CLINICAL TRIAL PROTOCOL

	Document Number:	**c03014699-05**
EudraCT No.:	2015-000392-28	
BI Trial No.:	1199.214 (SENSCIS™)	
BI Investigational Product(s):	Nintedanib	
Title:	A double blind, randomised, placebo-controlled trial evaluating efficacy and safety of oral nintedanib treatment for at least 52 weeks in patients with 'Systemic Sclerosis associated Interstitial Lung Disease'(SSc-ILD).	
Brief Title:	A trial to compare nintedanib with placebo for patients with scleroderma related lung fibrosis.	
Clinical Phase:	III	
Trial Clinical Monitor:	[redacted] Boehringer-Ingelheim Pharma GmbH & Co. KG Birkendorfer Strasse 65, 88397 Biberach an der Riss (Germany) Phone: [redacted] Fax: [redacted]	
Coordinating Investigators:	[redacted] Division of Rheumatology, University Hospital Zurich Gloriastrasse 25, 8091 Zurich (Switzerland) Phone [redacted] Fax [redacted] and [redacted] MD, MSCR Cleveland Clinic Lerner College of Medicine 9500 Euclid Avenue, Desk A90, Cleveland, OH 44195 (USA) Phone [redacted] Fax [redacted]	
Status:	**Final Protocol (Revised Protocol (based on Global Amendment No. 3))**	
Version and Date:	**Version: 4.0**	**Date: 15 Feb 2018**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		**Boehringer Ingelheim**	
Name of finished product:			
Name of active ingredient:		Nintedanib	
Protocol date: 22 Jul 2015	**Trial number:** 1199.214		**Revision date:** 15 Feb 2018

Title of trial:	A double blind, randomised, placebo-controlled trial evaluating efficacy and safety of oral nintedanib treatment for at least 52 weeks in patients with 'Systemic Sclerosis associated Interstitial Lung Disease'(SSc-ILD).
Coordinating Investigators:	[redacted] Division of Rheumatology, University Hospital Zurich Gloriastrasse 25, 8091 Zurich (Switzerland) Phone [redacted] Fax [redacted] MD, MSCR Cleveland Clinic Lerner College of Medicine 9500 Euclid Avenue, Desk A90, Cleveland, OH 44195 (USA) Phone [redacted] Fax
Trial site(s):	Multi-centre trial conducted in approximately 20 countries
Clinical phase:	III
Objective(s):	To investigate the efficacy and safety of 150 mg bid nintedanib in patients with Systemic Sclerosis associated Interstitial Lung Disease.
Methodology:	Parallel design, double blind, randomised, placebo-controlled trial with primary efficacy evaluation at week 52 and placebo-controlled treatment until last patient out (up to a maximum of 100 weeks).
No. of patients:	
total entered:	520 randomised
each treatment:	Nintedanib: 260 Placebo: 260

Name of company:		**Boehringer Ingelheim**	
Name of finished product:			
Name of active ingredient:		Nintedanib	
Protocol date: 22 Jul 2015	**Trial number:** 1199.214		**Revision date:** 15 Feb 2018

Diagnosis:	Patients diagnosed with Systemic Sclerosis associated Interstitial Lung Disease based upon classification according to the most recent ACR / EULAR criteria and HRCT (within previous 12 months), onset of Systemic Sclerosis (defined as first non-Raynaud symptom) not more than 5 years ago.
Main criteria for inclusion:	≥18 years; extent of fibrotic disease in the lung ≥10%; FVC ≥40% predicted; DLCO 30% to 89% predicted (corrected for Hb).
Test product(s):	Nintedanib
dose:	150 mg bid (300 mg daily) with possibility to interrupt or reduce to 100 mg bid (200 mg daily) to manage adverse events (AE).
mode of administration:	p.o.
Comparator products:	Placebo matching nintedanib
dose:	Not applicable
mode of administration:	p.o.
Duration of treatment:	52 weeks (primary endpoint) with continuation of blinded treatment to a maximum of 100 weeks.
Endpoints:	**Primary endpoint:** Annual rate of decline in FVC in mL over 52 weeks. **Key secondary endpoints (in the following order):** 1) Absolute change from baseline in the modified Rodnan Skin Score (mRSS) at week 52. 2) Absolute change from baseline in SGRQ total score at Week 52.

Name of company:		**Boehringer Ingelheim**	
Name of finished product:			
Name of active ingredient:		Nintedanib	
Protocol date: 22 Jul 2015	**Trial number:** 1199.214		**Revision date:** 15 Feb 2018

Endpoints (con´t):	**Secondary endpoint(s):** • Annual rate of decline in FVC in percent predicted over 52 weeks. • Absolute change from baseline in FVC in mL at week 52. • Relative change from baseline (%) of mRSS at week 52. • Time to all-cause mortality. • Absolute change from baseline at week 52 in CRISS index score. • Absolute change from baseline in DLCO (percent predicted) at week 52. • Absolute change from baseline at week 52 in digital ulcer net burden. • Absolute change from baseline in HAQ-DI score at week 52. • Absolute change from baseline in FACIT dyspnoea score at week 52.
Safety criteria:	Vital signs, physical examination, safety laboratory tests, 12-lead electrocardiogram, adverse events.
Statistical methods:	A random coefficient regression model (with random slopes and intercepts) for the primary endpoint and similar secondary endpoint, a Mixed Model Repeated Measures (MMRM) analysis for all other continuous secondary endpoints, and a Cox proportional hazards model as well as a Kaplan-Meier plot for the time to event endpoint.

FLOWCHART - MAIN TRIAL

Visit		**1**	**2**	**3**	**4**	**5**	**6**	**6a**	**7**	**7a**	**8**	**8a**	**9**	**Xa[18]** (9a, 10a, 11a)	**X[18]** (10, 11)	**12/ EOT**	**FU[19]**
	Screening		**Randomised Treatment Period***														**FU**
Weeks of treatment			**0**	**2**	**4**	**6**	**12**	**18**	**24**	**30**	**36**	**44**	**52**	**60 + every 16wk**	**68 + every 16wk**	**100**	**EOT + 4wk**
Day **Time window**	Before or at the latest at Visit 1	≥4d prior Visit 2	**1**	**15** **±3**	**29** **±3**	**43** **±3**	**85** **±3**	**127** **±7**	**169** **±7**	**211** **±7**	**253** **±7**	**309** **±7**	**365** **±7**	**±7**	**±7**	**701** **±7**	**+28** **+7**
Informed Consent[1]	X																
Send HRCT to central review[2]	X																
Demographics		X															
Medical history		X	X														
Adverse events, conc. therapy		X	X	X	X	X	X		X		X		X		X	X	X
In-/exclusion criteria		X	X														
Questionnaires (SGRQ, FACIT-dyspnoea, SHAQ, EQ-5D-5L, patient global VAS)[3]			X						X				X			X	
Review questionnaires for completeness			X						X				X			X	
Physical examination, vital signs		X	X	X	X	X	X		X		X		X		X	X	X
Collect/review/dispense menstruation calendar	X		X	X	X	X	X		X		X		X		X	X	X

Visit		**1**	**2**	**3**	**4**	**5**	**6**	**6a**	**7**	**7a**	**8**	**8a**	**9**	**Xa[18]** (9a, 10a, 11a)	**X[18]** (10, 11)	**12/ EOT**	**FU[19]**
	Screening		**Randomised Treatment Period***														**FU**
Weeks of treatment			**0**	**2**	**4**	**6**	**12**	**18**	**24**	**30**	**36**	**44**	**52**	**60 + every 16wk**	**68 + every 16wk**	**100**	**EOT + 4wk**
Day **Time window**	Before or at the latest at Visit 1	≥4d prior Visit 2	**1**	**15** ±3	**29** ±3	**43** ±3	**85** ±3	**127** ±7	**169** ±7	**211** ±7	**253** ±7	**309** ±7	**365** ±7	±7	±7	**701** ±7	**+28** +7
HCRU			X	X	X	X	X		X		X		X		X	X	
mRSS assessment			X				X		X		X		X		X	X	
Digital ulcer assessment			X				X		X		X		X		X	X	
Safety Laboratory (blood and urine)		X[4]	X	X	X	X	X	X[5]	X	X[5]	X	X[5]	X	X[5]	X	X	X
Pregnancy test[6]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK sample[7]					X				X								
Autoantibody assessment[8]		(X)	X						X				X				
Biomarker samples[9]			X		X				X				X				
DNA banking sample[10]			X														
SpO_2 (earlobe or forehead, resting)			X						X				X			X	
Spirometry (FVC)[11]		X	X	X	X	X	X		X		X		X		X	X	X
DLCO[11]		X	X						X				X			X	
12-lead ECG		X	X[12]						X				X			X	
Echocardiography[13]		X											X				

Visit		**1**	**2**	**3**	**4**	**5**	**6**	**6a**	**7**	**7a**	**8**	**8a**	**9**	**Xa**[18] **(9a, 10a, 11a)**	**X**[18] **(10, 11)**	**12/ EOT**	**FU**[19]
	Screening		**Randomised Treatment Period***														**FU**
Weeks of treatment			**0**	**2**	**4**	**6**	**12**	**18**	**24**	**30**	**36**	**44**	**52**	**60 + every 16wk**	**68 + every 16wk**	**100**	**EOT + 4wk**
Day **Time window**	Before or at the latest at Visit 1	≥4d prior Visit 2	**1**	**15** ±3	**29** ±3	**43** ±3	**85** ±3	**127** ±7	**169** ±7	**211** ±7	**253** ±7	**309** ±7	**365** ±7	±7	±7	**701** ±7	**+28** +7
Randomization			X														
IRT call/notification	X[14]		X		X		X		X		X		X		X	(X)	
Dispense trial medication			X		X		X		X		X		X		X		
Collect trial medication					X		X		X		X		X		X	X	
Compliance/drug accountability				X[20]	X	X[20]	X		X		X		X		X	X	
Physician global VAS			X						X				X			X	
Termination of trial medication[15]																X	
Vital status assessment[16]													X			X	
Conclude subject participation[17]																	X

Footnotes:

* In case of dose change (reduction or re-escalation) additional visits have to be included (refer to Section 6.2.4).
- In case of prematurely trial medication discontinuation, the patient completes end of treatment Visit (EOT and follow-up Visit (FU) 4 weeks later), the patient should be asked to come to future visits as planned (refer to Section 6.2.3).
- EOT assessments are the same as described for Visit 12. If EOT is performed at week 52, the Flowchart for Visit 9 is valid (i.e. Biomarker samples to be drawn).

[1] Before or at the latest at Visit 1. Informed consent (IC) needs to be signed before any procedure related to the trial is performed. All adverse events (AEs) and concomitant therapies (CTs) from the day of signing informed consent have to be recorded. The screening period (informed consent to Visit 2) must not be longer than 12 weeks.

[2] Review of high resolution computer tomography (HRCT) for extent of fibrotic disease in the lung (10% or more). Central review: a historical HRCT not older than 12 months should be sent; only if the patient does not have a HRCT within 12 months at Visit 1 but meets all other inclusion and no exclusion criteria, the HRCT can be performed for the purposes of participation in the trial (except for patients in Germany).

[3] Self-reported outcome questionnaires must always be done by the patients in a quiet place prior to any other visit procedure. Order of questionnaires: 1. SGRQ, 2. FACIT-dyspnoea, 3. SHAQ, 4. EQ-5D-5L, 5. Patient's global VAS.

[4] The safety lab of Visit 1 must be repeated if screening is longer than 6 weeks.

[5] Intermediate lab tests (a-Visit) do not necessarily need to be a site visit. Cautionary note: dependent on concomitant treatment additional safety monitoring should be considered at discretion of the investigator.

[6] ß-HCG will be performed at Visit 2 only, at central lab. Urine dipstick pregnancy tests will be provided centrally and should be performed in all women of childbearing potential every 4-6 weeks: at least at every visit and if necessary, additionally at home or at a local doctor / laboratory. If urine test is not acceptable to local authorities, a blood test can be done at a local laboratory. Women of childbearing potential will be instructed accordingly.

[7] PK samples will be taken at Visits 4 and 7 just before drug administration. Date and exact clock time of drug administration and blood sampling must be recorded on the eCRF. patients will be provided (Visits 3 and 6) with a PK card to support the record of the exact clock time of medication intake three days preceding PK sampling.

[8] anti-Topoisomerase antibodies (ATA) will be assessed at Visit 2, 7, and 9 (and at V1 if historically not available); anti-RNA polymerase III antibodies ((anti-)RNA Pol III) and anti-centromere antibodies (ACA) will be assessed at Visit 2 only.

[9] Biomarker samples will be taken just before drug administration. Date and exact clock time of drug administration and blood sampling must be recorded on the eCRF.

- Samples for Protein Biomarkers will be taken at Visits 2, 4, 7, 9, just before drug administration.
- One sample for prespecified DNA analyses will be taken at Visit 2.
- Samples for RNA expression analyses will be taken at Visits 2, 7, and 9, just before drug administration.

[10] DNA (Desoxyribo Nucleid Acid) banking sample: one blood sample will be taken from those eligible patients who signed a separate informed consent at Visit 2 (or on a subsequent visit); Participation is voluntary and is no prerequisite for participation in the trial.

[11] Order of lung function measurements: same time each visit ± 90 min, reference time at Visit 2: 1. FVC followed by patients rest; 2. DLCO.

[12] ECG will be performed (if possible prior to blood draw) at Visit 2 prior randomisation (only if abnormal at Visit 1).

[13] Echocardiography will at least be performed in patients with a history of pulmonary hypertension at screening (time window Visit 1 to Visit 2) and after 1 year (time window Visit 9 to Visit 9a).

[14] IRT needs to be notified at time point of informed consent (at the latest at Visit 1) to trigger trial medication shipments; ATA status (historical) will be entered at randomisation (Visit 2) at the latest.

[15] Termination of trial medication data needs to be collected any time trial medication is permanently discontinued.

[16] Vital status at 52 weeks and at 100 weeks or at the timepoint when patient's last full visit (i.e. EOT or V9, V10, V11, V12) would have been scheduled, whatever occurs earlier should be available for all patients. Permission to contact withdrawn patients for vital status assessment should be requested by site.

[17] Trial completion:

- At the end of the follow-up Visit for patients who have completed the trial on treatment as planned.
- After early discontinuation (end of treatment [EOT]) and follow-up Visit), if a patient refuses to attend future visits as originally planned.
- At the end of Visit 12 or at the global end of the trial for patients who discontinued trial medication early but came to future visits as planned.

[18] Same scheme should be repeated as often as needed: Visit 'X' stands for Visit 10 and Visit 11; Visit 'Xa' stands for Visits 9a, 10a, and 11a.

[19] The follow-up (FU) visit should be planned for 28 days (+7 days window) after last drug intake (end of treatment [EOT]).

