducted by an independent statistical center. Based on the prespecified stopping boundary of futility, and the totality of the information at interim, the IDMC will make a recommendation to the Sponsor on continuing or stopping the trial for futility. An independent panel of dermatologists will provide guidance for further investigation and interpretation of cutaneous AEs that are serious, are Grade 3 or higher, or are not responding to treatment, and make recommendations as to whether any subject-specific or trial-wide actions should be considered.	During the conduct of the trial, an Independent Data Monitoring Committee (IDMC) will monitor safety data on a regular basis (to be specified in the IDMC charter). The IDMC will also review the results of the interim futility analysis conducted by an independent statistical center. Based on the prespecified stopping boundary of futility, and the totality of the information at interim, the IDMC will make a recommendation to the Sponsor on continuing or stopping the trial for futility. An independent panel of dermatologists will provide guidance for further investigation and interpretation of cutaneous AEs that are serious, are Grade 3 or higher, or are not responding to treatment, and ~~make recommendations as to~~**advise the IDMC** whether any ~~subject-specific or trial-wide~~ actions **to modify clinical trial conduct** should be considered.
To harmonize description of key entry criteria within protocol	Synopsis; Diagnosis and key inclusion and exclusion criteria, second paragraph	17	Subjects must not have underlying conditions that constitute an inappropriate risk or contraindication for trial participation including, but not limited to: significant renal impairment, obstructive lung disease/emphysema, pulmonary arterial hypertension, another inflammatory connective tissue disease, and/or tuberculosis. The use of agents other than mycophenolate (MPS or MMF) considered by the Investigator to have immunomodulating, immunosuppressive, or potential scleroderma disease-modifying properties within 6 months of screening is not allowed.	Subjects must not have underlying conditions that constitute an inappropriate risk or contraindication for trial participation including, but not limited to: significant renal impairment, obstructive lung disease/emphysema, pulmonary arterial hypertension, another inflammatory connective tissue disease **(apart from scleroderma-associated myopathy, fibromyalgia, and secondary Sjögren's syndrome, which are allowed)**, and/or tuberculosis. The use of agents other than mycophenolate (MPS or MMF) considered by the Investigator to have immunomodulating, immunosuppressive, or potential scleroderma disease-modifying properties within 6 months of screening is not allowed.

Change	Section	Page	Previous Wording	New Wording
Specify period of observation after dosing	Synopsis; Investigational medicinal product; dose/mode of administration/dosing schedule	17	Abituzumab 1500 or 500 mg will be administered as an intravenous infusion over 1 hour once every 4 weeks with the last IMP administration at the Week 100 visit (2 years) on top of background therapy.	Abituzumab 1500 or 500 mg will be administered as an intravenous infusion over 1 hour once every 4 weeks**. Close observation of the subject is recommended for a period of at least 1 hour after administration of the IMP.** ~~with t~~**T**he last IMP administration **is** at the Week 100 visit (2 years) ~~on top of background therapy~~.
Specify period of observation after dosing	Synopsis; Reference therapy; dose/mode of administration/dosing schedule	17	Placebo (citrate buffered saline) will be administered as an intravenous infusion over 1 hour once every 4 weeks with the last administration at the Week 100 visit (2 years) on top of background therapy.	Placebo (citrate buffered saline) will be administered as an intravenous infusion over 1 hour once every 4 weeks**. Close observation of the subject is recommended for a period of at least 1 hour after administration.** ~~with t~~**T**he last administration **of placebo is** at the Week 100 visit (2 years) ~~on top of background therapy~~.
Addition of hematology time points to support DLCO assessments; clarification that timing of safety follow-up visits are after the last on-treatment visit; correction of typographical error in rich PK sampling time points	Schedules of Assessments	20-24	Refer to Amendment 3 - Tables 1 and 2, below.	Refer to Amendment 3 - Tables 1 and 2, below.

Change	Section	Page	Previous Wording	New Wording
To clarify role of the independent panel of dermatology experts	Section 3.3; sixth paragraph	29	The current safety profile of abituzumab monotherapy includes the identified risks, allergic reaction, and skin rash (Grades 1-2). […] The occurrence of AESI or cutaneous serious AEs (SAEs) will be reviewed by an independent panel of dermatologists to provide guidance for further investigation and interpretation of these events, and determine whether any subject-specific or trial-wide actions should be considered. An IDMC will review safety data to ensure safety of all subjects enrolled in the trial. If subjects have significant worsening of lung function, they may start rescue medication, as appropriate. No additional risk minimization measures are considered necessary at this time for studying the effects of abituzumab in subjects with SSc-ILD.	The current safety profile of abituzumab monotherapy includes the identified risks, allergic reaction, and skin rash (Grades 1-2). […] The occurrence of AESI or cutaneous serious AEs (SAEs) will be reviewed by an independent panel of dermatologists to provide guidance for further investigation and interpretation of these events, and ~~determine~~ **advise the IDMC** whether any ~~subject-specific or trial-wide~~ actions **to modify clinical trial conduct** should be considered. An IDMC will review safety data to ensure safety of all subjects enrolled in the trial. If subjects have significant worsening of lung function, they may start rescue medication, as appropriate. No additional risk minimization measures are considered necessary at this time for studying the effects of abituzumab in subjects with SSc-ILD.
To correct typographical error in the number of sites	Section 5.1; first paragraph	30	This is a Phase II, multicenter, double-blind, placebo-controlled, parallel-group trial to be conducted in adult male and female subjects with SSc-ILD who are treated with stable mycophenolate to explore the efficacy, safety, tolerability, and immunogenicity of multiple intravenous doses of abituzumab. Subjects must have had mycophenolate treatment for at least 6 months and remained at a stable dose (1.5 to 3 g/day of mycophenolate mofetil [MMF] or 1080 to 2160 mg/day of sodium mycophenolate [MPS]) for at least 3 months. The trial will be conducted at approximately 50 sites globally.	This is a Phase II, multicenter, double-blind, placebo-controlled, parallel-group trial to be conducted in adult male and female subjects with SSc-ILD who are treated with stable mycophenolate to explore the efficacy, safety, tolerability, and immunogenicity of multiple intravenous doses of abituzumab. Subjects must have had mycophenolate treatment for at least 6 months and remained at a stable dose (1.5 to 3 g/day of mycophenolate mofetil [MMF] or 1080 to 2160 mg/day of sodium mycophenolate [MPS]) for at least 3 months. The trial will be conducted at approximately ~~50~~ **60** sites globally.
To specify the order of patient-reported outcome assessments	Section 5.2.5, Efficacy, paragraph 12	37	The EQ-5D, measures health outcomes and is standardized for use across many indications and regions. It can be used for health outcomes including QoL and also economic analyses. Applicable to a wide range of health conditions and treatments, the EQ-5D health questionnaire provides a simple descriptive profile and a single-index value for health status.	The EQ-5D, measures health outcomes and is standardized for use across many indications and regions. It can be used for health outcomes including QoL and also economic analyses. Applicable to a wide range of health conditions and treatments, the EQ-5D health questionnaire provides a simple descriptive profile and a single-index value for health status. **Please note: Patient-reported Outcome questionnaires should be completed before any other procedures, as per the Schedules of Assessments (Table 1 and Table 2).**

Change	Section	Page	Previous Wording	New Wording
				Questionnaires will be performed in the following order: • **Patient's Global Assessment** • **SHAQ** • **Mahler BDI (at Day 1) followed by Mahler TDI at the subsequent visits, by the request of the author of the Mahler TDI** • **SGRQ** • **Leicester Cough Index** • **EQ-5D** • **Physician's Global Assessment (VAS).**
To add CCI endpoint	Section 5.2.6; first paragraph	37-38	CCI	CCI
To specify subjects with secondary Sjögren's syndrome are allowed.	Section 5.3.2; Exclusion Criterion 8	41	8. Current clinical diagnosis of another inflammatory connective tissue disease (eg, systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, or dermato/polymyositis); concomitant scleroderma-associated myopathy and fibromyalgia are allowed.	8. Current clinical diagnosis of another inflammatory connective tissue disease (eg, systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, or dermato/polymyositis); concomitant scleroderma-associated myopathy**,** ~~and~~ fibromyalgia**, and secondary Sjögren's syndrome** are allowed
To allow prophylactic treatment for *Pneumocystis jiroveci* pneumonia	Section 5.3.2; Exclusion Criterion 10	41	10. Active clinically significant viral, bacterial, or fungal infection, or any major episode of infection requiring hospitalization or treatment with parenteral anti-infectives within 4 weeks prior to screening or during the Screening Period, or completion of oral anti-infectives within 2 weeks before screening or use of oral anti-infectives during the Screening Period. Vaginal candidiasis, onychomycosis, and chronically suppressed oral herpes simplex virus	10. Active clinically significant viral, bacterial, or fungal infection, or any major episode of infection requiring hospitalization or treatment with parenteral anti-infectives within 4 weeks prior to screening or during the Screening Period, or completion of oral anti-infectives within 2 weeks before screening or use of oral anti-infectives during the Screening Period. Vaginal candidiasis, onychomycosis, and chronically suppressed oral herpes simplex virus would not be exclusionary. **Prophylaxis for *Pneumocystis jiroveci***