[20] Compliance / drug accountability only in case of dose reduction/increase

FLOWCHART – OPTIONAL SUBSTUDIES

Substudies are optional and independent from each other (by site specialty / experience)

Visit		**1**	**2**	**3**	**4**	**5**	**6**	**6a**	**7**	**7a**	**8**	**8a**	**9**	**Xa** (9a, 10a, 11a)	**X** (10, 11)	**12/ EOT**	**FU**
	Screening		**Randomised Treatment Period**														**FU**
Weeks of treatment			**0**	**2**	**4**	**6**	**12**	**18**	**24**	**30**	**36**	**44**	**52**	**60 + every 16wk**	**68 + every 16wk**	**100**	**EOT + 4wk**
Day **Time window**	Before or at the latest at Visit 1	≥ 4d before Visit 2	**1**	**15** ±3	**29** ±3	**43** ±3	**85** ±3	**127** ±7	**169** ±7	**211** ±7	**253** ±7	**309** ±7	**365** ±7	±7	±7	**701** ±7	**+ 28** +7
SUBSTUDY Informed Consent*	X																
HRCT optional SUBSTUDY[1]		X											X				
Skin Biopsy optional SUBSTUDY[2]			X				X						X				
Nailfold capillary microscopy optional SUBSTUDY[2]			X				X		X		X		X				

Footnotes:

* Substudies are optional and independent from each other. Substudy procedures should only be performed if a patient is eligible for the main trial and has signed a separate informed consent for the respective substudy. Informed consent for substudies is to be signed before performing substudy procedures (at the latest at Visit 2). Participation in either 1 or 2 or 3 substudies is possible.

The following rules apply for substudy assessments

[1] Baseline HRCT between Visit 1 and Visit 2; post treatment HRCT earliest at Visit 9 and latest at Visit 9a. The HRCT at week 52 should be performed in patients that received trial medication at least until Visit 7. The HRCT substudy will not be performed in Germany.

[2] Skin biopsy and nailfold capillary microscopy should be performed in patients on trial medication only.

TABLE OF CONTENTS

CLINICAL TRIAL PROTOCOL **1**
TITLE PAGE **1**
CLINICAL TRIAL PROTOCOL SYNOPSIS **2**
FLOWCHART - MAIN TRIAL **5**
FLOWCHART – OPTIONAL SUBSTUDIES **9**
TABLE OF CONTENTS **10**
ABBREVIATIONS **14**
1. INTRODUCTION **18**
1.1 MEDICAL BACKGROUND **18**
1.2 DRUG PROFILE **19**
2. RATIONALE, OBJECTIVES AND BENEFIT RISK ASSESSMENT **22**
2.1 RATIONALE FOR PERFORMING THE TRIAL **22**
2.2 TRIAL OBJECTIVES **23**
2.3 BENEFIT - RISK ASSESSMENT **23**
3. DESCRIPTION OF DESIGN AND TRIAL POPULATION **26**
3.1 OVERALL TRIAL DESIGN AND PLAN **26**
3.1.1 Administrative structure of the trial **27**
3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S) **28**
3.3 SELECTION OF TRIAL POPULATION **29**
3.3.1 Main diagnosis for trial entry **29**
3.3.2 Inclusion criteria **30**
3.3.3 Exclusion criteria **30**
3.3.4 Removal of patients from therapy or assessments **33**
3.3.4.1 Removal of individual patients from therapy 33
3.3.4.2 Discontinuation of the trial by the sponsor 34
4. TREATMENTS **36**
4.1 TREATMENTS TO BE ADMINISTERED **36**
4.1.1 Identity of BI investigational product(s) **36**
4.1.2 Method of assigning patients to treatment groups **36**
4.1.3 Selection of doses in the trial **36**
4.1.4 Drug assignment and administration of doses for each patient **36**
4.1.5 Blinding and procedures for unblinding **37**
4.1.5.1 Blinding 37
4.1.5.2 Unblinding and breaking the code 38
4.1.6 Packaging, labelling, and re-supply **38**
4.1.7 Storage conditions **39**

4.1.8 Drug accountability 39
4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT 40
4.2.1 Rescue medication, emergency procedures, and additional treatment(s) 40
4.2.1.1 Management of diarrhoea 40
4.2.1.2 Management of liver enzyme elevation 42
4.2.2 Restrictions 43
4.2.2.1 Restrictions regarding concomitant treatment 43
4.2.2.2 Cautionary notes 45
4.2.2.3 Restrictions on diet and life style 46
4.2.2.4 Restrictions regarding women of childbearing potential 46
4.3 TREATMENT COMPLIANCE 46

5. VARIABLES AND THEIR ASSESSMENT 47

5.1 TRIAL ENDPOINTS 47
5.1.1 Primary endpoint(s) 47
5.1.2 Secondary endpoint(s) 47
5.1.2.1 Key secondary endpoints 47
5.1.2.2 Secondary endpoints 47
5.1.3 Further endpoint(s) 47
5.2 ASSESSMENT OF EFFICACY 48
5.2.1 Assessment of FVC 48
5.2.2 Assessment of mRSS 49
5.2.3 Assessment of DLCO 49
5.2.4 Assessment of SpO_2 49
5.2.5 Assessment of Digital Ulcers 49
5.2.6 Assessment of questionnaires and derived outcomes 50
5.2.6.1 Saint George's Respiratory Questionnaire (SGRQ) 50
5.2.6.2 Functional Assessment of Chronic Illness Therapy-dyspnoea (FACIT- dyspnoea) 50
5.2.6.3 Scleroderma Health Assessment Questionnaire (SHAQ) 51
5.2.6.4 EuroQol 5-Dimensional quality of life Questionnaire (EQ-5D-5L) 51
5.2.6.5 Patient's and physician's global impression of health 52
5.2.6.6 Combined Response Index in Systemic Sclerosis (CRISS) 52
5.2.7 Disease progression 52
5.2.8 Nailfold capillary microscopy (substudy at dedicated sites only) 52
5.2.9 HRCT (substudy at dedicated sites only) 53
5.2.10 Skin biopsy (substudy at dedicated sites only) 53
5.3 ASSESSMENT OF SAFETY 54
5.3.1 Physical examination 54
5.3.2 Vital signs 54
5.3.3 Safety laboratory parameters 55
5.3.4 Electrocardiogram 56
5.3.5 Echocardiography 56
5.3.6 Other safety parameters 57
5.3.7 Assessment of adverse events 57
5.3.7.1 Definitions of AEs 57

5.3.8 Adverse event collection and reporting 60
5.4 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS 62
5.4.1 Assessment of pharmacokinetics 62
5.4.2 Methods of sample collection 62
5.4.3 Analytical determinations 62
5.4.4 Pharmacokinetic / pharmacodynamic relationship 62
5.5 ASSESSMENT OF EXPLORATORY BIOMARKER(S) 63
5.5.1 Methods and timing of sample collection 64
5.5.2 Analytical determinations 64
5.5.3 Biobanking 65
5.6 OTHER ASSESSMENTS 65
5.7 APPROPRIATENESS OF MEASUREMENTS 65
6. INVESTIGATIONAL PLAN 66
6.1 VISIT SCHEDULE 66
6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS 68
6.2.1 Screening 68
6.2.2 Treatment phase 69
6.2.3 Follow-up Visit and trial completion 74
6.2.4 Dose reduction visit / dose increase visit 76
6.2.5 Optional substudies 76
7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE 78
7.1 STATISTICAL DESIGN - MODEL 78
7.2 NULL AND ALTERNATIVE HYPOTHESES 78
7.3 PLANNED ANALYSES 79
7.3.1 Primary endpoint analyses 79
7.3.2 Secondary endpoint analyses 80
7.3.2.1 Analyses of the key secondary endpoints 80
7.3.2.2 Analyses of the other secondary endpoints 80
7.3.3 Further endpoint analyses 81
7.3.4 Safety analyses 81
7.3.5 Pharmacokinetic analyses 82
7.4 INTERIM ANALYSES 82
7.5 HANDLING OF MISSING DATA 82
7.5.1 Efficacy endpoints 82
7.5.2 Safety endpoints 84
7.5.3 Plasma concentrations 84
7.6 RANDOMISATION 84
7.7 DETERMINATION OF SAMPLE SIZE 84
8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS 87
8.1 TRIAL APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT 87
8.2 DATA QUALITY ASSURANCE 88

8.3 RECORDS 88
8.3.1 Source documents 88
8.3.2 Direct access to source data and documents 88
8.3.3 Storage period of records 89
8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS 89
8.4.1 Listedness 89
8.4.2 Expedited reporting to health authorities and IEC / IRB 89
8.5 STATEMENT OF CONFIDENTIALITY 89
8.6 END OF TRIAL 89
8.7 PROTOCOL VIOLATIONS 90
8.8 COMPENSATION AVAILABLE TO THE PATIENT IN THE EVENT OF TRIAL RELATED INJURY 90

9. REFERENCES 91

9.1 PUBLISHED REFERENCES 91
9.2 UNPUBLISHED REFERENCES 93

10. APPENDICES 95

10.1 LUNG FUNCTION CRITERIA 95
10.2 CREATININE CLEARANCE 95
10.3 PATIENT REPORTED OUTCOME QUESTIONNAIRES 96
10.3.1 SGRQ 96
10.3.2 Functional Assessment of Chronic Illness Therapy (FACIT-dyspnoea) 102
10.3.3 Scleroderma health assessment questionnaire (SHAQ) 108
10.3.4 EQ-5D-5L 111
10.4 PATIENTS GLOBAL IMPRESSION OF HEALTH 114
10.5 PHYSICIAN'S GLOBAL IMPRESSION OF PATIENTS'S HEALTH 115
10.6 HANDLING AND DERIVATION OF PHARMACOKINETIC PARAMETERS 116
10.6.1 Pharmacokinetic Methods 116

11. DESCRIPTION OF GLOBAL AMENDMENT(S) 117

ABBREVIATIONS

ACA	Anti-Centromere Antibodies
ACE	Angiotensin-Converting-Enzyme
ACR	American College of Rheumatology
AE(s)	Adverse Event(s)
AESI	Adverse Event of Special Interest
ALK	Alkaline Phosphatase
ALT	Alanine Aminotransferase
(anti-)RNA Pol III	Anti-RNA polymerase III Antibodies
AST	Aspartate Aminotransferase
ATA	Anti-Topoisomerase
ATS / ERS	American Thoracic Society / European Respiratory Society
AUC	Area Under the Curve
BGM	Specific fragment of MMP-9 and -12- mediated degradation of biglycan
BI	Boehringer Ingelheim
bid	Bis in die (twice daily dosing)
BLQ	Below Limit of Quantification
BNP	Brain Natriuretic Peptide
C1M	Specific fragment of MMP-2,9,13-mediated degradation of type I collagen
C3M	Specific fragment of MMP-9-mediated degradation of type III collagen
C5M	Specific fragment of MMP-2,9-mediated degradation of type V collagen
C6M	Specific fragment of MMP-2-mediated degradation of type VI collagen
CA	Competent Authority
CCL2/18	Chemokine (C-C Motif) Ligand 2/18
CI	Confidence Interval
CK	Creatine Kinase
Cmax	Maximum measured concentration of the analyte in plasma
CML	Local Clinical Monitor
CNS	Central Nervous System
CO	Carbon Monoxide
COHb	Carboxyhaemoglobin
COPD	Chronic Obstructive Pulmonary Disease
Cpre, ss	Pre-dose plasma concentrations at steady state
CRA(s)	Clinical Research Associate(s)
CRISS	Combined Response Index in Systemic Sclerosis
CRO	Clinical Research Organisation
CRPM	Specific fragment of MMP-1, -3, -8, -9, CatS/K, ADAMTS1-mediated degradation of C-reactive protein
CT	Concomitant Therapy
CTCAE	Common Terminology Criteria for Adverse Events
CTGF	Connective Tissue Growth Factor
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CXCL4	Chemokine (C-X-C motif) ligand 4

CYP3A4	Cytochrome P450 3A4
DDI	Drug-Drug Interaction
DEDP	Drug Exposure during Pregnancy
DILI	Drug-Induced Liver Injury
dL	Decilitre
DLCO	Carbon Monoxide Diffusion Capacity
DMC	Data Monitoring Committee
DNA	Desoxyribo Nucleid Acid
DoH	Declaration of Helsinki
DU	Digital Ulcer
EC	Ethics Committee
ECG	Electrocardiogram
ECM	Extra Cellular Matrix
eCRF	Electronic Case Report Form
EDTA	Ethylendiamine Tetraacetic Acid
e.g.	Example given
EMA	European Medicines Agency
EOT	End of Treatment
EQ-5D-5L	EuroQol 5-Dimensional quality of life Questionnaire (five-level version)
EudraCT	European Clinical Trials Database
EULAR	European League against Rheumatism
EuroQol Group	European Quality of Life Group
FACIT	Functional Assessment of Chronic Illness Therapy
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume in 1 second
FGFR	Fibroblast Growth Factor Receptor
FU	Follow-up
FVC	Forced Vital Capacity
g	Gram
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GI	Gastrointestinal
GLI	Global Lung Initiative
GP	General Practitioner
h	Hour
HAQ	Health Assessment Questionnaire
HAQ-DI	Health Assessment Questionnaire Disability Index
Hb	Haemoglobin
HCG	Human chorionic gonadotropin
HCRU	Health Care Resource Utilisation
Hct	Haematrocrit
HRCT	High Resolution Computer Tomography
HSCT	Hematopoietic Stem Cell Transplantation
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
i.e.	id est

IEC	Independent Ethics Committee
ILD	Interstitial Lung Disease
INR	International Normalised Ratio
IPF	Idiopathic Pulmonary Fibrosis
IRB	Institutional Review Board
IRF5	Interferon Regulatory Factor 5
IRT	Interactive Response Technology
ISF	Investigator Site File
ITT	Intention-to-treat
I.U. s.c.	International Unit sub cutaneous
KL6	Krebs von den Lungen-6
kPA	Kilopascal
Lck	Lymphocyte-specific protein tyrosine kinase
LC-MS / MS	Liquid Chromatography-Mass Spectroscopy
LDH	Lactate Dehydrogenase
Lyn	Lymphocyte antigen receptor-associated tyrosine kinases
MedDRA	Medical Dictionary for Drug Regulatory Activities
mg	Milligram
min	Minute
miRNA	Micro Ribonucleid Acid
mL	Milliliter
mm	Millimeter
mmHg	Millimetres of mercury
mmol	Millimolar
MMRM	Mixed Model Repeated Measures
mRSS	Modified Rodnan Skin Score
NOA	Not Analyzed
NOR	No Valid Result
NOS	No Sample
nRTK	Non-Receptor Tyrosine Kinase
PAH	Pulmonary Arterial Hypertension
(p) c-abl	(polyclonal) Abelson´s tyrosine kinase
PD	Pharmacodynamic
(p) PDGF / R	(polyclonal) Platelet Derived Growth Factor / Receptor
PFT	Pulmonary Function Test
P-gp	P-glycoproteine (MDR1)
PH	Pulmonary Hypertension
PI / IC	Patient Information / Informed Consent
PK	Pharmacokinetic
p.o.	per os (oral)
PROMIS	Patient-Reported Outcomes Measurement Information System's
PRO	Patient Reported Outcome
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
QT	Interval in the electrocardiogram from the onset of the QRS complex to the end of the T wave

RBC	Red Blood Cells
RDC	Remote Data Capture
REML	Restricted Maximum Likelihood
REP	Residual Effect Period
(m)RNA	(messenger) Ribonucleid Acid
RTK	Receptor Tyrosine Kinase
SAE	Serious Adverse Event
SGRQ	St. George's Respiratory Questionnaire
SHAQ	Scleroderma Health Assessment Questionnaire
SMA	Smooth Muscle Actin
SOP	Standard Operating Procedure
SpO_2	Saturation of oxygen
Src	Rous sarcoma viral oncogene
SSc	Systemic Sclerosis
STPD	Standard Temperature and Pressure, Dry
SUSAR	Suspected Unexpected Serious Adverse Reactions
TCM	Trial Clinical Monitor
TGF-ß1	Transforming Growth Factor ß1
TMF	Trial Master File
TSAP	Trial Statistical Analysis Plan
UGT1A1	UDP-glucuronosyltransferase polypeptide A1
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale
VEGF / R	Vascular Endothelial Growth Factor / Receptor
wk	Week

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Systemic Sclerosis (SSc) is a devastating disease of unknown etiology. The pathogenesis of SSc is characterized by systemic (multi-organ) immunological, vascular and fibrotic abnormalities. It is a rare disorder, an orphan disease, with prevalence rate of approximately 50 to 300 in US, 20 to 50 in Asia and 100 to 200 per million in Europe (R14-4918, R14-4927).

Patients suffer from multiple organ fibrosis, leading to chronic disability and premature death. Aside from skin, the lung is most often involved, but the disease may also manifest as proliferative and obliterative vascular abnormalities, kidney disease, oesophageal and gastrointestinal involvement (hypomotility), cardiac disorders, and muscle disease. SSc-related mortality is mainly driven by interstitial lung disease and pulmonary arterial hypertension. Median survival is 5–8 years in SSc associated Interstitial Lung Disease (ILD) (P14-07919).

No approved SSc treatment is available, and no treatment is considered to be the gold standard for chronic treatment of SSc-ILD. Immunosuppressive therapy has been proposed as a treatment of SSc with limited controlled data.

According to the EULAR treatment guidelines (P15-00879) there are no therapies mandated for SSc-ILD. Cyclophosphamide, a lymphocyte-modulating agent, may have some effect on forced vital capacity (FVC) (R14-5407). EULAR recommends considering cyclophosphamide for the treatment of SSc-ILD, but its use is limited in regard of treatment duration due to its toxicity. Methotrexate may be considered for treatment of skin manifestations of early diffuse SSc (P15-00879). Uncontrolled and retrospectively controlled studies suggest some immunosuppressive regimens (such as azathioprine, mycophenolate, tocilizumab, ciclosporine A) may have effect in selected manifestations of SSc. However, larger placebo-controlled studies are lacking (P15-00879). Endothelin receptor antagonists failed to show significant effects on pulmonary fibrosis outcomes in several large studies.

Based on pre-clinical and clinical evidence of antifibrotic activity of nintedanib in Idiopathic Pulmonary Fibrosis (IPF) and preclinical evidence of potential effects in SSc, along with an acceptable safety profile as demonstrated in clinical trials with nintedanib in IPF, investigation in a patient population with active SSc-ILD accompanied by varying degrees of skin and other organ fibrosis is medically rational. Nintedanib may offer a long term anti-fibrotic maintenance treatment option for SSc, a medical indication with high unmet medical need.

1.2 DRUG PROFILE

Nintedanib is a small molecule that inhibits a distinct spectrum of receptor tyrosine kinases (RTKs) and non-receptor tyrosine kinases (nRTKs) including VEGFR (vascular endothelial growth factor receptor), PDGFR (platelet-derived growth factor receptor), FGFR (fibroblast growth factor receptor), and Src family kinases (Src, Lck and Lyn belonging to a family of proto-oncogene tyrosine-protein kinases).

All of these growth factor pathways and their down-stream signal cascades have been demonstrated to be involved in the pathogenesis of fibrotic tissue remodelling.

In experiments with dermal fibroblasts from patients with SSc, nintedanib inhibited migration and proliferation reduced the expression of extracellular matrix markers and attenuated transformation to myofibroblast. In four animal models of SSc with different features, nintedanib effectively attenuated skin and lung fibrosis, reduced extracellular matrix deposition in skin and lung, attenuated myofibroblast accumulation in skin and lung and reduced dermal thickening. Nintedanib also reduced dermal microvascular endothelial cell apoptosis and effectively attenuated pulmonary vascular remodelling by reducing the number of vascular smooth muscle cells and occluded pulmonary vessels.

A soft gelatin capsule formulation of nintedanib is used in humans. Maximum plasma concentrations occur between 2 - 4 hours after oral administration. Steady state is latest reached within one week of dosing. After food intake, a trend towards an increased systemic exposure (around 20%) and a delayed absorption was observed compared to administration under fasted conditions. Nintedanib is preferentially distributed in plasma with a blood to plasma ratio of 0.87 and the terminal half-life is in the range of 7 to 19 h. The absolute bioavailability of nintedanib was slightly below 5%.

Nintedanib is mainly eliminated via faeces.

Coadministration of nintedanib with the P-glycoprotein (P-gp) inhibitor ketoconazole increased exposure to nintedanib by 60-70% based on area under the curve (AUC) and by 80% based on a maximum measured concentration of the analyte in plasma (Cmax) in a dedicated drug-drug interaction (DDI) trial.

In a DDI trial with the P-gp inducer rifampicin, exposure to nintedanib decreased to 50.3% based on AUC and to 60. 3% based on Cmax upon coadministration with rifampicin compared to administration of nintedanib alone.

Based on results from a dedicated DDI study (1199.229, c09712613), there was no clinically relevant PK interaction between nintedanib and pirfenidone when co-administered in patients with IPF.

In a dedicated DDI study in healthy volunteers (1199.239, c09412738), there was no clinically relevant pharmacokinetic effect of steady state bosentan treatment on nintedanib exposure.

The clinical efficacy of nintedanib has been studied in over 1400 patients with IPF in one phase II dose finding trial (TOMORROW) including four different doses of nintedanib, and two replicate phase III (INPULSIS 1 and 2) trials. These were randomised, double-blind, placebo-controlled trials comparing treatment with nintedanib twice daily to placebo for 52 weeks. A statistically significant reduction in the annual rate of decline of FVC (in mL) was demonstrated in patients receiving nintedanib 150 mg bid compared to patients receiving placebo. The treatment effect of nintedanib compared to placebo on FVC was consistent in all 3 studies, i.e. a relative reduction of decline of approximately 50%. Supporting the effect of nintedanib on slowing disease progression (P14-07514; P11-11216), nintedanib 150 mg bid significantly reduced the risk of first acute exacerbation compared with placebo in INPULSIS-2 and in the TOMORROW trial and reduced the risk of acute exacerbations (adjudicated) by 68% in a pre-specified sensitivity analysis of pooled data from the INPULSIS trials.

The safety profile of nintedanib has been investigated comprehensively. The proportion of patients with serious adverse events was similar in the nintedanib and placebo groups.

The risks of treatment with nintedanib in adult patients are primarily related to the gastrointestinal tract (nausea, vomiting, diarrhoea, abdominal pain, pancreatitis) and to drug-induced liver injury/increases in liver enzymes (aspartate aminotransferase [AST], alanine transaminase [ALT], alkaline phosphatase [ALK], gamma-glutamyl transferase [GGT] and bilirubin).

Based on data from clinical trials and post-marketing and supported by population pharmakokinetic models, patients with low body weight (<65 kg), Asian and female patients have a higher risk of liver enzyme elevations with nintedanib treatment.

The most frequently reported adverse event was diarrhoea, which was mild to moderate in intensity for the vast majority of patients and led to treatment discontinuation in less than five percent of patients treated with nintedanib. Weight decrease, decreased appetite and arterial hypertension have also been associated with nintedanib treatment.

Risks of nintedanib treatment also include hypertension, bleeding, thrombocytopenia, gastrointestinal perforations, thromboembolism and decreased appetite and decreased weight. Thus, patients treated with full-dose anticoagulation or at known risk for bleeding were excluded from the INPULSIS® trials. This has led to recommendations stating that patients at known risk for bleeding should be treated with nintedanib only if the anticipated benefit outweighs the potential risk. Although cardiac disorder adverse events were balanced between the nintedanib and placebo groups, a higher proportion of patients (1.6%) in the nintedanib groups had myocardial infarctions compared to the placebo groups (0.5%). Conversely, a lower proportion of patients in the nintedanib groups had other ischemic heart disease, which includes terms such as coronary artery disease, angina pectoris, coronary angioplasty, coronary artery stenosis, myocardial ischemia, coronary artery stent insertion,

electrocardiogram (ECG) ST segment depression. The clinical significance of this finding is unknown, and further observation is needed.

No evidence of QT prolongation was observed for nintedanib in the clinical trial program. As some tyrosine kinase inhibitors are known to exert an effect on QT, caution should be exercised when administered nintedanib in patients who may develop QT prolongation.

For patients finalizing the 52 week trial treatment in the TOMORROW and INPULSIS trials, participation in open label extension trials (1199.35 and 1199.33) was offered. Long term treatment in these still ongoing open label extension trials is confirming the safety profile observed in the phase II and III trials.

Nintedanib was developed in Idiopathic Pulmonary Fibrosis (IPF) and approved by Food and Drug Administration (FDA) and European Medicines Agency (EMA) in October 2014 and January 2015 respectively.
See also Investigator's Brochure (IB) nintedanib in Idiopathic Pulmonary Fibrosis, Systemic Sclerosis, Progressive Fibrosing Interstitial Lung Disease (c01783972-11) for more details.

2. RATIONALE, OBJECTIVES AND BENEFIT RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

As no approved SSc-ILD treatment is available, and internal organ fibrosis, especially lung fibrosis, leads to severe loss of function and ultimately results in death, there is a high unmet medical need to stop the fibrotic remodeling and thus prevent loss of organ function.

As a common practice, immunosuppressive agents (e.g. mycophenolate mofetil, cyclophosphamide, methotrexate, azathioprine, prednisone) are widely used to address the organ-specific manifestations. Currently no approved treatment is available addressing the interstitial lung manifestation of the disease.

Based upon the mechanism of action and the similarities of pathophysiology resulting in the same pro-fibrotic cascade described in both SSc-ILD and IPF (P14-07919), the pharmacological rationale for multiple tyrosine kinase inhibition in SSc-ILD is sound and promising. Pre-clinical evidence of anti-fibrotic activity of nintedanib in SSc and clinical evidence in IPF with an acceptable safety profile support the rationale of performing a trial in patients with SSc-ILD.

SSc-ILD is expected to be a co-manifestation with varying degrees of involvement of skin and other organs. From a mechanistic point of view and based on preclinical data, an effect of nintedanib on manifestations of the disease outside of the lung, for example skin effects, is also expected.

The rationale to conduct this Phase III trial in SSc-ILD can be summarized as follows:

- High unmet medical need
- Preclinical evidence for efficacy in SSc and SSc-ILD
- Anti-fibrotic efficacy of nintedanib proven in IPF patients (similar pattern regarding lung fibrosis)
- From a mechanistic point of view, treatment with nintedanib may also be beneficial on the disease outside of the lung, for example skin.

2.2 TRIAL OBJECTIVES

The objective of the trial is to assess the efficacy and safety of nintedanib in the treatment of SSc with ILD at a dose of 150 mg bid compared to placebo.

The primary objective is to demonstrate a reduction in the annual rate of decline in FVC in mL over 52 weeks in the nintedanib treatment group compared to the placebo group.

The main secondary objectives are to demonstrate efficacy in regard to skin fibrosis as assessed by the modified Rodnan Skin Score at week 52 and to demonstrate an improvement of patient's symptoms as measured by the SGRQ (Saint George's Respiratory Questionnaire) total score at week 52.

Other objectives are to assess safety and tolerability, mortality, the effects on different systemic organ manifestations of SSc, pharmacokinetics and the effects of nintedanib on patient's perception of his/her disease.

2.3 BENEFIT - RISK ASSESSMENT

Initiating and amplifying events in SSc-ILD and IPF are described to be different, but culminate in fibroblast activation and myofibroblast accumulation that represent the final common pathways of lung fibrosis in both SSc-associated ILD and IPF (P14-07919). Nintedanib inhibits migration, proliferation and transformation of fibroblasts and thereby addresses this common pathway.

As shown for IPF patients, patients with SSc-ILD may also benefit from lesser decline in lung function and hence slower disease progression as a result of treatment with nintedanib.

The safety profile and the tolerability of nintedanib are expected to be similar in patients with IPF and SSc-ILD. However, specific SSc-related sensitivities are considered by specific in/exclusion criteria for this trial.

Based on the efficacy and safety shown in IPF patients, and considering the similarity of the pharmacological rationale between IPF and SSc, the same dose regimen of 150 mg nintedanib bid is considered appropriate.

The risks of treatment with nintedanib have been well delineated in patients with the fibrotic lung disease IPF. These risks are primarily related to the gastrointestinal tract (nausea, vomiting, diarrhoea, abdominal pain), and are usually managed with supportive therapy and with temporary or permanent dose reduction to 100 mg bid. In some cases, temporary interruption or permanent drug discontinuation is necessary. A reduction in appetite and weight decrease has also been reported in patients treated with nintedanib. Patients with SSc may already suffer from gastrointestinal symptoms and will be monitored for such events. Parenteral fed patients will be excluded from the trial.

Increases in liver enzymes and bilirubin have been reported with the use of nintedanib. Cases of drug-induced liver injury (DILI) have been observed with nintedanib treatment. The majority of patients presented with mild to moderate liver enzyme elevation, which was in most cases transient upon dose reduction or treatment discontinuation. However, severe DILI with fatal outcome has also been reported. Liver enzymes must be followed closely during treatment (see also Section 4.2.1.2). Nintedanib must be dose-reduced, or interrupted in the event of hepatic toxicity and further treatment withheld until recovery of the abnormal laboratory parameters.

Concomitant therapies with a known overlap in side effects with nintedanib (e.g. gastrointestinal [GI] adverse events, increase of AST, ALT, bilirubin) or concomitant use of therapies that interact with metabolism of nintedanib (through UGT1A1 and P-gp) should be used with caution and patients should be closely monitored (see Section 4.2.2.2).

Potential risks of nintedanib treatment also include gastrointestinal perforations, thromboembolism and bleeding. Therefore, patients who have planned major elective surgery, suffer from severe peripheral vascular disease, requiring full dose therapeutic anticoagulation, fibrinolysis or high-dose antiplatelet therapy will be excluded from this trial. Patients with severe pulmonary hypertension will be excluded. Echocardiography is used to monitor patients with mild to moderate pulmonary hypertension.

The mode of action of nintedanib indicates a high potential for teratogenicity and embryotoxicity, including fetotoxicity and lethality. In women of childbearing potential receiving nintedanib, contraceptive measures must be employed 28 days before treatment initiation, during the treatment and for a period of 3 months after last drug intake.

To address the organ-specific manifestations, immunosuppressive agents (e.g. mycophenolate mofetil, cyclophosphamide, methotrexate, azathioprine, prednisone) are commonly used and needs to be considered although appropriate randomised-controlled data for these therapies are lacking.

A placebo arm is needed to allow for a true assessment of the effects of nintedanib on the rate of decline in FVC. To address current practice, patients without immunosuppressive background therapy as well as patients on a stable background therapy either of mycophenolate mofetil /sodium or methotrexate will be eligible for the trial. Rescue treatment is allowed in case of clinical deterioration of SSc, either in the lungs (FVC decrease ≥10% compared to baseline), in the skin (mRSS increase of >25% and >5 points compared to baseline) or at any other organ system (Section 4.2.2). By implementing these measures, the inclusion of a placebo arm is considered to be ethically justifiable.

Non-immunosupressant therapies for other SSc manifestations as for digital ulcers (e.g. bosentan), GI symptoms (e.g. proton pump inhibitors, prokinetic drugs), renal crisis (e.g. angiotensin-converting-enzyme inhibitor [ACE inhibitors]), PH / PAH (e.g. bosentan, sildenafil, epoprostenol) are not restricted. Cautionary notes are included in the protocol

(Section 4.2.2.2) with regard to such therapies whose safety profile could interfere with that of nintedanib.