Change	Section	Page	Previous Wording	New Wording
			would not be exclusionary.	**pneumonia according to local guidelines will be permitted.**
To exclude use of e-cigarettes	Section 5.3.2; Exclusion Criterion 16	42	16. Current smoker or smoking within 4 weeks of screening.	16. Current smoker **(including e-cigarettes)** or smoking within 4 weeks of screening.
To clarify allowable corticosteroid use	Section 5.3.2; Exclusion Criterion 18	42	18. Use of corticosteroids above 10 mg/day prednisone equivalent within 4 weeks of screening, during the Screening Period, or expected during the treatment period.	18. Use of **systemic** corticosteroids above 10 mg/day prednisone equivalent within 4 weeks of screening, during the Screening Period, or expected during the treatment period**. Inhaled corticosteroids are not considered systemic and are permitted. Topical corticosteroids are permitted.**
To exclude vaccine from 12 weeks prior to study until 3 months after the study.	Section 5.3.2; New Exclusion Criterion 28	41	Not applicable.	**28. Receipt of a live/attenuated vaccine within 12 weeks prior to the Screening Visit or subjects who are expecting to receive any live virus or bacterial vaccinations during the trial, or up to 3 months after the last dose of study drug, are not permitted. Seasonal influenza vaccination is permitted if the inactivated vaccine formulation is administered.**
To exclude subjects with recent or planned major surgery or major organ transplant	Section 5.3.2; New Exclusion Criteria 29 and 30	43	Not applicable.	**29. Major surgery requiring hospitalization within 4 weeks prior to the Screening Visit and any planned major surgery for the duration of the trial. Subjects with lung resection.** **30. Have a history of a major organ transplant (eg, heart, lung, kidney, or liver) or hematopoietic stem cell/marrow transplant or are due to receive transplantation.**
Specify period of observation after dosing	Section 6.2, Dosage and Administration	45	In the Double-blind Treatment Period, subjects will be randomized in a 2:2:1 ratio to receive one of the following treatments: abituzumab 1500 mg, placebo, or abituzumab 500 mg, respectively. Treatment will be given as an intravenous infusion over approximately 1 hour every 4 weeks with the last IMP administration at the Week 100 visit. The infusion time should not be less than 1 hour.	In the Double-blind Treatment Period, subjects will be randomized in a 2:2:1 ratio to receive one of the following treatments: abituzumab 1500 mg, placebo, or abituzumab 500 mg, respectively. Treatment will be given as an intravenous infusion over approximately 1 hour every 4 weeks**.** ~~with the last IMP administration at the Week 100 visit.~~ The infusion time should not be less than 1 hour. **Close observation of the subject is recommended for a period of at least 1 hour after administration of**

Change	Section	Page	Previous Wording	New Wording
				IMP. The last IMP/placebo administration will be at the Week 100 visit.
To clarify prior administration of vaccines	Section 6.5.1, Permitted Medications	46	Any medications, other than those excluded or listed as prohibited, that are considered necessary for the subject's welfare, and that do not interfere with the trial conduct or assessment, may be given at the Investigator's judgment. The Investigator will record all concomitant medications and procedures throughout the trial.	Any medications, other than those excluded or listed as prohibited, that are considered necessary for the subject's welfare, and that do not interfere with the trial conduct or assessment, may be given at the Investigator's judgment. The Investigator will record all concomitant medications and procedures throughout the trial. **Seasonal influenza vaccination is permitted if the inactivated vaccine formulation is administered. Prophylaxis for *Pneumocystis jiroveci* pneumonia according to local guidelines will be permitted.**
To clarify prior administration of vaccines	Section 6.5.2, Prohibited Medications	47	Medications for treatment of PAH are not permitted during the Screening or Double-blind Treatment Periods. These medications include, but are not limited to, phosphodiesterase-5 inhibitors (eg, sildenafil), ERAs (eg, bosentan), prostanoids (epoprostenol, treprostinil), and riociguat. These medications can be used for treatment of conditions other than PAH, such as Raynaud's symptoms. If subjects meet criteria for rescue medication (see Section 6.5.5), then such therapy can be initiated. The use of agents other than mycophenolate (MPS or MMF) considered by the Investigator to have immunomodulating, immunosuppressive, or potential scleroderma disease-modifying properties within 6 months of screening is not permitted.	Medications for treatment of PAH are not permitted during the Screening or Double-blind Treatment Periods. These medications include, but are not limited to, phosphodiesterase-5 inhibitors (eg, sildenafil), ERAs (eg, bosentan), prostanoids (epoprostenol, treprostinil), and riociguat. These medications can be used for treatment of conditions other than PAH, such as Raynaud's symptoms. If subjects meet criteria for rescue medication (see Section 6.5.5), then such therapy can be initiated. The use of agents other than mycophenolate (MPS or MMF) considered by the Investigator to have immunomodulating, immunosuppressive, or potential scleroderma disease-modifying properties within 6 months of screening is not permitted. **Receipt of a live/attenuated vaccine within 12 weeks prior to the Screening Visit is not permitted. Live virus or bacterial vaccinations during the trial, or up to 3 months after the last dose of study drug are not permitted.**
To clarify re-screening procedures	Section 7.1.1, Screening Period, second paragraph	53-54	If at screening, the subject meets all of the protocol inclusion and none of the exclusion criteria (including complete history of immunosuppressive, immunomodulating, and potential scleroderma disease modifying medications as well as history of other medications in the previous year), the subject	If at screening, the subject meets all of the protocol inclusion and none of the exclusion criteria (including complete history of immunosuppressive, immunomodulating, and potential scleroderma disease modifying medications as well as history of other medications in the previous year), the subject

Change	Section	Page	Previous Wording	New Wording
			will be considered as eligible and will be enrolled in the trial and randomized. Subjects who fail to meet the protocol-specified criteria for randomization or dosing, or withdraw their consent before randomization, are considered screening failures. If the Investigator feels a particular screening assessment is aberrant and retesting could confirm eligibility, these may be repeated under the same subject number, provided the retest is performed within the same screening period. A subject who was considered a screen failure may be re-screened (only once per subject), but a new subject number will be assigned and all screening assessments have to be repeated.	will be considered as eligible and will be enrolled in the trial and randomized. Subjects who fail to meet the protocol-specified criteria for randomization or dosing, or withdraw their consent before randomization, are considered screening failures. If the Investigator feels a particular screening assessment is aberrant and retesting could confirm eligibility, these may be repeated under the same subject number, provided the retest is performed within the same screening period. A subject who was considered a screen failure may be re-screened (only once per subject). **Re-screening is not encouraged. However, on a case-by-case basis with permission of the Medical Monitor and the Sponsor's Medical Director, a subject who has not met all of the eligibility criteria within the original screening period may be permitted to be re-screened one time. Each subject must be re-consented before re-screening occurs.** ~~, but a~~**A** new subject number will be assigned and all screening assessments have to be repeated.
Correction of typographical error	Section 7.3, second paragraph	55	In this trial, full volume HRCT of the chest will be performed at Sponsor-qualified imaging centers per guidelines outlined in an imaging manual. High resolution computer tomography will be performed on all trial subjects during the Screening Period and at Months 6, 12, and 24 (Weeks 26, 52, and 104; or early termination, if applicable). To ensure comparability, the same scan, equipment, method, and technique used during the baseline HRCT scan should be used for all the subsequent HRCT scans. For all subjects, HRCT scans will be performed at TLC with no contrast agent administration, reconstructed every 0.6 to 2 mm, using a low-dose protocol.	In this trial, full volume HRCT of the chest will be performed at Sponsor-qualified imaging centers per guidelines outlined in an imaging manual. High resolution computer tomography will be performed on all trial subjects during the Screening Period and at Months 6, 12, and 24 (Weeks ~~26~~**24**, 52, and 104; or early termination, if applicable). To ensure comparability, the same scan, equipment, method, and technique used during the baseline HRCT scan should be used for all the subsequent HRCT scans. For all subjects, HRCT scans will be performed at TLC with no contrast agent administration, reconstructed every 0.6 to 2 mm, using a low-dose protocol.
To clarify role of the independent panel of dermatology experts	Section 7.4.1.1, Adverse Events of Special Interest	58	All blistering or Grade ≥3 AEs in the skin and subcutaneous tissue disorders SOC will be designated as AESI. Any cutaneous reaction of Grade 1 or 2 that is not responding to specific treatment or is worsening will also be designated as an AESI. The occurrence of cutaneous AESI or	All blistering or Grade ≥3 AEs in the skin and subcutaneous tissue disorders SOC will be designated as AESI. Any cutaneous reaction of Grade 1 or 2 that is not responding to specific treatment or is worsening will also be designated as an AESI. The occurrence of cutaneous AESI or

Change	Section	Page	Previous Wording	New Wording
			SAEs will be reviewed by an independent panel of dermatologists to provide guidance for further investigation and interpretation of these events, and determine whether any subject-specific or trial-wide actions should be considered.	SAEs will be reviewed by an independent panel of dermatologists to provide guidance for further investigation and interpretation of these events, and ~~determine~~ **advise the IDMC** whether any ~~subject-specific or trial-wide~~ actions **to modify clinical trial conduct** should be considered.
Editorial revision to remove reference to pediatric patients, which is not applicable to this study	Section 7.4.1.2, paragraph 5, number 3.	59	3. Reduced BP after exposure to known allergen for that subject (minutes to several hours): a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP* ab. Adults: systolic BP of less than 90 mmHg or greater than 30% decrease from that person's baseline * Low systolic blood pressure for children is defined as less than 70 mmHg from 1 month to 1 year, less than (70 mmHg + [2 □ age]) from 1 to 10 years, and less than 90 mmHg from 11 to 17 years.	3. Reduced BP after exposure to known allergen for that subject (minutes to several hours): ~~a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*~~ ~~ab~~. Adults: systolic BP of less than 90 mmHg or greater than 30% decrease from that person's baseline ~~* Low systolic blood pressure for children is defined as less than 70 mmHg from 1 month to 1 year, less than (70 mmHg + [2 □ age]) from 1 to 10 years, and less than 90 mmHg from 11 to 17 years.~~
To allow HbA1c testing for subjects with diabetes	Section 7.4.3, Clinical Laboratory Assessments, third paragraph	63	Other laboratory assessments include the following: • Serum pregnancy test in female subjects of childbearing potential; • Urine pregnancy test in female subjects of childbearing potential, to be performed locally; • HIV, hepatitis C, and hepatitis B (HBsAg, hepatitis B core antibody [IgM and total]) serologies; • Tuberculosis testing as requested by Investigator.	Other laboratory assessments include the following: • Serum pregnancy test in female subjects of childbearing potential; • Urine pregnancy test in female subjects of childbearing potential, to be performed locally; • HIV, hepatitis C, and hepatitis B (HBsAg, hepatitis B core antibody [IgM and total]) serologies; • **HbA1c may be evaluated for subjects with diabetes, at the discretion of the Investigator and by forwarding a prior request to the Medical Monitor and notification to the Sponsor's Medical Director. Samples may be collected at any time point judged appropriate by the Investigator with Medical Monitor approval. Testing will be conducted by a local laboratory.** • Tuberculosis testing as requested by Investigator.
Update statistical team lead contact information	Sponsor Responsible Persons	87	PPD EMD Serono Research and Development Institute,	PPD PPD EMD Serono Research and Development Institute,