Safety will be monitored at site visits, including physical examinations, safety laboratory and specific monitoring procedures, to follow-up potential hepatic enzyme elevation, exclusion of pregnancy, electrocardiographic assessments, monitoring of renal function, hypertension and digital ulcers. In patients who develop severe symptoms of gastrointestinal toxicity not amenable to symptomatic treatment with standard measures or severe liver enzyme elevations or other severe adverse events as specified in Section 3.3.4, treatment with nintedanib must be discontinued and appropriate therapeutic measures taken.

An independent Data Monitoring Committee (DMC) will be reviewing safety data on a regular basis and whenever necessary, as detailed in the DMC charter. The DMC will review data in a blinded or unblinded manner, as deemed necessary. After each meeting, the DMC will recommend to the sponsor whether to continue, modify, or to terminate the trial.

Overall, the extrapolated benefit-risk ratio of chronic treatment of patients with SSc-ILD with nintedanib 150 mg bid, to be reduced to nintedanib 100 mg bid, interrupted or discontinued during periods of intolerability, is judged positive.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is a multi-centre, multi-national, prospective, randomised, placebo-controlled, double blind clinical trial to investigate the efficacy and safety of nintedanib at a dose of 150 mg bid, in patients with SSc-ILD.

The main efficacy analysis will be assessed at week 52. Patients will stay on treatment up to a maximum of 100 weeks in order to collect follow-up safety and efficacy information (Figure 3.1: 1).

Patients on treatment will have their end of treatment visit (EOT visit) at the same time or before the planned Visit 9 of the last randomised patient. The EOT visit will replace either Visit 9, 10, 11 or 12, whatever is the latest possible visit before or at the planned visit 9 of the last randomised patient. For these patients, the trial ends with the completion of the follow-up visit 28 days after the EOT. All patients who have concluded the trial on treatment will be offered the opportunity to enter an open label extension trial.

Patients, who discontinued treatment but agreed to come to further visits, the last visit will be either Visit 9, 10, 11 or 12, whatever is the latest possible visit before or at the planned visit 9 of the last patient randomized. A follow up visit is not needed for patients who discontinued trial drug earlier.

After signing informed consent (IC) before or at Visit 1, a HRCT will be collected and sent for central eligibility review.

The initial screening Visit (Visit 1) will be performed and patients will enter a screening period of maximum 12 weeks. For detailed procedural assessments of patient's eligibility, and refer to the Flowchart and Section 6.2.1.

After receiving the HRCT central review eligibility result, Visit 2 will be scheduled and collection of clinical and safety laboratory, review of all In- and Exclusion Criteria and randomization will be performed by phone or Internet, using an Interactive phone/web Response System (IRT).

Patients with confirmed SSc-ILD diagnosis will be randomised to either nintedanib or placebo in a 1:1 stratified randomization and in addition stratified by ATA status (positive or negative).

Concomitant treatment rules, dose reduction procedures and short term drug interruptions in case of adverse events are described in Section 4.2.

Patients who permanently discontinue trial medication will be asked to come to future visits as planned. This request will be outlined in the patient information / informed consent procedure prior to randomization. Patients who permanently discontinue trial medication will be asked for a vital status assessment 52 weeks and 100 weeks after their randomization or at

the timepoint when patient's last full visit would have been scheduled, whatever occurs earlier.

Patients who discontinue trial medication early (i.e. before week 100 or the global end of the trial) will not be eligible to enter the open label extension trial.

For each individual patient the trial period is from the signature of informed consent until their last visit.

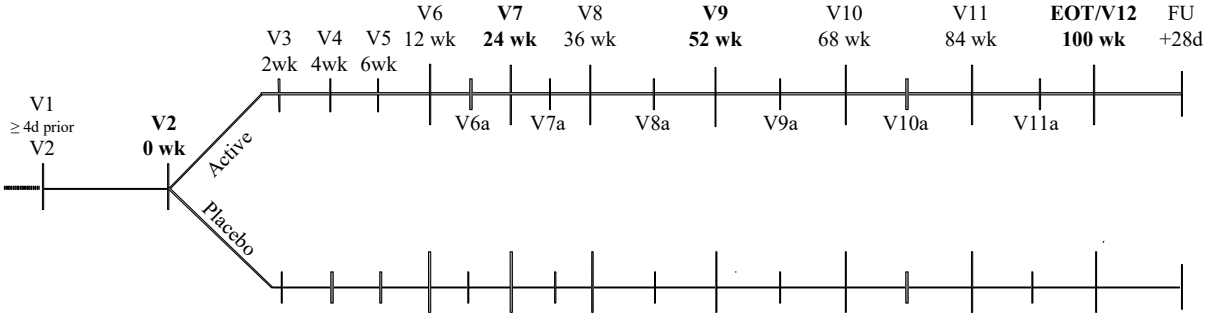


Figure 3.1: 1 Schedule of visits

3.1.1 Administrative structure of the trial

Two coordinating investigators, experts in the field of SSc, were assigned for the trial. The trial will be conducted at specialized referral centres experienced in the management of SSc-ILD.

SSc will be classified by the american college of rheumatology/european league against rheumatism (ACR / EULAR) 2013 criteria (R14-5055). Associated ILD will be assessed on chest HRCT by central review.

Central laboratory facilities will handle all laboratory analyses of the trial. Samples for intermediate measurements (liver enzymes, creatinine) and pregnancy tests may be collected at a local doctor by using trial specific lab kits that will be send to central laboratory for analyses.

Boehringer Ingelheim (BI) has appointed a Trial Clinical Monitor (TCM), responsible for coordinating all required activities, in order to manage the trial in accordance with applicable regulations and internal Standard Operation Procedures (SOPs), direct the clinical trial team in the preparation, conduct and reporting of the trial, order the materials as needed for the trial, ensure appropriate training and information of local clinical monitors (CML), Clinical Research Associates (CRAs), and Investigators of participating countries. Data Management and Statistical Evaluation will be done by BI according to BI SOPs. A list of responsible

persons and relevant local information (as protocol reference, if applicable) can be found in the ISF.

An independent adjudication committee will review all fatal cases and adjudicate all deaths due to cardiac or respiratory causes. The adjudication committee will also review all adverse events categorized as major adverse cardiovascular events (MACE).

An independent data monitoring committee (DMC) will conduct regular reviews of the trial safety data as detailed in Section 2.3 and in the DMC charter. The DMC may review the data in an unblinded fashion. Measures are in place to ensure blinding of the Sponsor, investigators and all other trial participants. The procedures to assess data and the flow of information between the Sponsor and the DMC are described in the DMC charter. The DMC recommendations will be stored in the Trial Master File (TMF).

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)

Patients with SSc-ILD will be included in this trial.

Placebo-controlled randomised trials provide the most robust results and are thus considered the most appropriate design, especially in rare patient populations, where multiple trials are not possible due to lack of patients.

Based on the efficacy and safety data collected in the development program of nintedanib in IPF, an adequately powered placebo-controlled Phase III trial of nintedanib (with the dose strength recommended for the treatment of IPF) will allow for sufficient efficacy and safety assessment in the SSc-ILD patient population, which has similarities to IPF in the underlying pathophysiology.

In situations where effective therapies are available, a placebo-controlled trial could be considered not to be ethical. Importantly, there is currently no approved pharmacotherapy to prevent progression of the ILD component of SSc, which is one of the main causes of death in patients with Systemic Sclerosis. To address the organ-specific manifestations, immunosuppressive agents (e.g. mycophenolate, cyclophosphamide, methotrexate, prednisone) are commonly used although randomised-controlled data for these therapies are scarce.

Preferably patients should not have a chronic immunosuppressive therapy when entering the trial. As chronic immunosuppressive therapy reflects the current clinical practice for treatment of progressive SSc-ILD, patients on background stable dose of mycophenolate mofetil / sodium or methotrexate are allowed in this trial.

Rescue treatment is allowed in case of clinically relevant deterioration of SSc, defined as either a FVC decrease ≥ 10% compared to baseline or a mRSS score increase by >25% and > 5 points or a relevant deterioration at any other organ system, see Section 4.2.2. By implementing these measures, the inclusion of a placebo arm is considered to be justified.

As a positive ATA status is associated with progression of ILD (R14-5409), the randomization of patients will be stratified to two patients groups (ATA negative or ATA positive).

The annual rate of FVC decline, the primary endpoint in the trial, is an indicator for progression of ILD in IPF patients and in SSc-ILD patients as well. Even if progression in SSc-ILD patients is known to be slower than in IPF patients, a 52 weeks exposure is considered appropriate to demonstrate efficacy based upon FVC decline and allows assessment of safety, tolerability and possible effects on other systemic manifestations of the disease.

Efficacy beyond 52 weeks until last patient out (up to a maximum of 100 weeks) will be assessed in an exploratory way.

3.3 SELECTION OF TRIAL POPULATION

A sufficient number of patients of either sex, 18 years of age or older, with a diagnosis of SSc-ILD will be enrolled in the trial (see Section 7.7 for sample size details). All patients are expected to be randomised in about 18 months of overall trial initiation (i.e. initiation of the first site).

The enrolment will be competitive.

No sufficient scientific data are currently available to either rule out or confirm efficacy of stable immunosuppressive treatment at baseline (mycophenolate or methotrexate), as allowed per protocol, for the enrolled study population. To be able to assess the treatment effect of nintedanib versus placebo in patients without mycophenolate or methotrexate background medication in the trial, recruitment of patients on stable dose of such background treatment may be restricted.

A maximum of 520 patients will be recruited by approximately 230 sites in about 33 countries worldwide. Sites will be experienced in the management of patient with SSc-ILD and are each expected to include approximately 3 patients.

Additional sites may be initiated and ‘non-productive’ sites may be closed to ensure sponsor’s timelines.

A log of all patients enrolled into the trial (i.e. who have signed informed consent) will be maintained in the Investigator’s site file (ISF) at the investigational site irrespective of whether they have been treated with investigational drug or not.

3.3.1 Main diagnosis for trial entry

Outpatients diagnosed with Systemic Sclerosis associated ILD (SSc-ILD) based upon classification according to the ACR / EULAR 2013 criteria (R14-5055) and a chest HRCT demonstrating fibrotic/interstitial changes are eligible for inclusion if they fulfil all the

inclusion criteria (Section 3.3.2) and do not present any of the exclusion criteria (Section 3.3.3).

Please refer to Section 8.3.1 (source documents) for the documentation requirements pertaining to the in- and exclusion criteria.

3.3.2 Inclusion criteria

1. Written informed consent consistent with ICH-GCP guidelines and local laws signed prior to entry into the trial and any trial related procedures.
2. Patient aged ≥18 years when signing his/her informed consent.
3. Patients must fulfil the 2013 ACR / EULAR classification criteria for SSc.
4. SSc disease onset (defined by first non-Raynaud symptom) must be within 7 years of Visit 1.
5. SSc related Interstitial Lung Disease pattern must be confirmed by HRCT performed within 12 months of Visit 1. The extent of fibrotic disease in the lung must be ≥10% on HRCT, assessed by central review.
6. FVC ≥40% of predicted normal at Visit 2 (refer to Appendix 10.1).
7. DLCO (corrected for Hb [Visit 1]): 30 % to 89% of predicted at Visit 2 (refer to Appendix 10.1).

3.3.3 Exclusion criteria

Laboratory parameter thresholds (Visit 1)

1. AST, ALT >1.5 x ULN.
2. Bilirubin >1.5 x ULN.
3. Creatinine clearance <30 mL/min calculated by Cockcroft–Gault formula (Appendix 10.2).

Laboratory parameters from Visit 1 have to satisfy the laboratory threshold values as shown above. Visit 2 laboratory results will be available only after randomization. In case at Visit 2 the results do no longer satisfy the entry criteria, the Investigator has to decide whether it is justified that the patient remains in the trial. The justification for decision needs to be documented. Laboratory parameters that are found to be abnormal at Visit 1 are allowed to be re-tested (once) if it is thought to be a measurement error (i.e. there was no abnormal result of this test in the recent history of the patient and there is no related clinical sign) or the result of a temporary and reversible medical condition, once that condition is resolved.

Lung diseases

4. Airway obstruction (pre-bronchodilator $FEV_1/FVC < 0.7$) at Visit 2.
5. In the opinion of the Investigator, other clinically significant pulmonary abnormalities.

Other diseases

6. Significant PH defined by any of the following:
    a. Previous clinical or echocardiographic evidence of significant right heart failure
    b. History of right heart catheterisation showing a cardiac index ≤ 2 l/min/m²
    c. PH requiring parenteral therapy with epoprostenol/treprostinil
7. Cardiovascular diseases, any of the following
    a. Severe hypertension, uncontrolled under treatment (≥160/100 mmHg), within 6 month of Visit 1
    b. Myocardial infarction within 6 months of Visit 1
    c. Unstable cardiac angina within 6 months of Visit 1
8. More than 3 digital fingertip ulcers at Visit 2 or a history of severe digital necrosis requiring hospitalization or severe other ulcers at discretion of the investigator.
9. Bleeding risk, any of the following
    a. Known genetic predisposition to bleeding.
    b. Patients who require
        i. Fibrinolysis, full-dose therapeutic anticoagulation (e.g. vitamin K antagonists, direct thrombin inhibitors, heparin, hirudin)
        ii. High dose antiplatelet therapy.

        [Note: Prophylactic low dose heparin or heparin flush as needed for maintenance of an indwelling intravenous device (e.g. enoxaparin 4000 I.U. s.c. per day), as well as prophylactic use of antiplatelet therapy (e.g. acetyl salicylic acid up to 325 mg/day, or clopidogrel at 75 mg/day, or equivalent doses of other antiplatelet therapy) are not prohibited].
    c. History of hemorrhagic central nervous system (CNS) event within 12 months of Visit 1.
    d. Any of the following within 3 months of Visit 1:
        i. Haemoptysis or haematuria
        ii. Active gastro-intestinal bleeding or GI – ulcers
        iii. Major injury or surgery (investigators judgement).

e. Coagulation parameters: International normalised ratio (INR) >2, prolongation of prothrombin time (PT) and partial thromboplastin time (PTT) by >1.5 x ULN at Visit 1.

10. History of thrombotic event (including stroke and transient ischemic attack) within 12 months of Visit 1.
11. Known hypersensitivity to the trial medication or its components (i.e. soya lecithin).
12. Other disease or conditions that may interfere with testing procedures (e.g. inability to tolerate interruption of supplemental oxygen for pulmonary function testing) or in the judgment of the Investigator may interfere with trial participation or may put the patient at risk when participating in this trial (e.g. severe GI symptoms due to SSc).
13. Life expectancy of <2.5 years for disease other than SSc in investigator assessment.
14. Patients with clinical signs of malabsorption or needing parenteral nutrition.

General exclusion criteria

15. Previous treatment with nintedanib or pirfenidone.
16. Other investigational therapy received within 1 month or 6 half-lives (whichever was greater) prior to screening Visit (Visit 1).
17. Treatment with
    a. Prednisone >10 mg/day or equivalent received within 2 weeks prior Visit 2,
    b. Azathioprine, hydroxychloroquine, colchizine, D-penicillamine, sulfasalazine, received within 8 weeks prior Visit 2,
    c. Cyclophosphamide, rituximab, tocilizumab, abatacept, leflunomide, tacrolimus, newer anti-arthritic treatments like tofacitinib and ciclosporine A, potassium para-aminobenzoate, received within 6 months prior Visit 2.
18. Unstable background therapy with either mycophenolate mofetil / sodium or methotrexate (combined therapy not allowed). Patients have to be either
    a. not on mycophenolate mofetil / sodium or methotrexate within at least 8 weeks prior Visit 2, or
    b. on stable therapy with either mycophenolate mofetil / sodium or methotrexate for 6 months prior Visit 2 and should stay stable on this background therapy for at least 6 months after randomization (for exclusion criterion 17 and 18, and pre-cautionary notes on concomitant medication refer to Section 4.2.2).
19. Previous hematopoietic stem cell transplantation (HSCT), or HSCT planned within the next year.
20. Major surgical procedures planned to occur during trial period.

21. Women who are pregnant, nursing, or who plan to become pregnant while in the trial.
22. Women of childbearing potential not willing or able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly as well as one barrier method for 28 days prior to and 3 months after nintedanib administration[1]. A list of contraception methods meeting these criteria is provided in the patient information.

    [1]Women of childbearing potential are defined as: Any female who has experienced menarche and does not meet the criteria for "women not of childbearing potential" defined as: Women who are postmenopausal (12 months with no menses without an alternative medical cause) or who are permanently sterilized (e.g. hysterectomy, bilateral oophorectomy, or bilateral salpingectomy).
23. In the opinion of the Investigator, active alcohol or drug abuse.
24. Patients not able to understand or follow trial procedures including completion of self-administered questionnaires without help.
25. Patients with underlying chronic liver disease (Child Pugh A, B, C hepatic impairment).
26. Patients with a history of Scleroderma Renal Crisis.

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients from therapy

The trial medication has to be permanently discontinued in the following circumstances

- The patient experiences signs of hepatic injury, defined in Section 5.3.7.1.
- In the opinion of the investigator, the patient experiences unacceptable adverse events despite dose adjustments and supportive care.
- Use of concomitant treatment: as defined in Section 4.2.2 “restrictions”.
- Parenteral feeding requirement.
- Pregnancy (refer to Section 5.3.6).
- If a patient becomes pregnant during the trial the investigational product needs to be stopped and the patient should be followed up until birth or otherwise termination of the pregnancy. The data of the patient will be collected and reported in the clinical trial report (CTR) until patient´s last visit and any events thereafter will be reported in the BI drug safety database. Refer to Section 5.3.6 for detailed information on event reporting in case of pregnancy.

In the following cases discontinuation of trial medication is highly recommended. Only in special circumstances, the Investigator, upon thorough assessment of all available clinical data and taking into consideration the potential risks associated with administration of nintedanib, may decide not to withdraw the trial medication, even though one or more of the below mentioned criteria are fulfilled. In such a case, continuation of treatment with trial

medication should be discussed with the patient, and the decision and reasoning documented in the source data.

- Major surgery, including any abdominal or intestinal surgery.
- Anti-coagulation. Patients who require full-dose therapeutic anticoagulation (e.g. vitamin K antagonists, heparin, hirudin, direct thrombin inhibitors, etc), or high-dose antiplatelet therapy. (Prophylactic low dose heparin or heparin flush as needed for maintenance of an indwelling intravenous device (e.g. enoxaparin 4000 I.U. s.c. per day), as well as prophylactic use of antiplatelet therapy (e.g. acetyl salicylic acid up to 325 mg/day, or clopidogrel at 75 mg/day, or equivalent doses of other antiplatelet therapy is allowed.).
- Major thrombo-embolic events e.g. stroke, deep vein thrombosis, pulmonary embolism, myocardial infarction.
- Increased risk of bleeding e.g. hemorrhagic CNS event, gross / frank haemoptysis or haematuria, active gastro-intestinal bleeding or GI-ulcers.

For conditions that allow treatment interruption please refer to Section 4.2.1.

Permanent discontinuation of trial medication (prematurely): if a patient permanently discontinues the trial medication prematurely, it is of utmost importance for the robustness and integrity of the trial results that his/her lung function parameters, other efficacy endpoints and safety data are further recorded until the end of the trial. Patients, who prematurely discontinue trial medication, will be asked to follow their original visit schedule (except the laboratory 'a-Visits'. refer to Section 6.2.2).

Vital status should be collected for all patients at week 52 and at week 100 or at the timepoint when with their last full visit would have been scheduled, whatever occurs earlier. Removal of individual patients from trial participation

An individual patient is to be withdrawn from trial participation if the patient withdraws consent for trial participation, without the need to justify the decision.
Given the patient's agreement, the patient will undergo the procedures for trial discontinuation and follow up as outlined in the Flowchart and Section 6.2.3.
For all patients, the reason for withdrawal (e.g. adverse events) must be recorded in the Electronic Case Report Form (eCRF). These data will be included in the trial database and will be reported.

3.3.4.2 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons:

- Failure to meet expected enrolment goals overall or at a particular trial site

- Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial
- Violation of Good Clinical Practice (GCP), the Clinical Trial Protocol (CTP), or the contract disturbing the appropriate conduct of the trial

[redacted]

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

4.1.1 Identity of BI investigational product(s)

Table 4.1.1: 1 Identity of BI investigational products

	Nintedanib	**Placebo**
Substance:	Nintedanib	-
Pharmaceutical formulation:	Soft gelatine capsule	Soft gelatine capsule
Source:	BI Pharma GmbH & Co. KG	BI Pharma GmbH & Co. KG
Unit strength:	150 mg, 100 mg	Placebo to 150 mg, 100 mg
Posology:	bid	bid
Route of administration:	Oral (swallowed)	Oral (swallowed)

4.1.2 Method of assigning patients to treatment groups

At Visit 1, patients who meet all entrance criteria will enter a screening period.

When a patient is qualified for entry into the randomised treatment period at Visit 2, treatment will be assigned via Interactive Response Technology (IRT). To facilitate the use of the IRT, the Investigator will receive all necessary instructions for using the IRT.

4.1.3 Selection of doses in the trial

Based on the efficacy, safety and dose-finding from trials investigating nintedanib in IPF, TOMORROW (P11-11216), INPULSIS I and INPULSIS II (P14-07514), a dose of 150 mg bid was selected. With 150 mg bid, acceptable tolerability in Systemic Sclerosis patients is expected based on the risk profile seen in IPF patients. Lower starting doses may not be expected to demonstrate efficacy based on the dose ranging trial (TOMORROW) in IPF. However, to manage adverse events, the dose may be reduced to 100 mg bid temporarily or permanently (refer to Section 4.2.1 and Section 6.2.4).

4.1.4 Drug assignment and administration of doses for each patient

The treatment for an individual patient will be assigned by means of an IRT contact during Visits 2, 4, 6, 7, 8, 9, 10, and 11. Patient will receive either active drug at a dosage of 150 mg bid or placebo bid.

Trial medication will consist of 1 capsule twice daily throughout the trial. Wallets covering 4 30 days + 5 days reserve treatment (1 wallet = 6 blisters with 10 capsules each, plus 1 blister reserve) will be dispensed to the patient:

- 1 wallet at day 1 (randomization = Visit 2) (30 days plus 5 days reserve).

- 2 wallets at Visit 4 (60 days plus 10 days reserve).
- 3 wallets at Visit 6 and Visit 7 (90 days plus 15 days reserve).
- 4 wallets at Visit 8 (120 days plus 20 days reserve).
- 4 wallets at Visit 9, 10 and 11 respectively (120 days plus 20 days reserve).

Trial medication will be administered orally on a twice daily basis (bid). The patients should swallow the trial medication unchewed together with a glass of water (~250 mL), and should observe a dose interval of 12 hours. Trial medication needs to be taken at the same time every day (between 06:00 and 11:00 in the morning, and between 18:00 and 23:00 in the evening). Because nintedanib may cause stomach discomfort, it is recommended to take the trial medication with food intake.

A forgotten dose should be skipped if the time window to the next dose is less than 8 hours. The next dose should be taken as scheduled.

The investigational product should only be dispensed to participating patients according to the protocol by authorised personnel as documented in the form “Investigator’s Trial Staff”.

In case of adverse events requiring dose reduction between planned visits, an additional site visit is required. 100 mg bid (or matching placebo) will be assigned by means of an IRT call from the Investigator (refer to Section 6.2.4). The color of capsules (100 mg capsule or corresponding placebo) will be slightly different but the packaging will remain the same (same number of capsules per blister and same number of blisters per wallet).

The dose can be reduced without prior interruption, i.e., immediately stepping down from 150 mg bid to 100 mg bid if necessary due to adverse events which requires a special trial visit according to procedures described in Section 4.2.1.

If the reduced dose is well tolerated, re-escalation is possible within 4 weeks (after the dose reduction visit), which if it occurs between scheduled trial visits will also require a special trial visit according to procedures described in Section 4.2.1.

Patients experiencing adverse events requiring temporary interruption of trial medication may re-start trial medication according to procedures described in Section 4.2.1.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

This trial is a double-blind trial.

Trial medication is identified by a medication code number. Packaging and labelling will be otherwise identical. The booklet cover page for 150 mg and 100 mg nintedanib and the respective corresponding placebo is differently coloured. Colour, size and shape of

nintedanib and placebo capsules are indistinguishable within dose strength, but are different between dose strengths.

Patients, investigators and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial (apart from the DMC) will remain blinded with regard to the randomised treatment assignments until after database lock.

The randomization code will be kept secret by the sponsor's clinical trial support up to database lock.

The DMC may review unblinded data upon request, and only under conditions that ensure that patients, investigators and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial will remain blinded.

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available to the Investigator store manager via IRT. It must only be used in an emergency situation when the identity of the trial medication must be known to the Investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. The reason for unblinding must be documented in the source documents along with the date and the initials of the person who broke the code and information needs to be entered on the appropriate eCRF page.

For Japan:

In this blinded trial, an emergency code break will be available to the Investigator / the sub-Investigators via the IRT system. This code break may only be accessed in emergency situations when the identity of the trial medication must be known to the Investigator / the sub-Investigators in order to provide appropriate medical treatment or if required to assure the safety of trial participants. Each site receives a manual from the IRT provider that contains instructions on how to unblind the treatment of a patient via the IRT (via 24-hour emergency helpline). If the code break for a patient is accessed, the Sponsor must be informed immediately. The reason for accessing the code break, together with the date, must be documented on the appropriate eCRF page. In case third party needs to break the code, however, when the Investigator cannot be reached, the code can be opened by calling emergency code manager.

4.1.6 Packaging, labelling, and re-supply

Primary trial material will be capsules containing 150 mg of nintedanib (or 100 mg of nintedanib if dose is reduced), and matching placebo. All trial medication will be packaged in blister cards. Each blister card will contain 10 capsules. Seven blisters cards will be packaged into one child-resistant tamper-evident wallet (i.e. 70 capsules/wallet). Each wallet will be labelled with a multi-language booklet according to the requirements of the participating countries.

One wallet covers for one month of treatment.

Details of packaging and the description of the label will be provided in the ISF.

Initial supply and further re-supplies will be managed by an IRT. The IRT will assign an appropriate kit to each patient according to the randomization list that are generated by the Sponsor and not known by the trial personnel.

Re-supplies of trial medication are planned due to the short expiry date and the long duration of the trial. The medication for re-supply will be packaged in an identical manner as the medication for initial supply.

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation.

If the storage conditions are found to be outside the specified range, the local clinical monitor (as provided in the list of contacts) must be contacted immediately.

All unused trial medication must be returned to the Sponsor or appointed CRO. Receipt, usage and return must be documented on the respective forms. Account must be given for any discrepancies.

4.1.8 Drug accountability

The Investigator will receive the investigational drugs delivered by a clinical research organisation (CRO) appointed by the Sponsor, when the following requirements are fulfilled:

- Approval of the trial protocol by the institutional review board (IRB) / ethics committee (EC).
- Availability of a signed and dated clinical trial contract between the Sponsor and the head of the investigational site.
- Approval/notification of the regulatory authority, e.g. competent authority.
- Availability of the curriculum vitae of the Principal Investigator.
- Availability of a signed and dated clinical trial protocol.
- In countries where it is required, availability of the proof of a medical license for the Principal Investigator.
- In the US, availability of Form 1572.

The Investigator must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the Sponsor or appointed CRO.

These records will include dates, quantities, batch / serial numbers, expiry ('use-by') dates, and the unique code numbers assigned to the investigational product and trial patients. The Investigator will maintain records that document adequately that the patients were provided the doses specified in Section 4.1.4 and reconcile all investigational products received from the Sponsor. At the time of return to the Sponsor or appointed CRO, the Investigator must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the Investigator's possession.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

4.2.1 Rescue medication, emergency procedures, and additional treatment(s)

Rescue medications to reverse the action of nintedanib are not available.

Dose reduction (from 150 mg bid to 100 mg bid) or treatment interruption should be considered to manage adverse events. No further dose reduction is possible for patients on the 100 mg bid regimen. In case of persistent adverse events observed at this dose, or severe effects at 150 mg bid, permanent treatment discontinuation should be considered.

Treatment interruption and reduction and reescalation are repeatedly possible.

Table 4.2.1: 1 Allowed treatment reduction / interruption periods:

	AEs considered drug related	**AEs not considered drug related**
Maximum interruption	4 weeks	8 weeks
Recommended restart	with reduced dose (100 mg bid)	with the same dose (100 mg bid or 150 mg bid)
Re-escalation	within 4 weeks to 150 mg bid	----

4.2.1.1 Management of diarrhoea

Other causes for diarrhoea should always be considered and treated accordingly (e.g. viral infections, SSc related diarrhoea, bacterial overgrowth, antibiotic treatment).

Diarrhoea should be managed as early as possible after onset of first symptoms with standard antidiarrhoeal symptomatic treatment, e.g. loperamide.

If diarrhoea persists despite optimal symptomatic treatment, treatment interruption and dose reduction of nintedanib should be considered based on the recommendations described in Table 4.2.1.1: 1.

Table 4.2.1.1: 1 Management of diarrhoea (considered related to trial medication)

Description	Symptomatic Treatment*	Action with trial medication
Diarrhoea with increase of <4 stools per day over baseline[1].	Initiate anti-diarrhoeal medicines at first signs of symptoms (e.g. 4 mg loperamide followed by 2 mg after each loose stool or every 2-4 hours to a maximum of 16 mg/day) until bowel movements cease for 12 hours.	Continue same trial medication dose.
Diarrhoea with increase of 4 to 6 stools per day over baseline[1].	Initiate/continue anti-diarrhoeal medicines; If diarrhoea of this severity persists for ≥48 to 72 hours assess for dehydration and electrolyte imbalance; In addition, consider IV fluids and electrolyte replacement as clinically indicated.	If diarrhoea persists for ≥48 to 72 hours despite optimal symptomatic care: 1. Interrupt trial medication until recovery. 2. Reduce dose to 100 mg bid after recovery. 3. Re-escalate to 150 mg bid within 4 weeks if deemed clinically appropriate.
Diarrhoea with increase of ≥7 stools per day over baseline[1]; stool incontinence, or life threatening consequences.	Follow recommendations above. In addition, consider stool work-up to exclude infectious colitis; adequate IV fluid replacement ≥24 hours, hospitalisation as clinically indicated; consider referral to a GI specialist to rule out potential differential diagnoses.	1. Interrupt trial medication until recovery. 2. Reduce dose to 100 mg bid after recovery. 3. Consider re-escalation within 4 weeks to 150 mg bid if deemed clinically appropriate. In case of reoccurrence of diarrhoea of this severity despite optimal symptomatic treatment and dose reduction, treatment with trial medication should be permanently discontinued.