Change	Section	Page	Previous Wording	New Wording
			Inc. 45A Middlesex Turnpike Billerica, MA 01821 USA PPD PPD PPD	Inc. 45A Middlesex Turnpike Billerica, MA 01821 USA PPD PPD PPD

Amendment 3 - Table 1 Schedule of Assessments – Screening through Week 52

Trial Period	Screening	Weeks During Double-blind Treatment Period (Visit Window ±3 days)														
Week		0	2	4	8	12	16	20	24	28	32	36	40	44	48	52
Trial Day	-28 to -1	1	15	29	57	85	113	141	169	197	225	253	281	309	337	365
Informed consent	X															
Inclusion/exclusion criteria	X	X[a]														
CCI																
Pharmacokinetic informed consent (Rich PK sampling only)	X															
Demographic data	X															
SSc-ILD and other medical history, medications, surgery/procedures	X															
HRCT	X								X							X
12-lead ECG (locally read)	X								X							X
Tuberculosis assessment	X															
Serum virology (HIV, HCV, HBV)	X															
Serum pregnancy test [c]	X															
PT, aPTT, TSH, and NT pro-BNP	X															
Urine pregnancy test [c,d]		X		X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X	X[e]	X	X[e]	X[e]	X[e]	X[e]	X	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X
Vital signs, weight, height [f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Mahler BDI/TDI and SGRQ [g]		X				X			X			X				X
Patient's Global Assessment, Leicester Cough Index, SHAQ, EQ-5D, and Physician's Global Assessment [g]		X							X							X
Randomization		X														
IMP administration		X		X	X	X	X	X	X	X	X	X	X	X	X	X

Trial Period	Screening	Weeks During Double-blind Treatment Period (Visit Window ±3 days)														
Week		0	2	4	8	12	16	20	24	28	32	36	40	44	48	52
Trial Day	-28 to -1	1	15	29	57	85	113	141	169	197	225	253	281	309	337	365
PK sampling [h]		X		X	X		X									
Rich PK sampling [i]		~~X~~	X	~~X~~	~~X~~		~~X~~									
Routine hematology, clinical chemistry, urinalysis dipstick [j]	X	X	X	X	X	X	X	X	X		X	**X**	X		X	X
Pulmonary function tests (FVC, TLC) with DLCO [k]	X	X				X			X			X				X
mRSS		X				X			X			X				X
Digital ulcer counts[l]		X				X			X			X				X
Serum for ADA		X							X							X
Sample for autoantibodies		X							X							X
CCI																
Concomitant medications/procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events [n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

ADA = antidrug antibodies; AE = adverse event; aPTT = activated partial thromboplastin time; BDI = Baseline Dyspnea Index; DLCO = diffusion capacity of the lung for carbon monoxide; ECG = electrocardiogram; FVC = forced vital capacity; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HRCT = high-resolution computed tomography; IMP = investigational medicinal product; mRSS = modified Rodnan skin score; PK = pharmacokinetic; PT = prothrombin time; SGRQ = St. George Respiratory Questionnaire; SHAQ = Scleroderma Health Assessment Questionnaire; SSc-ILC = systemic sclerosis-associated interstitial lung disease; TDI = Transition Dyspnea Index; TLC = total lung capacity; TSH = thyroid-stimulating hormone; VAS = visual analog scale.

a Subject eligibility (based on screening assessments of the inclusion and exclusion criteria) must be checked again on Day 1 prior to randomization.

CCI

c For women of childbearing potential or who are postmenopausal for less than 2 years. At Day 1, if the urine test is negative, the subject can be randomized and receive the first dose of IMP.

d Performed locally per local constraints and regulations.

e Focused physical examination only, according to standard of care.

f Vital signs include 10-minute seated arterial blood pressure, pulse rate, and body temperature. Height will be measured at Day 1 only. Weight will be measured at Weeks 0, 24, 52, 76, and 104. Body weight will be measured with a balance beam scale, if possible.

g Questionnaires should be completed before any other procedures are performed. Questionnaires should be performed in the following order: Patient's Global Assessment, SHAQ, Mahler BDI (at Day 1) followed by Mahler TDI at the subsequent visits, SGRQ, Leicester Cough Index, and EQ-5D. **The Mahler BDI/TDI administrator must be blinded to other assessments.** The Physician's Global Assessment (VAS) may be performed after other assessments at the visit are completed.

h For all subjects, samples will be collected predose and immediately after the end of IMP infusion at Weeks 0 (Day 1), 4, 8, and 16.

i For subjects who have provided informed consent for the rich PK sampling, additional samples will be collected on Days 3, 5, 15, and 22 (in addition to the pre- and postdose samples at Weeks 0, 4. 8, and 16; see footnote h).

j See Section 7.4.3 for list of routine laboratory assessments. Urine protein:creatinine ratio to be performed if dipstick urinalysis reveals at least 3+ protein. Microscopic urinalysis to be performed if blood is present.

k The TLC should be performed at Weeks 0, 24, 52, 76, and 104. The DLCO measurements will be corrected for hemoglobin level, and spirometry assessments will be centrally adjudicated.

l Digital ulcers are those distal to the metacarpal phalangeal joints. New or worsening digital ulcers, or at any other site on the body, will be captured as AEs.

CCI [redacted]

n Adverse events should also be assessed for occurrence during the periods between trial visits.

Amendment 3 - Table 2 Schedule of Assessments – Week 56 through Safety Follow-up

Trial Period	Weeks During Double-blind Treatment Period (Visit Window ±5 days)														Safety Follow-up Number weeks post last ~~dose~~ visit (±5 days)		Survival Follow-up Post Last Trial Visit
Week	56	60	64	68	72	76	80	84	88	92	96	100	104	ET[a]	4	12	Every 12 Weeks
Trial Day	393	421	449	477	505	533	561	589	617	645	673	701	729				
HRCT													X	X			
12-lead ECG (locally read)						X							X	X		X	
Urine pregnancy test [b,c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical examination	X[d]	X[d]	X[d]	X[d]	X[d]	X	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X	X	X[d]	X	
Vital signs, weight [e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Mahler TDI and SGRQ [f]			X			X			X				X	X		X	
Patient's Global Assessment, Leicester Cough Index, SHAQ, EQ-5D, and Physician's Global Assessment [f]						X							X	X			
IMP administration	X	X	X	X	X	X	X	X	X	X	X	X					
Routine hematology, clinical chemistry, urinalysis [g]		X	**X**	X		X		X	**X**	X		X	X	X	X	X	
Pulmonary function tests (FVC, TLC) with DLCO [h]			X			X			X				X	X		X	
mRSS			X			X			X				X	X		X	
Digital ulcer counts [i]			X			X			X				X	X		X	
Serum for ADA						X							X	X	X	X	
Sample for autoantibodies													X	X			
CCI																	
Concomitant	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Trial Period	Weeks During Double-blind Treatment Period (Visit Window ±5 days)														Safety Follow-up Number weeks post last ~~dose~~ visit (±5 days)		Survival Follow-up Post Last Trial Visit
Week	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**	**ET[a]**	**4**	**12**	**Every 12 Weeks**
Trial Day	**393**	**421**	**449**	**477**	**505**	**533**	**561**	**589**	**617**	**645**	**673**	**701**	**729**				
medications/procedures																	
Adverse events[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital status[k]																	X

ADA = antidrug antibodies; AE = adverse event; BDI = Baseline Dyspnea Index; DLCO = diffusion capacity of the lung for carbon monoxide; ECG = electrocardiogram; ET = early termination; FVC = forced vital capacity; HRCT = high resolution computed tomography; IMP = investigational medicinal product; mRSS = modified Rodnan skin score; SGRQ = St. George Respiratory Questionnaire; SHAQ = Scleroderma Health Assessment Questionnaire; TDI = Transition Dyspnea Index; TLC = total lung capacity; VAS = visual analog scale.

a Subjects who discontinue IMP for any reason should complete the ET visit as soon as possible, but within 2 weeks of IMP discontinuation, and then the remaining scheduled trial visits. At a minimum, the subject is expected to complete the trial visits at Weeks 12, 24, 36, 52, 64, 76, 88, and 104, as well as the Safety Follow-up period Week 12 visit. Subjects with discontinued IMP can come to the other scheduled visits during the trial period according to the Investigator's judgment. Subjects who withdraw from the treatment period would have an early termination visit followed by entrance into the Safety Follow-up Period. Subjects who withdraw from the trial (eg, withdraw consent, lost to follow up, or death; see Section 5.5.2) would not have any additional trial visits. All subjects will be followed up by the site approximately every 12 weeks for survival from the subject's last trial visit until death or the end of the trial.

b For women of childbearing potential or who are postmenopausal for less than 2 years. Positive urine pregnancy tests should be confirmed with a serum test. If the serum pregnancy test is subsequently positive, the subject will be withdrawn from IMP.

c Performed locally per local constraints and regulations.

d Focused physical examination only, according to standard of care.

e Vital signs include 10-minute seated arterial blood pressure, pulse rate, and body temperature. Weight will be measured at Weeks 0, 24, 52, 76, and 104. Body weight will be measured with a balance beam scale, if possible.

f Questionnaires should be completed before any other procedures are performed. Questionnaires should be performed in the following order: Patient's Global Assessment, SHAQ, Mahler BDI (at Day 1) followed by Mahler TDI at the subsequent visits, SGRQ, Leicester Cough Index, and EQ-5D. **The Mahler BDI/TDI administrator must be blinded to other assessments.** The Physician's Global Assessment (VAS) may be performed after other assessments at the visit are completed.

g See Section 7.4.3 for list of routine laboratory assessments. Urine protein:creatinine ratio to be performed if dipstick urinalysis reveals at least 3+ protein. Microscopic urinalysis to be performed if blood is present.

h The TLC should be performed at Weeks 0, 24, 52, 76, and 104. The DLCO measurements will be corrected for hemoglobin level, and spirometry assessments will be centrally adjudicated.

l Digital ulcers are those distal to the metacarpal phalangeal joints. New or worsening digital ulcers, or at any other site on the body, will be captured as AEs.

j Adverse events should also be assessed for occurrence during the periods between trial visits.

k Survival follow-up: All subjects will be assessed for survival every 12 weeks (± 1 week) from the last trial visit until death or end of the trial.