Footnotes:

* Other causes for diarrhoea should always be considered and treated accordingly (e.g. viral infections, SSc related diarrhoea, bacterial overgrowth, antibiotic treatment)

[1] Baseline defined as usual stools/day prior randomisation.

4.2.1.2 Management of liver enzyme elevation

Evaluate the concomitant use of other drugs known to cause liver enzyme elevations. For a detailed guidance on how to manage liver enzyme elevations, please refer to Table 4.2.1.2: 1.

Table 4.2.1.2: 1: Recommendations for managing liver enzyme elevations

	AST or ALT increase to			Signs of hepatic injury* (Section 5.3.6)
	>1.5x to <3x ULN	≥3x to <5x ULN and no signs of hepatic injury (Section 5.3.6)	≥5x to <8x ULN and no signs of hepatic injury (Section 5.3.6)	
Visit 2 (randomization)	Withdraw trial medication or justify continuation[1]	Withdraw trial medication	Withdraw trial medication	Withdraw trial medication
Any other Visit	Continue as planned[2]	Reduce dose or interrupt trial medication [3]	Interrupt trial medication	Withdraw trial medication
		Close observation[4] After 2 weeks or any time later	Close observation[4] After 2 weeks or any time later	**CLINICAL EVALUATION OF HEPATIC-INJURY** (Section 5.3.6)
	<3x ULN	≥3x ULN	<3x ULN	≥3x ULN
	Reduced: return to initial dose. Interrupted: restart at reduced dose. Monitor bi-weekly for at least 8 weeks	Permanently discontinue trial medication Close observation[4]	Restart at reduced dose Monitor weekly for 4 weeks, then bi-weekly for at least 8 weeks	Permanently discontinue trial medication. Close observation[4]

Footnotes:

*Signs of hepatic injury are defined as

- ALT and/or AST ≥8 fold ULN
- ALT and/or AST ≥3 fold ULN and total bilirubin ≥2 fold ULN
- ALT and/or AST ≥3 fold ULN and unexplained INR >1,5
- ALT and/or AST ≥3 fold ULN and unexplained eosinophilia (>5%)
- ALT and/or AST ≥3 fold ULN and appearance of fatigue, nausea, vomiting, right upper abdominal quadrant pain or tenderness, fever and/or rash

[1] Investigator to confirm in writing that continuation is justified (e.g. intermittent fluctuation of transaminases).
[2] According to visit schedule. Consider additional control visits as adequate.
[3] To be decided by Investigator, based on individual risk assessment.
[4] Close observation: Re-test ALT and AST, alkaline phosphatase, total bilirubin, and eosinophils within 48 to 72 hours, then approximately 7 days, then approximately 2 weeks by using intermediate visit lab kit.

Initial assessment of liver enzyme elevation should be performed at the investigational site. Blood samples for additional monitoring may be collected at the investigational site, primary care physician or external laboratory with specific trial lab kits and sent to the central laboratory for analysis.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Medication as individually indicated per discretion of the investigator is allowed unless covered by medication restrictions in Table 4.2.2.1:1.

In case of a clinically significant deterioration of SSc, initiation of additional therapy is allowed as described in Table 4.2.2.1:1. Detailed (S)AE information following such events should be recorded in the eCRF.

Clinically significant deterioration is defined as:

- An absolute decline since baseline in FVC percent predicted >10% (for example, if FVC percent predicted changes from 70% at baseline to less than 60%), or
- A relative change from baseline in mRSS of >25% and an absolute change from baseline of >5 points, or
- Clinically significant deterioration in other organ systems or clinical parameters at the discretion of the investigator.

Other causes for FVC decline (i.e. respiratory tract infection) should be excluded.

Please also refer to cautionary notes (Section 4.2.2.2).

Table 4.2.2.1:1. Medication restrictions and requirements

	Prior to randomisation	**During treatment period**	**After EOT attending future visits**
Anticoagulant and antiplatelet therapies			
Full dose therapeutic anticoagulation	permitted note: coagulation parameters will be measured at Visit 1	NOT permitted discontinuation of trial medication is highly recommended	permitted
High-dose antiplatelet therapy[1]	permitted	NOT permitted discontinuation of trial medication is highly recommended	permitted
Low dose antiplatelet therapy[2]	permitted	permitted	permitted
Prophylactic low dose heparin or heparin flush[3]	permitted	permitted	permitted
Immunosuppressive agents			
Stable therapy with mycophenolate mofetil / sodium	permitted if stable for at least 6 months prior V2 (otherwise washout for 8 weeks prior V2)	pre-trial dose to be continued[4]	permitted
Stable therapy with methotrexate	permitted if stable for at least 6 months prior V2 (otherwise washout for 8 weeks prior V2)	pre-trial dose to be continued[4]	permitted
Azathioprine	NOT permitted 8 weeks prior Visit 2	NOT permitted except for deterioration[4]	permitted
Cyclophosphamide	NOT permitted 6 month prior Visit 2	NOT permitted except for deterioration[4]	permitted
Ciclosporine A	NOT permitted 6 month prior Visit 2	NOT permitted except for deterioration[4]	permitted
Corticosteroids			
Prednisone ≤10 mg or equivalent	permitted	permitted	permitted

Table 4.2.2.1:1. Medication restrictions and requirements (con't)

	Prior to Randomisation	**During Treatment Period**	**After End of Treatment attending future visits**
Prednisone >10 mg/day	NOT permitted 2 weeks prior Visit 2	NOT permitted except for deterioration[4]	permitted
Other restricted medications			
Hydroxychloroquine Colchizine, D-penicillamine, sulfasalazine	NOT permitted 8 weeks prior Visit 2	NOT permitted except for deterioration[4]	permitted
Rituximab, tocilizumab, abatacept, leflunomide, tacrolimus, newer anti-arthritic treatments like tofacitinib, potassium para-aminobenzoate	NOT permitted 6 month prior Visit 2	NOT permitted except for deterioration[4]	Permitted
Pirfenidone	NOT permitted	NOT permitted	NOT permitted
Nintedanib **(outside of the trial)**	NOT permitted	NOT permitted	NOT permitted
Other investigational drugs	washout 1 month or 6 half-lives (whichever is greater) prior Visit 1	NOT permitted	NOT permitted

Footnotes:

*it is not allowed to switch between mycophenolate mofetil and mycophenolate sodium

[1] e.g. acetyl salicylic acid >325 mg/day, or clopidogrel >75 mg/day, or equivalent doses of other antiplatelet therapy.
[2] e.g. acetyl salicylic acid up to 325 mg/day, or clopidogrel up to 75 mg/day, or equivalent doses of other antiplatelet therapy.
[3] As needed for maintenance of an indwelling intravenous device (e.g. enoxaparin 4000 I.U. s.c. per day)
[4] Initiation / change in dose permitted in case of clinically significant deterioration, defined as:

- Absolute decline since baseline in FVC percent predicted >10% (for example, if FVC percent predicted changes from 70% at baseline to less than 60%), or
- Relative change from baseline in mRSS of >25% and an absolute change from baseline of >5 points, or
- Clinically significant deterioration in other organ systems or clinical parameters at the discretion of the investigator.

4.2.2.2 Cautionary notes

As nintedanib is a substrate of P-gp and, to a minor extent, CYP3A4, concomitant use of P-gp and CYP3A4 inhibitors (e.g. erythromycin) with nintedanib may increase exposure to nintedanib. Patients taking potent P-gp inhibitors (e.g. ketoconazole, erythromycin or ciclosporine) should be monitored closely for tolerability of nintedanib.

Concomitant use of P-gp and CYP3A4 inducers (e.g. carbamazepine, phenytoin, and St. John's wort) with nintedanib may decrease exposure to nintedanib. For patients taking potent P-gp inducers, selection of alternatative treatment with no or minimal P-gp induction should be considered.

As the most common side effects known for nintedanib are GI effects, the concomitant use of medication with an overlapping safety profile (e.g. mycophenolate mofetil/ sodium) should be carefully considered.

Nintedanib is also associated with increases in liver enzymes and bilirubin. If in addition to the trial medication, a treatment is introduced that is known to induce AST/ALT elevations (e.g. methotrexate, bosentan), adequate measures should be taken to ensure patients safety: perform additional measurement of liver enzymes (ALT and AST, alkaline phosphatase, total bilirubin, and eosinophils) every 2 weeks for approximately 6 weeks, by using intermediated (a-visit) trial lab kit.

4.2.2.3 Restrictions on diet and life style

There are no restrictions on diet and life style.

4.2.2.4 Restrictions regarding women of childbearing potential

The anti-angiogenic properties of nintedanib indicate a high potential for teratogenicity and embryotoxicity, including fetotoxicity and lethality. In women of childbearing potential receiving nintedanib, contraceptive measures must be employed 28 days before treatment initiation, during the trial and for a period of 3 months after last drug intake.

4.3 TREATMENT COMPLIANCE

Patients are requested to bring all remaining trial medication including empty package material with them when attending visits.

Based on capsule counts, treatment compliance will be calculated as the number of capsules taken, divided by the number of capsules which should have been taken according to the scheduled period, multiplied by 100. Compliance will be verified by the on-site monitor authorized by the Sponsor.

$$\text{Treatment compliance (\%)} = \frac{\text{Number of capsules actually taken} \times 100}{\text{Number of capsules which should have been taken}}$$

If the number of doses taken is not between 80-120%, site personnel will explain the patient the importance of treatment compliance.

5. VARIABLES AND THEIR ASSESSMENT

5.1 TRIAL ENDPOINTS

5.1.1 Primary endpoint(s)

The primary efficacy endpoint is the annual rate of decline in FVC in mL over 52 weeks.

5.1.2 Secondary endpoint(s)

5.1.2.1 Key secondary endpoints

The key secondary endpoints are:

1. Absolute change from baseline in the mRSS at week 52.
2. Absolute change from baseline in SGRQ total score at week 52.

5.1.2.2 Secondary endpoints

- Annual rate of decline in FVC in percent predicted over 52 weeks.
- Absolute change from baseline in FVC in mL at week 52.
- Relative change from baseline (%) of mRSS at week 52.
- Time to all-cause mortality.
- Absolute change from baseline at week 52 in CRISS index score.
- Absolute change from baseline in DLCO in percent predicted at week 52.
- Absolute change from baseline in digital ulcer net burden at week 52.
- Absolute change from baseline in HAQ-DI score at week 52.
- Absolute change from baseline in FACIT dyspnoea score at week 52.

5.1.3 Further endpoint(s)

- Proportion of patients with a relative decline since baseline in FVC (mL) at week 52 of >5%.
- Proportion of patients with a relative decline since baseline in FVC (mL) at week 52 of >10%.
- Absolute change from baseline in SpO_2 (oxygen saturation, expressed in percent) at rest evaluated at week 52.
- Proportion of patients with an absolute change from baseline in mRSS at week 52 of ≥5 points.
- Absolute change from baseline at week 52 in SHAQ domain scores (individual visual analogue scale [VAS] scores).

- Absolute change from baseline at week 52 in FACIT functional limitation score.
- Absolute change from baseline at week 52 in SGRQ domain scores.
- Absolute change from baseline at week 52 in EQ-5D-5L VAS score.
- Absolute change from baseline at week 52 in patient global-VAS score.
- Absolute change from baseline at week 52 in physician global-VAS score.
- Proportion of patients with disease progression at week 52 as defined in Section 5.2.7.

Additional explorative measures derived from further endpoint assessments will be described in detail in the trial statistical analysis plan (TSAP).

Efficacy data collected beyond week 52 will be analysed in a descriptive manner only (see TSAP for details).

PK endpoints will include pre-dose concentration of BIBF 1120, BIBF 1202 and BIBF 1202-glucuronide as specified in Section 5.4.

5.2 ASSESSMENT OF EFFICACY

5.2.1 Assessment of FVC

FVC will be assessed with the FlowScreen® spirometer which will be supplied to all participating sites. Central reading will be conducted along the 2005 ATS/ERS Guideline.

Spirometry measurements must be performed according to ATS/ERS 2005 guideline (P05-12782), including daily calibration of the spirometer, and regular calibration of the calibration pump. Spirometry will be conducted while the patient is in a seated position. The test will be done in triplicate (three curves to be provided), and the best result selected according to the guidelines. Spirometry results captured by spirometers provided by the sponsor will be electronically transmitted and confirmed by central reading.

Feedback will be provided to Investigators about unacceptable readings.

The best of three efforts will be defined as the highest FVC, obtained on any of the three blows meeting the ATS/ERS criteria with preferably a maximum of five maneuvers.

For each patient, the spirometric measurements will always start at approximately the same time of the day (with ±90 minutes maximum difference, time will be recorded), with reference to baseline measurement (Visit 2).

On days of clinic visits, patients must refrain from strenuous activity at least 12 hours prior to pulmonary function testing. Smoking should be discouraged throughout the visit days (clinic visit) and will not be permitted in the 30-minute period prior to spirometry. Patients should also avoid cold temperatures, environmental smoke, dust, or areas with strong odours (e.g. perfumes). If treated with bronchodilators, washout of 24 hours for long acting and 8 hours for short acting bronchodilators should be observed before spirometry.

Further instructions regarding FVC measurements will be provided in the site's ISF.

5.2.2 Assessment of mRSS

The modified Rodnan Skin Score (mRSS) consists of an evaluation of patient's skin thickness rated by clinical palpation using a 0–3 scale (0=normal skin; 1=mild thickness; 2=moderate thickness; 3=severe thickness with inability to pinch the skin into a fold) for each of 17 surface anatomic areas of the body: face, anterior chest, abdomen, (right and left separately) fingers, forearms, upper arms, thighs, lower legs, dorsum of hands and feet. These individual values are added and the sum is defined as the total skin score (R15-1205).

Further instructions regarding mRSS assessment will be provided in the ISF.

5.2.3 Assessment of DLCO

The site will use its own carbon monoxide diffusion capacity (DLCO) equipment and conduct all measurements with the same DLCO equipment (e.g. if several devices would be available at the site). Single-breath DLCO will be carried out according to the ATS / ERS guideline on DLCO measurements (R06-2002). DLCO and the corresponding alveolar volume will be measured at time points given in the Flowchart. Before beginning the test, the maneuvers should be demonstrated and the subject carefully instructed.

DLCO values will be adjusted for the most recent haemoglobin value (Appendix 10.1). For predicted normal values, different sites may use different prediction formulas, based on the method used to measure DLCO. In any case, the calculation method used must be in compliance with the ATS/ERS guideline on DLCO measurements (R06-2002) and the prediction formula appropriate for that method. Raw data (gas mixture, equation used for prediction of normal, further adjustments made if so) must be traced.

The DLCO assessment should always be performed after the FVC assessment and should always be started approximately the same time a day i.e. with ±90 minutes maximum difference between start of the tests at baseline (Visit 2).

Further instructions regarding DLCO measurements will be provided in the ISF.

5.2.4 Assessment of SpO_2

Oxygen saturation (SPO_2) will be measured at rest by standard pulse oximetry (unaffected skin of earlobe or forehead) and the recorded value will be entered in eCRF.

5.2.5 Assessment of Digital Ulcers

Net ulcer burden is defined as the number of new digital ulcers (DU) plus the number of DUs that have been verified at any earlier assessment during the trial.

A DU is defined as an area of loss of continuity of both epithelial coverage and of part of the dermal tissue. If covered by a scab and there is no debridement performed, the decision whether there is an ulcer with loss of continuity of both epithelial coverage and part of the dermal tissue is by investigator's clinical judgement. Only DUs distal to the proximal interphalangeal joints and vascular in origin are assessed.

Digital ulcer net burden will be assessed by counting total number of digital ulcers at the time points indicated in the Flowchart. The absolute change is calculated by counting of ulcers at time point minus number of ulcers at baseline.

Further instructions regarding Digital Ulcers assessment will be provided in the ISF.

5.2.6 Assessment of questionnaires and derived outcomes

The patient should complete patient reported outcome (PROs) questionnaires on his/her own in the pre-specified order defined in the Flowchart in a quiet area/room prior to any other trial-related examination. Site personnel will check the answers of the patients in the questionnaires for completeness prior to the patient leaving the site, but the response to each item should not be scrutinized. In instances where a patient cannot give or decide upon a response, no response should be recorded. The scores will then be transcribed into the eCRF by designated site-personnel.

The PRO questionnaires should be presented and filled out in the following order:

1. Saint George's Respiratory Questionnaire (SGRQ)
2. Functional Assessment of Chronic Illness Therapy (FACIT-dyspnoea)
3. Scleroderma Health Assessment Questionnaire (SHAQ)
4. EuroQol 5-Dimensional quality of life Questionnaire (EQ-5D-5L)
5. Patient global impression of health VAS.

5.2.6.1 Saint George's Respiratory Questionnaire (SGRQ)

The St George´s Respiratory Questionnaire (SGRQ, R98-0966) measures health status in patients with chronic airflow limitation. It comprises 2 parts which cover three domains (symptoms, activities and impacts) with scores ranging from 0 (no impairment) to 100 (worst possible).
The SGRQ (Appendix 10.3.1) will be self-administered by the patient at visits indicated in indicated in the Flowchart and Section 6.

5.2.6.2 Functional Assessment of Chronic Illness Therapy-dyspnoea (FACIT- dyspnoea)

The FACIT-dyspnoea is a questionnaire that was developed using the National Institutes of Health's Patient-Reported Outcomes Measurement Information System's (PROMIS)

databank (R11-1366). Originally developed with patients with Chronic Obstructive Pulmonary Disease (COPD), it assesses shortness of breath and its impact on 10 different activities of daily living. Recent evidence suggests that the FACIT-dyspnoea may have good measurement properties in patients with Systemic Sclerosis (R14-5056; R14-5045).

Patients should be instructed to read the brief directions at the top of the page. After the patient's correct understanding has been confirmed, he/she should be encouraged to complete every item in order without skipping any. Patients should be encouraged to circle the response that is most applicable. If, for example, a patient is not currently receiving any treatment, the patient should circle “not at all” to the question “I am bothered by side effects of treatment.”

The FACIT-dyspnoea (Appendix 10.3.2) will be self-administered by the patient at visits indicated in the Flowchart and Section 6.

5.2.6.3 Scleroderma Health Assessment Questionnaire (SHAQ)

The SHAQ includes the Health Assessment Questionnaire Disability Index (HAQ-DI) and 6 additional visual analog scales of relevance to patients with Systemic Sclerosis (P14-16917).

The Health Assessment Questionnaire (HAQ) is a questionnaire that has been used frequently in rheumatological disorders including Systemic Sclerosis, assessing function/activities of daily living with 20 items in 8 categories, namely dressing and grooming, hygiene, arising, reach, eating, grip, walking, and common daily activities (P14-16916; R14-5058).

Each category has at least two sub-category questions. Within each category, patients report the amount of difficulty they have in performing the specific sub-category items. There are four response options ranging from No Difficulty to Unable to Do, scored 0-3. A global score (the HAQ disability index, or HAQ-DI) will be calculated from the category scores.

The 6 additional visual analog scales of relevance to patients with Systemic Sclerosis are pain, a patient global assessment of limitation, vascular involvement, digital ulcers, lung involvement and gastrointestinal involvement. Scores from these scales are not incorporated into the overall score of the HAQ-DI.

The SHAQ (Appendix 10.3.3) will be self-administered by the patient at visits indicated in the Flowchart and Section 6. Detailed Further instructions regarding the SHAQ administration to the patient and scoring is provided in the ISF.

5.2.6.4 EuroQol 5-Dimensional quality of life Questionnaire (EQ-5D-5L)

The EQ-5D-5L was developed by the European Quality of Life Group (EuroQol Group) and is a standardised instrument for use as a measure of health outcome (R96-2382). The version used in this trial is the new five-level version (EQ-5D-5L).

The questionnaire essentially consists of 2 pages. The first page is the descriptive system with 5 questions to the patient´s health state today. Each question captures one dimension of health (e.g. mobility, self-care) and has five levels to answer. The second page records the patient´s self-rated health status of today on a vertical graduated (0 to 100) visual analogue scale.

The EQ-5D-5L (Appendix 10.3.4) will be self-administered by the patient at visits indicated in the Flowchart and Section 6.

5.2.6.5 Patient's and physician's global impression of health

The patient's global impression of health visual analog scale (VAS; Appendix 10.4) will be self-administered by the patient at visits indicated in the Flowchart and Section 6.

The physician's global impression of health VAS (Appendix 10.5) will be filled out by the patient's physician at visits outlined in the Flowchart after all other trial procedures have been completed.

The global impression of health VAS is a scale comprised of a horizontal line, about 10 centimetres (100 mm) in length, anchored by verbal descriptors. The respondent places a vertical line to the VAS line at the point that represents the intensity of the effect in question. The length of the VAS is imperative on paper, as the score is determined using a ruler and measuring the distance between the anchors (range from about 0 to 100 mm) (R15-2010).

5.2.6.6 Combined Response Index in Systemic Sclerosis (CRISS)

The Combined Response Index in Systemic Sclerosis (CRISS) is based on the mRSS, FVC percent predicted, HAQ-DI, patient's global impression of overall health VAS and physician's global impression of patient's overall health VAS, as well as the absence of significant worsening of interstitial lung disease, a new scleroderma renal crisis, left ventricular failure or pulmonary arterial hypertension (R15-1207).

5.2.7 Disease progression

For the assessment of the proportion of patients with disease progression, any the following definition will apply:

- An absolute decline since baseline in FVC percent predicted >10%
- A relative change from baseline in mRSS of >25% and an absolute change from baseline of >5 points
- Death

5.2.8 Nailfold capillary microscopy (substudy at dedicated sites only)

Scleroderma pattern and changes will be assessed by nailfold capillaroscopy using the site's own equipment, more specifically with a nailfold videocapillaroscope which allows digital

storage of the images with magnification (x 200). The software should allow a grid of one linear mm to be placed on the images that have been stored in order to count the number of capillaries in each picture. All measures will be conducted preferably by the same person.

Nailfold videocapillaroscopy will be performed as indicated in the Substudy Flowchart.

Images will be sent to central reading. Change from baseline in number of capillaries (density) will be assessed centrally by counting capillaries per linear mm. Further assessments might include abnormal shapes e.g. (neo) angiogenesis.

Detailed instructions for the nailfold capillary microscopy substudy will be provided in the site's ISF. Results may be included into the clinical trial report or reported separately.

5.2.9 HRCT (substudy at dedicated sites only)

High resolution CT (HRCT) in the substudy will be performed as indicated in the Substudy Flowchart and according to the specifications provided in the ISF. All scans on each patient will be completed on the same scanner used for the baseline CT and accredited for use by the Central Imaging Vendor.

Whenever possible the same technician will complete the scans.

All scans will be digitally transferred for central review. Central review will be completed by the same reference radiologist where possible as for all previous scans for that patient.

The following assessments of structural change in the lungs will be determined on each scan:

- Quantitative lung fibrosis score and quantitative total ILD score
- Mean lung attenuation, skewness, and kurtosis on density histograms

The following assessments of structural change on HRCT may be determined on each scan:

- Gastrointestinal Assessment / Assessment of the oesophagus

HRCTs should be performed only if ≥ 3 months have elapsed since the previous HRCT.

The HRCT substudy results may be included into the CTR or reported separately.

5.2.10 Skin biopsy (substudy at dedicated sites only)

Skin biopsy assessment will evaluate changes of certain protein and ribonucleid acid (RNA) markers pre- and post-treatment. Therefore two 3 mm punch biopsies will be taken at visits indicated in the Substudy Flowchart (one for protein/immunhistochemistry and one for RNA analysis). Further details are provided in Section 5.5 and the ISF. Results may be included into the clinical trial report or reported separately.

5.3 ASSESSMENT OF SAFETY

5.3.1 Physical examination

Complete physical examination will be performed at timepoints indicated in the Flowchart. All abnormal findings at baseline will be recorded on the Baseline Condition eCRF page. New abnormal findings or worsening of baseline conditions detected at the subsequent physical examinations will be recorded as adverse events on the appropriate eCRF page.

5.3.2 Vital signs

Systolic and diastolic blood pressure and pulse rate will be measured with the patient seated after having rested. All abnormal findings at baseline will be recorded on the baseline condition eCRF page. New abnormal findings or worsening of baseline conditions detected at the subsequent physical examinations will be recorded as adverse events on the appropriate eCRF page.

5.3.3 Safety laboratory parameters

The laboratory tests at regular site visits will include:

Category	Laboratory test
Haematology	Red blood cell count (RBC) Haemoglobin (Hb) Haematocrit (Hct) Mean corpuscular volume White blood cell count including differential Platelet count
Biochemistry	Aspartate aminotransferase (AST) Alanine transaminase (ALT) Gamma-glutamyl transferase (GGT) Alkaline phosphatase (ALK) Creatine kinase (CK) Lactate dehydrogenase (LDH) Total protein Total bilirubin Brain natriuretic peptide (BNP, only at V2, 7, 9,V12/EOT) Creatinine Glucose (non fasting) Uric acid Thyroid stimulating hormone (only at V2, 7, 9, V12/EOT) ß-HCG (at Visit 2 only)
Electrolytes	Sodium Potassium Calcium Chloride Inorganic phosphorus
Coagulation	International normalized ratio (INR) Partial thromboplastin time (PTT) Prothrombin time (PT)
Urinalysis	pH, glucose, erythrocytes, leukocytes, protein, nitrite (semiquantitative measurements; -, +, ++, +++)
Local Urine dipstick pregnancy test in all women of childbearing potential. If urine test is not acceptable to local authorities, a blood test must be done at a local laboratory.	

The laboratory tests at intermediate 'a' visits will include:

Category	Laboratory test
Biochemistry	Total protein, creatinine, electrolytes and liver function (AST, ALT, GGT, alkaline phosphatase, and total bilirubin)
Urinalysis	pH, glucose, erythrocytes, leukocytes, protein, nitrite (semiquantitative measurements; -, +, ++, +++)
Local Urine dipstick pregnancy test in all women of childbearing potential. If urine test is not acceptable to local authorities, a blood test must be done at a local laboratory.	

Overall about 230 mL blood will be taken for standard safety laboratory during the course of the trial.

Creatinine clearance will be calculated based on serum creatinine according to Cockcroft and Gault (R96-0690, Appendix 10.2).

If laboratory values indicate abnormality, adequate and more frequent blood sampling may be performed at the discretion of the Investigator.

In case of liver function value elevations, close monitoring must be ensured by the Investigator. Refer to Section 4.2.1.2 for monitoring elevations and Section 3.3.4 for withdrawal criteria.

Laboratory analysis will be done using central laboratory services. Venous whole blood will be collected in appropriate syringes provided by the Sponsor through the assigned central laboratory. Details regarding centrifuge, processing, storage and shipment of samples will be determined by the central laboratory in accordance with the Sponsor. The Investigators will be informed and instructed by the central lab and detailed documentation will be included in the ISF.

5.3.4 Electrocardiogram

Regular 12 lead Electrocardiograms (ECGs) are conducted during the trial with site's own equipment. Rate, rhythm and repolarisation changes have to be evaluated, compared to previous tracings, and assessed for clinical relevance.

Clinically relevant findings must be entered as adverse events.

5.3.5 Echocardiography

Doppler echocardiography will at least be performed in patients with a prior history of pulmonary hypertension at time of screening (note: severe PH patients are excluded according to Section 3.3.3).

Each site will use their own equipment to evaluate e.g. right and left ventricular function, atrial size, ventricular morphology and the presence of valvular abnormalities and/or pericardial effusion.

Patients with a known history of PH that refuse or are not able to have echocardiograms will be excluded from the trial.

Clinically relevant findings must be entered as adverse events.

5.3.6 Other safety parameters

Worsening or new onset of SSc organ involvement (e.g. renal, cardiac, GI, vasculopathy) will be assessed via evaluation of adverse events / serious adverse events.

5.3.7 Assessment of adverse events

5.3.7.1 Definitions of AEs

Adverse event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily has to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Serious adverse event

A serious adverse event (SAE) is defined as any AE which:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability or incapacity,
- Is a congenital anomaly/birth defect

  or
- Is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Life-threatening in this context refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe.

Every new occurrence of cancer must be reported as a serious event regardless of the duration between discontinuation of the drug and the occurrence of the cancer.

For Japan, the following events will be handled as "deemed serious for any other reason". An AE which possibly leads to disability will be reported as an SAE:

AEs considered "always serious"

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of AEs, which by their nature, can always be considered to be "serious" even though they may not have met the criteria of an SAE as given above.

The latest list of "always serious AEs" can be found in the Remote Data Capture (RDC) system (list of implied serious adverse events). These events should always be reported as SAEs as described in Section 5.3.7.

Adverse events of special interest (AESIs)

The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESI need to be reported to the Sponsor's Pharmacovigilance Department within the same timeframe that applies to SAE, see Section 5.3.7.

Adverse events relating to gastrointestinal perforation and hepatic injury will be considered AESIs.

Hepatic injury

In this trial protocol, signs of hepatic injury are defined as:

- ALT and/or AST ≥8 fold ULN
- ALT and/or AST ≥3 fold ULN and total bilirubin ≥ 2 fold ULN*
- ALT and/or AST ≥3 fold ULN and unexplained INR > 1,5*
- ALT and/or AST ≥3 fold ULN and unexplained eosinophilia (>5%)*
- ALT and/or AST ≥3 fold ULN and appearance of fatigue, nausea, vomiting, right upper abdominal quadrant pain or tenderness, fever and/or rash

* in the same blood draw sample.

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to immediately stop the trial medication and need to be followed up according to the "DILI checklist" provided in the ISF.

In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST and total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

Intensity of AEs

The intensity of the AE should be judged based on the following:

Mild: Awareness of sign(s) or symptom(s) that is/are easily tolerated

Moderate: Enough discomfort to cause interference with usual activity

Severe: Incapacitating or causing inability to work or to perform usual activities

In addition the intensity of diarrhoea adverse events should be classified and recorded in the eCRF according to the Common Terminology Criteria for adverse events (CTCAE) version 4 (R10-4848, Table 5.3.7:1).

Table 5.3.7:1 CTCAE Categorisation for diarrhoea

CTCAE Grade	**Diarrhoea**
1	Increase of <4 stools per day over baseline
2	Increase of 4 to 6 stools per day over baseline
3	Increase of ≥7 stools per day over baseline; incontinence
4	Life threatening consequences
5	Death

Causal relationship of AEs

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Yes: There is a reasonable causal relationship between the investigational product administered and the AE.

No: There is no reasonable causal relationship between the investigational product administered and the AE.