Amendment 4 (applicable only to sites in the USA, Argentina, Australia, Israel, and Turkey)

(not included in this document)

Amendment 5

This is a global amendment, effective 26 July 2017.

Rationale

The purpose of this protocol amendment is to:

- Clarify that the mycophenolate regimen must be the same stable dose for at least 2 month prior to entering the trial.
- Extend the possible duration of the Screening Period to 6 weeks (42 days), extending the possible total duration of the trial to 122 weeks.
- Allow for changes in mycophenolate background therapy in cases of worsening of ILD on HRCT that are considered significant by the Investigator.
- Remove the assessment of TLC.
- Reduce the time window restrictions on the use of immunomodulating, immunosuppressive, or disease-modifying agents from 6 months to 2 months (or 5 months for cyclophosphamide).
- Specify that a ratio of FVC % predicted to DCLO % predicted of ≥ 1.8 is acceptable if right heart catheterization within 3 months of Screening revealed no pulmonary hypertension.
- Add an exclusion criterion excluding subjects with severe gastrointestinal disease requiring parenteral nutrition.
- Add subgroup analysis and adjustment of the mixed-effects model by duration of prior mycophenolate use at baseline (< 6 months versus ≥ 6 months).
- Clarify the source of instructions in the absence of a manual of procedures.
- Clarify procedures for IMP administration in the event of out-of-window visits.
- CCI [redacted]
- Specify that randomization will be stratified by duration of mycophenolate use at baseline (< 6 months and ≥ 6 months), in addition to baseline FVC % predicted (< 70% versus ≥ 70%).
- Permit the use of stable doses of hydroxychloroquine and chloroquine administration for at least 4 weeks prior to the Screening Period.
- Specify procedures for unblinding in the review of interim analysis results and in PK analyses.
- Remove the requirements of repeating HRCT if completed within 2 months of the re-screening visit or any TB tests if completed within 3 months of the re-screening visit.
- Clarify the measurement of bicarbonate as an estimator of total carbon dioxide in clinical chemistry assessments.
- Specify the plans for blinded sample size review after at least 50% of subjects complete their first year of treatment.

- Clarify the description of protocol deviations as clinically important, rather than major.

The changes to be made to the clinical trial protocol and the rationale for the key scientific changes are described below.

Major Scientific Changes

Removal of TLC endpoint and assessment: Other secondary efficacy endpoints are considered to sufficiently address the effect of abituzumab on pulmonary function, including assessment of FCV % and DLCO %. Eliminating TLC assessment removes the requirement of performing body plethsmography testing, affording a lower burden on subjects and trial site staff.

Review of sample size: A blinded sample size review is now planned after at least 50% of the subjects complete their first year on treatment. This review will either lead to an increase in the total sample size or to a continuation of the trial with the original sample size. Bias will be adjusted for, and if the adjusted standard deviation is more than 10% larger than the hypothesized standard deviation, then the sample size may be increased by up to 40 subjects.

Administrative and Editorial Changes

The Schedule of Assessments was updated as follows:

- Extended the possible duration of the Screening Period to 6 weeks (42 days).
- CCI [redacted].
- Removed the assessment of TLC.
- Clarified the schedule for rich PK sampling on Days 3, 5, 15, and 22.

The Sponsor's Medical Responsible contact was changed from PPD to PPD. The date and version number of the protocol were changed throughout and minor typographical errors were corrected. Minor editorial revisions were made to enhance reader understanding.

List of Changes

Changes to the clinical trial protocol text are presented in the table below. Additions and amended text are shown in bold. If the original clinical trial protocol text was already bold, changes are shown in bold and underlined; deletions are marked using strike-through.

Comparison with Clinical Trial Protocol Version 4.0, 14 September 2016 (Amendment No. 3)

Change	Section	Page	Previous Wording	New Wording
Change in Sponsor's Responsible Medical	Title Page	1	Medical Responsible: PPD EMD Serono Research & Development Institute, Inc. 45A Middlesex Turnpike Billerica, MA, 01821 USA Telephone number: PPD Fax number: PPD	Medical Responsible: PPD EMD Serono Research & Development Institute, Inc. 45A Middlesex Turnpike Billerica, MA, 01821 USA Telephone number: PPD PPD Fax number: PPD
To clarify that the mycophenolate regimen must be the same stable dose for at least 2 month prior to the Screening Visit.	Synopsis, Methodology, first paragraph	12	Subjects must be currently treated with mycophenolate for at least 6 months and at a stable dose (1.5 to 3 g/day of mycophenolate mofetil [MMF] or 1080 to 2160 mg/day of sodium mycophenolate [MPS]) for at least 3 months.	Subjects must be currently treated with ~~mycophenolate for at least 6 months and at a stable dose (1.5 to 3 g/day of mycophenolate mofetil [MMF] or 1080 to 2160 mg/day of sodium mycophenolate [MPS]) for at least 3 months~~ **the same mycophenolate regimen (stable dose) in a range of 1.5 to 3 g/day of mycophenolate mofetil (MMF) or 1080 to 2160 mg/day of sodium mycophenolate (MPS) for at least 2 months prior to the Screening Visit and continued through Day 1 of the Treatment Period**.
To extend the possible duration of the Screening Period.	Synopsis, Methodology, third paragraph	12	The trial is composed of a Screening Period, a Double-blind Treatment Period, a Safety Follow up Period, and Survival Follow-up as follows: • Screening Period: duration of up to 4 weeks; however, subjects should have the Day 1 visit as soon as possible after eligibility for the trial has been confirmed.	The trial is composed of a Screening Period, a Double-blind Treatment Period, a Safety Follow up Period, and Survival Follow-up as follows: • Screening Period: duration of up to ~~4~~ **6** weeks; however, subjects should have the Day 1 visit as soon as possible after eligibility for the trial has been confirmed.
To clarify that the use of nonbiologic immunosuppressants would require discontinuation of mycophenolate treatment.	Synopsis, Methodology, sixth paragraph 5.1, Overall Trial Design and Plan, sixth paragraph 6.5.5, Management of Specific Adverse Events or Adverse	13, 31, 50	If an immunosuppressant (such as cyclophosphamide [oral or intravenous]) is initiated, then mycophenolate must be discontinued.	If ~~an~~ **a nonbiologic** immunosuppressant (such as cyclophosphamide [oral or intravenous]) is initiated, then mycophenolate must be discontinued.

Change	Section	Page	Previous Wording	New Wording
	Drug Reactions, third paragraph, second bullet			
To allow for changes in background therapy in cases of worsening ILD on HRCT that are considered by the Investigator.	Synopsis, Methodology, second-to-last paragraph	14	New onset or worsening of manifestations of scleroderma that are not captured by the pulmonary function tests, modified Rodnan skin score (mRSS), or digital ulcer count, should be reported as AEs. During the conduct of the trial, an Independent Data Monitoring Committee (IDMC) will monitor safety data on a regular basis (to be specified in the IDMC charter). […]	New onset or worsening of manifestations of scleroderma that are not captured by the pulmonary function tests, modified Rodnan skin score (mRSS), or digital ulcer count, should be reported as AEs. **If the ILD on HRCT worsens significantly according to the Investigator, then subjects can have the mycophenolate treatment increased to the protocol-specified maximal dose (ie, 3 g/day MMF or 2160 mg/day MPS).** During the conduct of the trial, an Independent Data Monitoring Committee (IDMC) will monitor safety data on a regular basis (to be specified in the IDMC charter). […]
To remove assessment of TLC.	Synopsis, Secondary Efficacy Endpoints Section 8.3.2	15, 66	[…] • Absolute change from baseline in FVC % predicted up to Week 104; • Absolute change from baseline in total lung capacity (TLC) % predicted up to Week 104; • Absolute change from baseline in DLCO % predicted up to Week 104; […]	[…] • Absolute change from baseline in FVC % predicted up to Week 104; ~~• Absolute change from baseline in total lung capacity (TLC) % predicted up to Week 104;~~ • Absolute change from baseline in DLCO % predicted up to Week 104; […]
To clarify that the mycophenolate regimen must be the same stable dose for at least 2 month prior to entering the trial.	Synopsis, Diagnosis and Key Inclusion and Exclusion Criteria, first paragraph	17	Male or female subjects between 18 and 75 years of age who provide written consent and fulfill the 2013 American College of Rheumatology/European League Against Rheumatism criteria for classification of SSc, have been taking mycophenolate for at least 6 months with a stable dose (1.5 to 3 g/day of MMF or 1080 to 2160 mg/day of MPS) for at least 3 months, have at least 5% fibrosis of the lung on HRCT according to central reading, have a disease duration of < 7 years from the first non-Raynaud's symptom, DLCO ≥ 30% predicted, FVC 40% to 85% predicted, ratio of FVC to DLCO % predicted < 1.8, and agree to use a highly effective method of	Male or female subjects between 18 and 75 years of age who provide written consent and fulfill the 2013 American College of Rheumatology/European League Against Rheumatism criteria for classification of SSc, have been taking ~~mycophenolate for at least 6 months with a stable dose (1.5 to 3 g/day of MMF or 1080 to 2160 mg/day of MPS) for at least 3 months~~ **the same mycophenolate regimen (stable dose) in a range of 1.5 to 3 g/day of MMF or 1080 to 2160 mg/day of MPS for at least 2 months prior to the Screening Visit and continued through Day 1 of the Treatment Period**, have at least 5% fibrosis of the lung on HRCT according to

Change	Section	Page	Previous Wording	New Wording
			contraception for the duration of their participation in the trial meet the inclusion criteria.	central reading, have a disease duration of < 7 years from the first non-Raynaud's symptom, DLCO ≥ 30% predicted, FVC 40% to 85% predicted, ratio of FVC to DLCO % predicted < 1.8, and agree to use a highly effective method of contraception for the duration of their participation in the trial meet the inclusion criteria.
To reduce the time window restrictions on the use of immunomodulating, immunosuppressive, or disease-modifying agents.	Synopsis, Diagnosis and Key Inclusion and Exclusion Criteria, second paragraph	17	The use of agents other than mycophenolate (MPS or MMF) considered by the Investigator to have immunomodulating, immunosuppressive, or potential scleroderma disease-modifying properties within 6 months of screening is not allowed.	The use of agents other than mycophenolate (MPS or MMF) considered by the Investigator to have immunomodulating, immunosuppressive, or potential scleroderma disease-modifying properties within ~~6~~ **2** months of **the** ~~s~~**S**creening **Visit** is not allowed **(or 5 months prior to the Screening Visit for cyclophosphamide)**.
To extend the possible duration of the Screening Period.	Synopsis, Planned Trial and Treatment Duration Per Subject	17	The planned total duration of the trial period with study visits is up to 120 weeks for each subject, including a 4-week Screening Period, a 104-week Double-blind Treatment Period, and a 12-week Safety Follow-up Period.	The planned total duration of the trial period with study visits is up to ~~120~~ **122** weeks for each subject, including a ~~4-week~~ **6-week** Screening Period, a 104-week Double-blind Treatment Period, and a 12-week Safety Follow-up Period.
	Section 5.1, second paragraph	30	The planned total duration of the trial is up to 120 weeks […]: • Screening Period: duration of up to 4 weeks […].	The planned total duration of the trial is up to ~~120~~ **122** weeks […]: • Screening Period: duration of up to ~~4~~ **6** weeks […].
To specify adjustment of the mixed-effects model by duration of prior mycophenolate use at baseline.	Synopsis, Statistical Analysis, last paragraph Section 8.5.2, first paragraph	18, 70	The model will include random coefficients for intercept and time, fixed-effect terms for treatment and time, treatment-by-time as the interaction term, and adjusting for baseline FVC, age, sex, and height.	The model will include random coefficients for intercept and time, fixed-effect terms for treatment and time, treatment-by-time as the interaction term, and adjusting for baseline FVC, **duration of prior mycophenolate use at baseline,** age, sex, and height.
To extend the possible duration of the Screening Period. To clarify the schedule of rich PK sampling. CCI [redacted]	Schedules of Assessments	20-24	Refer to Amendment 5 - Tables 1 and 2, below.	Refer to Amendment 5 - Tables 1 and 2, below.

Change	Section	Page	Previous Wording	New Wording
CCI To remove TLC-related assessments.				
To clarify the source of instructions in the absence of a manual of procedures.	Section 2, second-to-last paragraph	25	Details of structures and associated procedures will be defined in a separate Manual of Operations, which will be prepared under the supervision of the clinical trial leader.	Details of structures and associated procedures will be defined in ~~a separate Manual of Operations, which will be prepared under the supervision of the clinical trial leader~~ **the instructions and/or flow charts provided by each of the third-party vendors participating in the EMR200017-014 trial**.
To clarify that the mycophenolate regimen must be the same stable dose for at least 2 month prior to entering the trial.	Section 5.1, first paragraph	30	Subjects must have had mycophenolate treatment for at least 6 months and remained at a stable dose (1.5 to 3 g/day of mycophenolate mofetil [MMF] or 1080 to 2160 mg/day of sodium mycophenolate [MPS]) for at least 3 months.	Subjects must have ~~had mycophenolate treatment for at least 6 months and remained at a stable dose (1.5 to 3 g/day of mycophenolate mofetil [MMF] or 1080 to 2160 mg/day of sodium mycophenolate [MPS]) for at least 3 months~~ **received the same mycophenolate treatment (ie, stable dose) in a range of 1.5 to 3 g/day of mycophenolate mofetil (MMF) or 1080 to 2160 mg/day of sodium mycophenolate (MPS) for at least 2 months prior to the Screening Visit and continued through Day 1 of the Treatment Period**.
To remove assessment of TLC.	Section 5.1, 11th paragraph	31	During the Double-blind Treatment Period, efficacy assessments will include evaluations of pulmonary function (forced vital capacity [FVC], total lung capacity [TLC], DLCO), HRCT, and PRO questionnaires.	During the Double-blind Treatment Period, efficacy assessments will include evaluations of pulmonary function (forced vital capacity [FVC]~~, total lung capacity [TLC],~~ **and** DLCO), HRCT, and PRO questionnaires.
To reduce the time window restrictions on the use of immunomodulating, immunosuppressive, or disease-modifying agents.	Section 5.2.3, last paragraph	34	Immunosuppressant and other potentially disease-modifying treatment use within 6 months of screening is likewise excluded in order to decrease confounding trial results.	Immunosuppressant and other potentially disease-modifying treatment use within ~~6~~ **2** months of **the ~~s~~Screening Visit (or cyclophosphamide use within 5 months of the Screening Visit)** is likewise excluded in order to decrease confounding trial results.
To clarify the source of instructions in the absence of a manual of procedures.	Section 5.2.4, last paragraph	35	Detailed procedures for performing pulmonary function assessments are included in a separate manual of procedures.	Detailed procedures for performing pulmonary function assessments are included in ~~a separate manual of procedures~~**the Instructions for Use** PPD **and Procedural Manual for DLCO testing provided by** PPD .

Change	Section	Page	Previous Wording	New Wording
To align discussion with the removal of the TLC-related endpoint.	Section 5.2.5, third paragraph	35	Total lung capacity as an additional lung function measurement will be included as a secondary endpoint. Forced vital capacity will also be assessed using categorical measures to define potential responders.	~~Total lung capacity as an additional lung function measurement will be included as a secondary endpoint.~~ Forced vital capacity will also be assessed using categorical measures to define potential responders.
To specify that a ratio of FVC % predicted to DCLO % predicted of ≥ 1.8 is acceptable if right heart catheterization within 3 months of Screening revealed no pulmonary hypertension, and to clarify the procedure for rounding FVC % predicted values.	Section 5.3.1	39	4. According to central readings: DLCO ≥ 30% predicted, FVC 40% to 85% predicted, and ratio of FVC % predicted to DLCO % predicted < 1.8. If these criteria are met, then HRCT of lungs will be performed, and must show at least 5% fibrosis for subjects to be eligible.	4. According to central readings: DLCO ≥ 30% predicted, FVC 40% to 85% predicted[1], and ratio of FVC % predicted to DLCO % predicted < 1.8. **A ratio of FVC % predicted to DLCO % predicted ≥ 1.8 is acceptable if right heart catheterization within 3 months of Screening revealed no pulmonary hypertension.** If these criteria are met, then HRCT of lungs will be performed, and must show at least 5% fibrosis for subjects to be eligible. [1] **The FVC % predicted that is reported by central reading will be rounded to the nearest whole number. If the number that follows the decimal point is ≤ 4, the FVC % predicted will be rounded down to the next whole number; if it is ≥ 5, the FVC % predicted will be rounded up to the next whole number.**
To clarify that the mycophenolate regimen must be the same stable dose for at least 2 month prior to entering the trial.	Section 5.3.1	39	5. Use of mycophenolate for at least 6 months before the Screening Visit. The dose must be stable for at least 3 months prior to screening and be in the range as follows: MMF 1.5 to 3 g/day, MPS 1080 to 2160 mg/day.	5. Use of ~~mycophenolate for at least 6 months before the Screening Visit. The dose must be stable for at least 3 months prior to screening and be in the range as follows: MMF 1.5 to 3 g/day, MPS 1080 to 2160 mg/day~~**the same mycophenolate regimen (ie, stable dose) in a range of 1.5 to 3 g/day of MMF or 1080 to 2160 mg/day or MPS, for at least 2 months prior to the Screening Visit and continued through Day 1 of the Treatment Period**.
To clarify the window for detection of pulmonary hypertension using right heart catheterization prior to the Screening Visit.	Section 5.3.2	41	7. Pulmonary hypertension that fulfills at least one of the following: […] • At screening, N-terminal prohormone brain natriuretic peptide (NT pro-BNP) > 3× the upper limit of normal (ULN), unless, for example, right heart catheterization performed within 2 months did not reveal pulmonary hypertension.	7. Pulmonary hypertension that fulfills at least one of the following: […] • At screening, N-terminal prohormone brain natriuretic peptide (NT pro-BNP) > 3× the upper limit of normal (ULN), unless, for example, right heart catheterization performed within ~~2~~ **3** months **of the Screening Visit** did not reveal pulmonary

Change	Section	Page	Previous Wording	New Wording
				hypertension.
To reduce the time window restrictions on the use of immunomodulating, immunosuppressive, or disease-modifying agents, with the exception of cyclophosphamide.	Section 5.3.2	42	17. Use of agents other than mycophenolate (MPS or MMF) considered by the Investigator to have immunomodulating, immunosuppressive, or potential scleroderma disease-modifying properties within 6-months of screening. Examples of these agents include, but are not limited to, pirfenidone, nintedanib, cyclophosphamide, methotrexate, azathioprine, leflunomide, calcineurin inhibitors, D-penicillamine, Potaba, and AIMSPRO. Hydroxychloroquine or chloroquine are permitted if dose has been stable for at least 4 weeks before screening.	17. Use of agents other than mycophenolate (MPS or MMF) considered by the Investigator to have immunomodulating, immunosuppressive, or potential scleroderma disease-modifying properties within ~~6~~ **2** months of **the** ~~s~~**S**creening **Visit**. Examples of these agents include, but are not limited to, pirfenidone, nintedanib, ~~cyclophosphamide,~~ methotrexate, azathioprine, leflunomide, calcineurin inhibitors, D-penicillamine, Potaba, and AIMSPRO. **The use of cyclophosphamide within 5 months of the Screening Visit is not permitted.** Hydroxychloroquine or chloroquine are permitted if dose has been stable for at least 4 weeks before **the** ~~s~~**S**creening **Visit**.
To exclude subjects with a history of anti-CD20 B-cell depleting therapy within 6 months of the Screening Visit.	Section 5.3.2	42	20. History of anti-CD20 B-cell depleting therapy, eg, rituximab or ocrelizumab.	20. History of anti-CD20 B-cell depleting therapy, eg, rituximab or ocrelizumab**, within 6 months prior to the Screening Visit**.
To clarify exclusion of subjects with a history of lung resection.	Section 5.3.2	43	29. Major surgery requiring hospitalization within 4 weeks prior to the Screening Visit and any planned major surgery for the duration of the trial. Subjects with lung resection.	29. Major surgery requiring hospitalization within 4 weeks prior to the Screening Visit and any planned major surgery for the duration of the trial. Subjects with **a history of** lung resection.
To exclude subjects with severe gastrointestinal disease requiring parenteral nutrition.	Section 5.3.2	43	30. Have a history of a major organ transplant (eg, heart, lung, kidney, or liver) or hematopoietic stem cell/marrow transplant or are due to receive transplantation.	30. Have a history of a major organ transplant (eg, heart, lung, kidney, or liver) or hematopoietic stem cell/marrow transplant or are due to receive transplantation. **31. Severe gastrointestinal disease requiring parenteral nutrition.**
To clarify procedures for IMP administration in the event of out-of-window visits.	Section 6.2, last paragraph	46	In the Double-blind Treatment Period, subjects will be randomized in a 2:2:1 ratio to receive one of the following treatments: abituzumab 1500 mg, placebo, or abituzumab 500 mg, respectively. Treatment will be given as an intravenous infusion over approximately 1 hour every 4 weeks. The infusion time should not be less than 1 hour. Close	In the Double-blind Treatment Period, subjects will be randomized in a 2:2:1 ratio to receive one of the following treatments: abituzumab 1500 mg, placebo, or abituzumab 500 mg, respectively. Treatment will be given as an intravenous infusion over approximately 1 hour every 4 weeks. The infusion time should not be less than 1 hour. Close

Change	Section	Page	Previous Wording	New Wording
			observation of the subject is recommended for a period of at least 1 hour after administration of IMP. The last IMP/placebo administration will be at the Week 100 visit.	observation of the subject is recommended for a period of at least 1 hour after administration of IMP. The last IMP/placebo administration will be at the Week 100 visit. **If administration of IMP or placebo cannot be performed within the specified protocol visit window, the decision to administer IMP or placebo outside of the window will be determined on a case-by-case basis after a discussion with the Medical Monitor and the Sponsor's Medical Director.**
To specify that stratification will occur by duration of mycophenolate use at baseline.	Section 6.3, first paragraph	46	After completion of all screening evaluations, all eligible subjects will be randomly allocated in a 2:2:1 randomization ratio to 1 of the 3 treatment groups: abituzumab 1500 mg, placebo, or abituzumab 500 mg, respectively. Randomization in permuted blocks will be conducted by a central interactive voice/web response system (IVRS/IWRS) provider. Randomization will be stratified by baseline FVC % predicted (< 70% versus ≥ 70%).	After completion of all screening evaluations, all eligible subjects will be randomly allocated in a 2:2:1 randomization ratio to 1 of the 3 treatment groups: abituzumab 1500 mg, placebo, or abituzumab 500 mg, respectively. Randomization in permuted blocks will be conducted by a central interactive voice/web response system (IVRS/IWRS) provider. Randomization will be stratified by baseline FVC % predicted (< 70% versus ≥ 70%) **and by duration of mycophenolate use at baseline (< 6 months versus ≥ 6 months)**.
To permit the use of stable doses of hydroxychloroquine and chloroquine administration for at least 4 weeks prior to the Screening Visit.	Section 6.5.1, fourth paragraph	47	Dosing of mycophenolate must be kept stable during the Double-blind Treatment Period, unless a change in dose is warranted by clinically meaningful disease progression (see Section 6.5.5).	Dosing of mycophenolate must be kept stable during the Double-blind Treatment Period, unless a change in dose is warranted by clinically meaningful disease progression (see Section 6.5.5). **Hydroxychloroquine or chloroquine are permitted if dose has been stable for at least 4 weeks prior to the Screening Visit.**
To clarify restrictions on the use of immunomodulating, immunosuppressive, or disease-modifying agents, including cyclophosphamide.	Section 6.5.2, second paragraph	48	The use of agents other than mycophenolate (MPS or MMF) considered by the Investigator to have immunomodulating, immunosuppressive, or potential scleroderma disease-modifying properties within 6 months of screening is not permitted.	The use of agents other than mycophenolate (MPS or MMF) considered by the Investigator to have immunomodulating, immunosuppressive, or potential scleroderma disease-modifying properties within ~~6~~ **2** months of **the** ~~s~~**S**creening **Visit** is not permitted. **The use of cyclophosphamide within 5 months of the Screening Visit is not permitted.**
To allow for changes in background	Section 6.5.5, last paragraph	50	If a subject discontinues IMP, then the subject should complete the early termination visit and then the	If a subject discontinues IMP, then the subject should complete the early termination visit and then the

Change	Section	Page	Previous Wording	New Wording
therapy in cases of worsening ILD on HRCT that are considered significant by the Investigator.			remaining scheduled visits (refer to Table 1 and Table 2). All subjects will be followed up by the site for survival from the last visit on trial until death or end of the trial. New onset or worsening of manifestations of scleroderma that are not captured by the pulmonary function tests, mRSS, or digital ulcer score, should be reported as AEs. On the eCRF AE page, such events should be marked as 'yes' in response to the question "Is this a manifestation of worsening scleroderma?"	remaining scheduled visits (refer to Table 1 and Table 2). All subjects will be followed up by the site for survival from the last visit on trial until death or end of the trial. New onset or worsening of manifestations of scleroderma that are not captured by the pulmonary function tests, mRSS, or digital ulcer score, should be reported as AEs. On the eCRF AE page, such events should be marked as 'yes' in response to the question "Is this a manifestation of worsening scleroderma?". **If the ILD on HRCT worsens significantly according to the Investigator, then subjects can have the mycophenolate treatment increased to the protocol-specified maximal dose (i.e., 3 g/day MMF or 2160 mg/day MPS).**
To specify procedures for unblinded review of interim analysis results.	Section 6.10, fifth paragraph	53	An independent statistical center will support the IDMC for safety analysis and the interim futility analysis.	An independent statistical center will support the IDMC for safety analysis and the interim futility analysis. **A team from the Sponsor, independent of the CRO trial team, will be tasked with review of the unblinded interim analysis results. Details will be provided in the Firewall Charter.**
To clarify unblinding procedures for PK analyses.	Section 6.10, sixth paragraph	53	The primary analysis will be performed by the Sponsor/CRO staff while the trial is ongoing for subjects who are still under trial treatment during the second year. To ensure the integrity of the trial conduct, results of primary analysis will be generated on the aggregate group level and reviewed by a restricted group to limit initial dissemination. The access of individual treatment information will be controlled so as not to impact the trial conduct. The sites and subjects remain blinded until the end of the trial. It is acknowledged that in the case of safety events, certain subject treatment information may be unintentionally revealed in the aggregate output of the primary analysis.	The primary analysis will be performed by the Sponsor/CRO staff while the trial is ongoing for subjects who are still under trial treatment during the second year. To ensure the integrity of the trial conduct, results of primary analysis will be generated on the aggregate group level and reviewed by a restricted group to limit initial dissemination. The access of individual treatment information will be controlled so as not to impact the trial conduct. The sites and subjects remain blinded until the end of the trial. **The bioanalytical laboratory(ies) responsible for the analysis of the PK samples will be allowed to be unblinded to treatment so as not to analyze the samples from the placebo-treated subjects. The subject identifiers will be masked from any results of the PK analyses transferred to the**

Change	Section	Page	Previous Wording	New Wording
				Sponsor before the final database lock. It is acknowledged that in the case of safety events, certain subject treatment information may be unintentionally revealed in the aggregate output of the primary analysis.
To extend the possible duration of the Screening Period.	Section 7.1.1, first paragraph	54	The subject's eligibility will be assessed at a Screening Visit that will occur within 28 days prior to Day 1.	The subject's eligibility will be assessed at a Screening Visit that will occur within ~~28~~ **42** days prior to Day 1.
To remove the requirement of repeating HRCT or QuantiFERON-TB tests during re-screening if completed within 2 or 3 months, respectively, of the re-screening visit.	Section 7.1.1, second paragraph	54	Re-screening is not encouraged. However, on a case-by-case basis with permission of the Medical Monitor and the Sponsor's Medical Director, a subject who has not met all of the eligibility criteria within the original screening period may be permitted to be re-screened one time. Each subject must be re-consented before re-screening occurs. A new subject number will be assigned and all screening assessments have to be repeated.	Re-screening is not encouraged. However, on a case-by-case basis with permission of the Medical Monitor and the Sponsor's Medical Director, a subject who has not met all of the eligibility criteria within the original screening period may be permitted to be re- screened one time. **An HRCT would not need to be repeated if completed within 2 months of the re-screening visit. Any TB test, including negative TB skin test with purified protein derivative, QuantiFERON-TB, or T-SPOT, would not need to be repeated if completed within 3 months of the re-screening visit.** Each subject must be re-consented before re-screening occurs. A new subject number will be assigned and all screening assessments have to be repeated.
To remove assessment of TLC.	Section 7.3, first and third paragraph	56	Efficacy assessments include evaluation of lung function (FVC, DLCO, and TLC) and lung abnormalities on HRCT. […] For all subjects, HRCT scans will be performed at TLC with no contrast agent administration, reconstructed every 0.6 to 2 mm, using a low-dose protocol.	Efficacy assessments include evaluation of lung function (FVC, **and** DLCO~~, and TLC~~) and lung abnormalities on HRCT. […] For all subjects, HRCT scans will be performed ~~at TLC~~ with no contrast agent administration, reconstructed every 0.6 to 2 mm, using a low-dose protocol.
To clarify the source of instructions in the absence of a manual of procedures.	Section 7.4.3, second paragraph	63	Samples will be collected, processed, and stored in accordance with the directions provided in a separate Manual of Operations.	Samples will be collected, processed, and stored in accordance with the directions provided in ~~a separate Manual of Operations~~**the** PPD **Flow Chart**.
To clarify measurement used	Section 7.4.3,	63	Total carbon dioxide	~~Total carbon dioxide~~ **Bicarbonate**

Change	Section	Page	Previous Wording	New Wording
as an estimator of total carbon dioxide.	Table 4			
To clarify the source of instructions in the absence of a manual of procedures.	Section 7.5, last paragraph	64	Instructions for the collection, storage, handling, and shipping of PK samples will provided in the Manual of Operations.	Instructions for the collection, storage, handling, and shipping of PK samples will provided in the ~~Manual of Operations~~PPD **Flow Chart**.
CCI	Section 7.5, third paragraph	64	CCI	CCI .
To clarify the source of instructions in the absence of a manual of procedures.	Section 7.6, last paragraph	65	Details about the laboratory and CCI sampling and processing procedures and transportation will be provided in the Manual of Operations.	Details about the laboratory and CCI sampling and processing procedures and transportation will be provided in the ~~Manual of Operations~~PPD **Flow Chart**.
To specify the plans for blinded sample size review.	Section 8.1, first paragraph	65	The inclusion of abituzumab 500 mg in conjunction with abituzumab 1500 mg will support abituzumab exposure-response analysis for dosing optimization.	The inclusion of abituzumab 500 mg in conjunction with abituzumab 1500 mg will support abituzumab exposure-response analysis for dosing optimization. **A blinded sample size review is planned after at least 50% of the subjects complete their first year on treatment. The review will either lead to an increase in the total sample size or to a continuation of the trial with the original sample size. Following Kieser 2003, the estimated one-sample variance will be adjusted for bias. If the adjusted standard deviation is more than 10% larger than the hypothesized standard deviation (ie, 330 mL or more), then the sample size may be increased by up to 40 subjects. Details will be provided in the Statistical Analysis Plan.**
To specify that stratification will also occur by duration of mycophenolate use at baseline.	Section 8.2, last paragraph	65	Randomization will be conducted in permuted blocks by a central IVRS/IWRS provider and stratified by baseline FVC % predicted (< 70% versus ≥ 70%).	Randomization will be conducted in permuted blocks by a central IVRS/IWRS provider and stratified by baseline FVC % predicted (< 70% versus ≥ 70%) **and by duration of mycophenolate use at baseline (< 6 months versus ≥ 6 months)**.
To clarify the description of	Section 8.4.3, first	69	The Per-Protocol (PP) Population will consist of all randomized and treated subjects who do not have	The Per-Protocol (PP) Population will consist of all randomized and treated subjects who do not have

Change	Section	Page	Previous Wording	New Wording
protocol deviations as clinically important.	paragraph		any major protocol deviations. Subjects will be analyzed according to their randomized treatment. The following are criteria for inclusion in the PP Population: • Compliance with all entry criteria; • Absence of major clinical trial protocol violations with respect to factors likely to affect the efficacy of treatment; • Adequate compliance with and sufficient exposure to IMP. The criteria will be defined in detail in the Statistical Analysis Plan and major protocol violators to be excluded from the PP Population will be identified prior the database lock for the primary analysis.	any ~~major~~ **clinically important** protocol deviations. Subjects will be analyzed according to their randomized treatment. The following are criteria for inclusion in the PP Population: • Compliance with all entry criteria; • Absence of ~~major~~ **clinically important** clinical trial protocol violations with respect to factors likely to affect the efficacy of treatment; • Adequate compliance with and sufficient exposure to IMP. The criteria will be defined in detail in the Statistical Analysis Plan**,** and ~~major~~ **clinically important** protocol violators to be excluded from the PP Population will be identified prior the database lock for the primary analysis.
To add duration of prior mycophenolate use to subgroup analysis.	Section 8.5.1, last paragraph	70	The subgroups of interest will be prespecified in the Statistical Analysis Plan, including the stratification factor, baseline FVC % predicted (< 70% versus ≥ 70%).	The subgroups of interest will be prespecified in the Statistical Analysis Plan, including the stratification factor**s of**~~,~~ baseline FVC % predicted (< 70% versus ≥ 70%)~~,~~ **and duration of prior mycophenolate use (< 6 months versus ≥ 6 months)**.
To specify adjustment of the mixed-effects model by duration of prior mycophenolate use at baseline.	Section 8.5.3, first paragraph	71	Analysis of Key Secondary Efficacy Endpoints The key secondary endpoints will be tested for abituzumab 1500 mg versus placebo, using data for subjects on trial treatment, in the following order after the primary endpoint is met. 1. The Mahler TDI at Week 52 will be analyzed using a mixed-effects model adjusting for baseline FVC% predicted and Mahler BDI. 2. The absolute change in SGRQ total score at Week 52 will be analyzed using a mixed effects model adjusting for baseline FVC% predicted and baseline SGRQ score. 3. The absolute change from baseline in mRSS at Week 52 in subjects with dcSSc at baseline will be analyzed using a mixed effects model adjusting for baseline FVC% predicted and	Analysis of Key Secondary Efficacy Endpoints The key secondary endpoints will be tested for abituzumab 1500 mg versus placebo, using data for subjects on trial treatment, in the following order after the primary endpoint is met. 1. The Mahler TDI at Week 52 will be analyzed using a mixed-effects model adjusting for baseline FVC% predicted**, duration of prior mycophenolate use at baseline,** and Mahler BDI. 2. The absolute change in SGRQ total score at Week 52 will be analyzed using a mixed effects model adjusting for baseline FVC% predicted**, duration of prior mycophenolate use at baseline,** and baseline SGRQ score. 3. The absolute change from baseline in mRSS at

Change	Section	Page	Previous Wording	New Wording
			baseline mRSS. 4. The absolute change from baseline in QLF in the region of highest severity at Week 52 will be analyzed using an ANCOVA model adjusting for baseline FVC% predicted and baseline QLF. 5. Overall survival will be analyzed using a stratified log-rank test and presented by Kaplan Meier estimates and 95% confidence interval, including the survival data available up to the analysis cut-off date. A Cox proportional hazards regression model will be used to obtain hazard ratios and 95% confidence intervals adjusting for baseline FVC% predicted. […] Analysis of Other Secondary Efficacy Endpoints […] A Cox proportional hazards regression model will be used to obtain hazard ratios and 95% confidence intervals adjusting for baseline FVC % predicted.	Week 52 in subjects with dcSSc at baseline will be analyzed using a mixed effects model adjusting for baseline FVC% predicted**, duration of prior mycophenolate use at baseline,** and baseline mRSS. 4. The absolute change from baseline in QLF in the region of highest severity at Week 52 will be analyzed using an ANCOVA model adjusting for baseline FVC% predicted**, duration of prior mycophenolate use at baseline,** and baseline QLF. 5. Overall survival will be analyzed using a stratified log-rank test and presented by Kaplan Meier estimates and 95% confidence interval, including the survival data available up to the analysis cut-off date. A Cox proportional hazards regression model will be used to obtain hazard ratios and 95% confidence intervals adjusting for baseline FVC% predicted **and duration of prior mycophenolate use at baseline**. […] Analysis of Other Secondary Efficacy Endpoints […] A Cox proportional hazards regression model will be used to obtain hazard ratios and 95% confidence intervals adjusting for baseline FVC % predicted **and duration of prior mycophenolate use at baseline**.
To clarify the source of instructions in the absence of a manual of procedures.	Section 10.1, first paragraph	76	Refer to the Manual of Operations for eCRF handling guidelines.	Refer to the ~~Manual of Operations~~ **eCRF Completion Guidelines** for eCRF handling ~~guidelines~~ **instructions**.
Change in Sponsor's Protocol Lead	Signature Page – Protocol Lead	83	PPD EMD Serono Research & Development Institute, Inc. 45A Middlesex Turnpike Billerica, MA, 01821 USA Telephone number: PPD Fax number: PPD PPD	PPD PPD EMD Serono Research & Development Institute, Inc. 45A Middlesex Turnpike Billerica, MA, 01821 USA Telephone number: PPD Fax number: PPD

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				PPD
Change in Sponsor's PPD	Sponsor Responsible Persons	87	PPD EMD Serono Research and Development Institute, Inc. 45A Middlesex Turnpike Billerica, MA 01821 USA PPD PPD PPD	PPD PPD EMD Serono Research and Development Institute, Inc. 45A Middlesex Turnpike Billerica, MA 01821 USA PPD PPD
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Amendment 5 – Table 1 Schedule of Assessments – Screening through Week 52

Trial Period	Screening	Weeks During Double-blind Treatment Period (Visit Window ±3 days)																	
Week		0			2	3	4	8	12	16	20	24	28	32	36	40	44	48	52
Trial Day	~~-28~~ 42 to -1	1	3	5	15	22	29	57	85	113	141	169	197	225	253	281	309	337	365
Informed consent	X																		
Inclusion/exclusion criteria	X	X[a]																	
CCI																			
Pharmacokinetic informed consent (Rich PK sampling only)	X																		
Demographic data	X																		
SSc-ILD and other medical history, medications, surgery/procedures	X																		
HRCT	X											X							X
12-lead ECG (locally read)	X											X							X
Tuberculosis assessment	X																		
Serum virology (HIV, HCV, HBV)	X																		
Serum pregnancy test [c]	X																		
PT, aPTT, TSH, and NT pro-BNP	X																		
Urine pregnancy test [c,d]		X					X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X			X[e]		X	X[e]	X[e]	X[e]	X[e]	X	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X

Trial Period	**Screening**	**Weeks During Double-blind Treatment Period (Visit Window ±3 days)**																	
Week		**0**			**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**
Trial Day	**~~-28~~ 42 to -1**	**1**	**3**	**5**	**15**	**22**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**
Vital signs, weight, height [f]	X	X			X		X	X	X	X	X	X	X	X	X	X	X	X	X
Mahler BDI/TDI and SGRQ [g]		X							X			X			X				X
Patient's Global Assessment, Leicester Cough Index, SHAQ, EQ-5D, and Physician's Global Assessment [g]		X										X							X
Randomization		X																	
IMP administration		X					X	X	X	X	X	X	X	X	X	X	X	X	X
PK sampling [h]		X					X	X		X									
Rich PK sampling [i]			**X**	**X**	X	**X**													
Routine hematology, clinical chemistry, urinalysis dipstick [j]	X	X			X		X	X	X	X	X	X		X	X	X		X	X
Pulmonary function tests (FVC, ~~TLC) with~~ DLCO**)** [k]	X	X							X			X			X				X
mRSS		X							X			X			X				X
Digital ulcer counts [l]		X							X			X			X				X
Serum for ADA		X										X							X
Sample for autoantibodies		X										X							X
CCI [redacted]																			

Trial Period	**Screening**	**Weeks During Double-blind Treatment Period (Visit Window ±3 days)**																	
Week		**0**			**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**
Trial Day	**~~28~~ 42 to -1**	**1**	**3**	**5**	**15**	**22**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**
CCI																			
Concomitant medications/procedures	X	X			X		X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events [no]	X	X			X		X	X	X	X	X	X	X	X	X	X	X	X	X

ADA = antidrug antibodies; AE = adverse event; aPTT = activated partial thromboplastin time; BDI = Baseline Dyspnea Index; DLCO = diffusion capacity of the lung for carbon monoxide; ECG = electrocardiogram; FVC = forced vital capacity; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HRCT = high-resolution computed tomography; IMP = investigational medicinal product; mRSS = modified Rodnan skin score; PK = pharmacokinetic; PT = prothrombin time; SGRQ = St. George Respiratory Questionnaire; SHAQ = Scleroderma Health Assessment Questionnaire; SSc-ILC = systemic sclerosis-associated interstitial lung disease; TDI = Transition Dyspnea Index; ~~TLC = total lung capacity;~~ TSH = thyroid-stimulating hormone; VAS = visual analog scale.

a Subject eligibility (based on screening assessments of the inclusion and exclusion criteria) must be checked again on Day 1 prior to randomization.

CCI

c For women of childbearing potential or who are postmenopausal for less than 2 years. At Day 1, if the urine test is negative, the subject can be randomized and receive the first dose of IMP.

d Performed locally per local constraints and regulations.

e Focused physical examination only, according to standard of care.

f Vital signs include 10-minute seated arterial blood pressure, pulse rate, and body temperature. Height will be measured at Day 1 only. Weight will be measured at Weeks 0, 24, 52, 76, and 104. Body weight will be measured with a balance beam scale, if possible.

g Questionnaires should be completed before any other procedures are performed. Questionnaires should be performed in the following order: Patient's Global Assessment, SHAQ, Mahler BDI (at Day 1) followed by Mahler TDI at the subsequent visits, SGRQ, Leicester Cough Index, and EQ-5D. The Mahler BDI/TDI administrator must be blinded to other assessments. The Physician's Global Assessment (VAS) may be performed after other assessments at the visit are completed.

h For all subjects, samples will be collected predose and immediately after the end of IMP infusion at Weeks 0 (Day 1), 4, 8, and 16.

i For subjects who have provided informed consent for the rich PK sampling, additional samples will be collected on Days 3, 5, 15, and 22 (in addition to the pre- and postdose samples at Weeks 0, 4, 8, and 16; see footnote h).

j See Section 7.4.3 for list of routine laboratory assessments. Urine protein:creatinine ratio to be performed if dipstick urinalysis reveals at least 3+ protein. Microscopic urinalysis to be performed if blood is present.

k ~~The TLC should be performed at Weeks 0, 24, 52, 76, and 104.~~ The DLCO measurements will be corrected for hemoglobin level, and spirometry assessments will be centrally adjudicated.

l Digital ulcers are those distal to the metacarpal phalangeal joints. New or worsening digital ulcers, or at any other site on the body, will be captured as AEs.

CCI

CCI [redacted]

~~no~~ Adverse events should also be assessed for occurrence during the periods between trial visits.

Amendment 5 – Table 2 Schedule of Assessments – Week 56 through Safety Follow-up

Trial Period	**Weeks During Double-blind Treatment Period (Visit Window ±5 days)**														**Safety Follow-up Number weeks post last visit (±5 days)**		**Survival Follow-up Post Last Trial Visit**
Week	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**	**ET[a]**	**4**	**12**	**Every 12 Weeks**
Trial Day	**393**	**421**	**449**	**477**	**505**	**533**	**561**	**589**	**617**	**645**	**673**	**701**	**729**				
HRCT													X	X			
12-lead ECG (locally read)						X							X	X		X	
Urine pregnancy test [b,c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical examination	X[d]	X[d]	X[d]	X[d]	X[d]	X	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X	X	X[d]	X	
Vital signs, weight [e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Mahler TDI and SGRQ [f]			X			X			X				X	X		X	
Patient's Global Assessment, Leicester Cough Index, SHAQ, EQ-5D, and Physician's Global Assessment [f]						X							X	X			
IMP administration	X	X	X	X	X	X	X	X	X	X	X	X					
Routine hematology, clinical chemistry, urinalysis [g]		X	X	X		X		X	X	X		X	X	X	X	X	
Pulmonary function tests~~ (FVC, TLC) with~~ DLCO) [h]			X			X			X				X	X		X	
mRSS			X			X			X				X	X		X	
Digital ulcer counts [i]			X			X			X				X	X		X	
Serum for ADA						X							X	X	X	X	
Sample for autoantibodies													X	X			
CCI																	
Concomitant medications/procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Trial Period	Weeks During Double-blind Treatment Period (Visit Window ±5 days)														Safety Follow-up Number weeks post last visit (±5 days)		Survival Follow-up Post Last Trial Visit
Week	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**	**ET[a]**	**4**	**12**	**Every 12 Weeks**
Trial Day	**393**	**421**	**449**	**477**	**505**	**533**	**561**	**589**	**617**	**645**	**673**	**701**	**729**				
Adverse events [j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital status [k]																	X

ADA = antidrug antibodies; AE = adverse event; BDI = Baseline Dyspnea Index; DLCO = diffusion capacity of the lung for carbon monoxide; ECG = electrocardiogram; ET = early termination; FVC = forced vital capacity; HRCT = high resolution computed tomography; IMP = investigational medicinal product; mRSS = modified Rodnan skin score; SGRQ = St. George Respiratory Questionnaire; SHAQ = Scleroderma Health Assessment Questionnaire; TDI = Transition Dyspnea Index; ~~TLC = total lung capacity;~~ VAS = visual analog scale.

a Subjects who discontinue IMP for any reason should complete the ET visit as soon as possible, but within 2 weeks of IMP discontinuation, and then the remaining scheduled trial visits. At a minimum, the subject is expected to complete the trial visits at Weeks 12, 24, 36, 52, 64, 76, 88, and 104, as well as the Safety Follow-up period Week 12 visit. Subjects with discontinued IMP can come to the other scheduled visits during the trial period according to the Investigator's judgment. Subjects who withdraw from the treatment period would have an early termination visit followed by entrance into the Safety Follow-up Period. Subjects who withdraw from the trial (eg, withdraw consent, lost to follow up, or death; see Section 5.5.2) would not have any additional trial visits. All subjects will be followed up by the site approximately every 12 weeks for survival from the subject's last trial visit until death or the end of the trial.

b For women of childbearing potential or who are postmenopausal for less than 2 years. Positive urine pregnancy tests should be confirmed with a serum test. If the serum pregnancy test is subsequently positive, the subject will be withdrawn from IMP.

c Performed locally per local constraints and regulations.

d Focused physical examination only, according to standard of care.

e Vital signs include 10-minute seated arterial blood pressure, pulse rate, and body temperature. Weight will be measured at Weeks 0, 24, 52, 76, and 104. Body weight will be measured with a balance beam scale, if possible.

f Questionnaires should be completed before any other procedures are performed. Questionnaires should be performed in the following order: Patient's Global Assessment, SHAQ, Mahler BDI (at Day 1) followed by Mahler TDI at the subsequent visits, SGRQ, Leicester Cough Index, and EQ-5D. The Mahler BDI/TDI administrator must be blinded to other assessments. The Physician's Global Assessment (VAS) may be performed after other assessments at the visit are completed.

g See Section 7.4.3 for list of routine laboratory assessments. Urine protein:creatinine ratio to be performed if dipstick urinalysis reveals at least 3+ protein. Microscopic urinalysis to be performed if blood is present.

h ~~The TLC should be performed at Weeks 0, 24, 52, 76, and 104.~~ The DLCO measurements will be corrected for hemoglobin level, and spirometry assessments will be centrally adjudicated.

l Digital ulcers are those distal to the metacarpal phalangeal joints. New or worsening digital ulcers, or at any other site on the body, will be captured as AEs.

j Adverse events should also be assessed for occurrence during the periods between trial visits.

k Survival follow-up: All subjects will be assessed for survival every 12 weeks (± 1 week) from the last trial visit until death or end of the trial.