5.3.8 Adverse event collection and reporting

The following must be collected and documented on the appropriate eCRF by the Investigator:

From signing the informed consent through to the end of the residual effect period (REP) of at least 28 days after the date of last dose, all AEs (serious and non-serious) will be collected. If a patient discontinues trial medication but continues to attend future visits, all AEs (serious and non-serious) should be collected until the patient completes the trial. AEs starting on or after the date of first dose of trial medication, and up to 28 days after the date of last dose will be considered as on-treatment.

After the individual patient's end of trial the investigator does not need to actively monitor the patient for AEs but should only report relevant SAEs and relevant AESIs of which the investigator may become aware of.

AE reporting to sponsor and timelines

The Investigator must report SAEs, and non-serious AEs which are relevant for the reported SAE on the BI SAE form via fax immediately (within 24 hours) to the Sponsor's unique entry point (country specific contact details will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions the Investigator could inform the Sponsor upfront via telephone. This does not replace the requirement to complete and fax the BI SAE form.

For Japan:

All SAEs and AESIs must be reported immediately to the head of the trial site.

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information.

Information required

For each AE, the Investigator should provide the information requested on the appropriate eCRF pages and the BI SAE form (if applicable), e.g. onset, end date, intensity, treatment required, outcome, seriousness, and action taken with the investigational drug(s). The Investigator should determine the causal relationship to the trial medication and the trial procedures outlined under Section 6.2.

The following should also be recorded as an (S)AE in the eCRF and SAE form (if applicable):

- Worsening of the underlying disease or of other pre-existing conditions
- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the Investigator.

If such abnormalities already pre-exist prior trial inclusion they will be considered as baseline conditions.

All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been sufficiently characterized, or no further information can be obtained.

Pregnancy:

In the rare case that a female subject participating in this clinical trial becomes pregnant after having taken trial medication, the Investigator must report immediately (within 24 hours) the drug exposure during pregnancy (DEDP) to the Sponsor's unique entry point (country-specific contact details will be provided in the ISF). The pregnancy monitoring form for clinical trials (Part A) should be used.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the Sponsor's unique entry point on the pregnancy monitoring form for clinical trials (Part B).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE, only the pregnancy monitoring form for clinical trials and not the SAE form is to be completed. If there is an SAE associated with the pregnancy then the SAE has to be reported on the SAE form in addition.

The ISF will contain the pregnancy monitoring form for clinical trials (Part A and B).

Safety monitoring and adverse events with additional information collection:

- An independent data monitoring committee (DMC) will conduct regular reviews of the trial safety data as detailed in Section 2.3 and in the DMC charter.
- An independent adjudication committee will review all fatal cases (to review the primary cause of death). The independent adjudication committee (AC) will also review all adverse events categorized as major adverse cardiovascular events (MACE).

  Before providing any copy of patients' source documents to the sponsor the investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number) have properly been removed or redacted to ensure patient confidentiality.
- Additional details (on top of standard AE and SAE reporting) will be collected in the eCRF for the adverse event 'Diarrhea' and the adverse events in the subordinate Standard MedDRA Query (SMQ) 'Haemorrhage terms, excluding laboratory terms'.

5.4 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.4.1 Assessment of pharmacokinetics

Plasma concentration monitoring of nintedanib (BIBF 1120) and its two main metabolites BIBF 1202 and BIBF 1202-glucuronide will be performed in order to assess drug exposure in the SSc-ILD patient population. PK plasma sampling will be conducted at Visit 4 and 7 just before drug administration and hence the pharmacokinetic parameter Cpre, ss will be determined. The pharmacokinetic parameter will be included in the clinical trial report.

5.4.2 Methods of sample collection

A detailed description of sample collection and handling is provided in the ISF. For quantification of drug plasma concentrations of nintedanib (BIBF 1120) and its metabolites BIBF 1202 and BIBF 1202- glucuronide, venous blood will be collected using a pre-labeled potassium ethylenediamine-tetraacetic acid (EDTA) containing blood drawing tube.

Overall about 7 mL blood will be taken for pharmacokinetic measurement during the course of the trial.

Date and exact clock time of drug administration and blood sampling at Visit 4 and 7 must be recorded on the eCRF. Additionally, the date and exact clock time of drug administration for the three days preceding the visit where blood sampling for PK is performed must be recorded.

5.4.3 Analytical determinations

Nintedanib (in form of its free base BIBF 1120 BS), its metabolites BIBF 1202 (in form of the free zwitterion BIBF 1202 ZW) and the acylglucuronid thereof (BIBF 1202 glucuronide) plasma concentrations will be determined by a validated assay based on liquid chromatography-tandem-mass spectrometry (LC-MS / MS).

The procedures and specifications of the analytical method are available at the bioanalytical site ([redacted]

5.4.4 Pharmacokinetic / pharmacodynamic relationship

It is planned to investigate via modeling the relationship between nintedanib exposure and efficacy (primary efficacy endpoint) and safety (gastro-intestinal side effects and liver enzyme increase). In addition, pharmacokinetic / pharmacodynamic (PK / PD) relationships might be explored with selected exploratory biomarkers. The results will be reported separately.

5.5 ASSESSMENT OF EXPLORATORY BIOMARKER(S)

In order to better understand the effects of nintedanib on local and systemic aspects of SSc disease, mechanistic and disease related biomarkers will be assessed in the skin and peripheral blood of randomised patients.

Biomarkers related to SSc pathology will be explored pre and post treatment with nintedanib in serum, plasma, and whole blood RNA and will be correlated with the clinical endpoints.

Skin biopsies will be evaluated pre and post treatment for (epi)dermal thickness and the presence of proteins such as SMA, PDGFR, p-PDGFR, c-abl, and p-c-abl using histology/immunohistochemistry methods. RNA expression will also be assessed in skin biopsies pre and post treatment.

Note: Participation in the skin biopsy sampling is voluntary and not a prerequisite for participation in the trial.

Biomarkers that might be evaluated

- Protein biomarker: VEGF, PDGF, CCL2, CCL18, CXCL4, KL6, TGF-ß1, CTGF, IL-6, CRP, CA 125, CA 19-9, Cyfra 25.1, ECM turnover (BGM, C1M, C3M, C5M, C6M, CRPM, Pro-C3, Pro-C6, C4M2, P4NP7S, VICM), miRNAs related to SSc such as miR-30b (Visit 2, 4, 7 and 9)
- Autoantibodies: anti-topoisomerase antibodies (ATA) (Visit 2, 7 and 9), anti-RNA polymerase III antibodies ((anti-)RNA Pol III) (only at Visit 2), anti-Centromere antibodies (ACA) (only at Visit 2)
- mRNA expression levels in whole blood (Visit 2, 7 and 9)
- Skin biopsy substudy: mRNA expression levels, (epi)dermal thickness and histology analysis (optional after separate informed consent at Visits 2, 6 and 9)
- pre-specified genetic markers for SSc, such as IRF5
- Metabolome profile

Overall about 118 mL blood will be taken for explorative biomarker assessment and banking during the course of the trial.

Remaining serum, plasma and RNA samples may be used for method development and evaluation and will be stored for a maximum of 3 years upon signature of the clinical trial report.

5.5.1 Methods and timing of sample collection

Whole blood will be collected for the preparation of serum, plasma and RNA expression analysis. For substudy participants, skin biopsies will be collected for RNA expression analysis.

Collection time points are outlined in the Flowchart and respective footnotes.

Correct, complete and legible documentation of drug administration and blood sampling times is mandatory to obtain data of adequate quality for biomarker analysis.

A detailed description of biomarker sample collection and sample handling is provided in the ISF.

5.5.2 Analytical determinations

All biomarkers assessed in this trial are considered exploratory and assays, qualified according to sponsor's procedures, will be used for analyses.

Protein biomarkers will be analysed in EDTA plasma or serum using qualified assays. Characteristics of the analytical methods for the analysis of plasma and serum biomarkers will be given in detail in the analytical report.

Autoantibody analysis from serum samples will be processed at a central laboratory. Characteristics of the analytical method for the analysis will be given in detail in the analytical report.

The first biopsy collected in 10% neutral buffered formalin will be used for histology / immunohistochemistry assessment. Characteristics of the analytical method for the analysis will be given in detail in the analytical report.

The second biopsy collected in a RNA later microtube will be used to gene expression analysis. Therefore the RNA is first homogenized using a Precellys Tissue RNA Kit and then RNA is purified using a Qiagen RNeasy Kit. For RNA expression analysis from whole blood samples RNA is directly purified by using a Qiagen RNeasy Kit. RNA quantity and quality of samples will additionally be checked using the Agilent RNA 6000 Nano Assay Protocol. Genome-wide expression profiling will be performed by RNA sequencing including bioinformatics analysis. Further characteristics of the analytical method for the analysis will be given in detail in the analytical report.

Changes in serum, plasma, histology / immunohistochemistry and gene expression (RNA) levels will be summarized over time pre and post treatment with nintedanib.

All assessed Biomarkers will either be analysed at the sponsor or at a CRO. The results of biomarker analyses may be included into the clinical trial report, or reported separately.

5.5.3 Biobanking

DNA banking:

For countries participating in the optional DNA banking, one blood sample will be used for desoxyribo nucleid acid (DNA) banking if participation and the separate informed consent is agreed upon by the patient as noted below. [redacted].

Note: Participation in the DNA banking is voluntary and not a prerequisite for participation in the trial. The DNA banking sample will be stored after separate informed consent is given in accordance with local ethical and regulatory requirements.

One 8.5 mL blood sample for DNA banking will be collected in PAXgene blood DNA tube at or after Visit 2 for those patients who signed a separate informed consent for DNA banking. Blood samples collected in PAXgene blood DNA tubes should be stored and shipped at a temperature of about -20°C or below.

5.6 OTHER ASSESSMENTS

For the purpose of a separate health economic analysis (such as cost-utility analysis), health care resource utilisation (HCRU) data will be collected throughout the trial. Resource use data collected for calculating direct costs will include unscheduled hospitalisations, healthcare provider visits, and emergency room/intensive care unit use. Non-medical resource use data will include changes in work productivity.

The economic evaluation of the HCRU data will not be part of the clinical trial report but reported separately.

5.7 APPROPRIATENESS OF MEASUREMENTS

The measures conducted for primary, key secondary and secondary endpoints are using standard methods. Measures conducted for exploratory further endpoints might be new methodologies already used in clinical trials in SSc but not yet validated for this rare disease.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

There is one screening visit (which may be preceded by a separate informed consent visit) and up to 11 visits planned within the 100 weeks treatment period (52 weeks until primary endpoint and additional 48 weeks on treatment), plus intermediate blood analyses and one follow-up Visit. The trial will last until:

- Follow-up visit of the last randomized patient if he/she completed 52 weeks of treatment, or
- Visit 9 of the last randomized patient if he/she discontinued treatment early but agreed to come to future visits as planned, or
- Follow-up visit of the last randomized patient if he/she discontinued treatment prematurely and did not agree to come to future visits

Approximately at this timepoint all ongoing patients will have their last trial visits and trial completion (patients on treatment will have an EOT and follow-up visit; patients who discontinue treatment early will have their next scheduled visit immediately).

After giving his/her informed consent, the patient will be screened for inclusion and exclusion criteria for the trial at Visit 1.

Visit 2 can be performed once the results from central laboratory of Visit 1 and central HRCT review are obtained. If for any reason the screening phase for an individual patient lasts for more than 6 weeks, then the laboratory examination for Visit 1 has to be repeated before randomization. The screening phase should not be longer than 12 weeks.

Rescreening is possible, rescreened patients will be assigned a new patient number.

The patient will be randomised at Visit 2 if all inclusion and none of the exclusion criteria are fulfilled.

The results of laboratory parameters from Visit 2 will become available only after Visit 2. Therefore, laboratory results from Visit 2 cannot qualify as exclusion criteria; laboratory results from Visit 1 will be used instead. In case laboratory results of Visit 2 would retrospectively fulfill an exclusion criterion, the patient should not continue receiving trial medication unless continuation is justified in writing by the Investigator.

Visits 2, 3, 4 and 5 will occur every 2 weeks. Visit 6 will be scheduled 6 weeks later, Visits 7 and 8 are planned every 12 weeks and further Visits (9, 10, 11 and 12/EOT) are planned every 16 weeks. Visits 6a, 7a, 8a, 9a, 10a and 11a (a-Visits) are intermediate laboratory control visits.

The samples for the ‘a-Visits’ may be drawn locally (i.e. local general practitioner [GP]). The Investigator would in that case give the required documentation to the patient, with the

corresponding trial kit for the respective 'a-Visit' to be sent to the central lab even if not at the trial site. Information, agreement and training of the respective local GP for blood draw will be ensured on an individual site basis consulting the sponsor's local monitor.

Pregnancy test will be performed in women of childbearing potential every 4-6 weeks. Urine dipstick test will be done at every visit and will be provided for at home pregnancy testing as soon as visit intervals are > 6 weeks (2 to 3 pregnancy test dipsticks to take home. Women of childbearing potential will be instructed accordingly.

The primary endpoint Visit 9 is scheduled 52 weeks after randomization, occurring 16 weeks after Visit 8. Visit 10, 11 and 12/EOT are scheduled every 16 weeks from Visit 9.

A window of ±3 days for the Visits 3 to 6, ±7 days for Visits 6a to 12 is allowed to accommodate scheduling problems. If a delay is observed for a particular visit, the original calendar schedule should be kept for subsequent visits (delays should not accumulate).

If treatment is discontinued, regardless if prematurely, after 100 weeks, or at the global end of the trial, an end of treatment visit (EOT) will be performed.

A follow-up visit has to be organized 28 days (+ 7 days) after the end of treatment visit.

Patients who have been treated until the predefined end of the trial will have the possibility to participate in an extension trial to receive nintedanib open label.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening

All trial procedures at selected visits will be done according to Flowchart and footnotes and the CTP.

Informed consent (before or at the latest at Visit1)

- Informed consent will be obtained prior to patient participation in the trial, which includes any medication washout procedures or restrictions as well as HRCT transfer to central review. Upon obtaining informed consent, the patient will be instructed on the medication washout and other restrictions needed.
- At selected sites performing one or more substudies, patients should be invited during the informed consent process to participate in the respective substudy(ies).
- Patients will be asked to give informed consent to the DNA banking sample (please note: the DNA banking sample must not be taken prior to Visit 2). Participation is voluntary and is not a prerequisite for participation in the trial.
- A preliminary check of in-/exclusion criteria is recommended at time of informed consent to avoid unnecessary washout procedures in non-eligible patients.
- A historical HRCT not older than 12 months will be sent for central review after investigator's evaluation of fibrosis extent to be in accordance to inclusion criterion 5 (Section 3.3.2). Only if the patient will not have a HRCT within 12 months at scheduled Visit 1 timepoint but meets all other inclusion and no exclusion criteria, the HRCT can be performed for the purposes of participation in the trial (exception: in Germany, no HRCT will be performed for the purposes of participation in the trial).
- Site personnel will perform a screening call in IRT to ensure in-time trial medication shipment.
- Upon obtaining informed consent the patient will receive:
    - A trial identification card.
    - Women of childbearing potential will receive a menstruation calendar.

Patient material templates will be provided by the sponsor.

Observations and procedures at Visit 1

- If a separate informed consent Visit was not done, obtaining informed consent and the above mentioned procedures will be done prior to any further procedure at this visit.
- Demographics will be recorded.

- Medical history including pre-existing conditions will be recorded.
- Concomitant therapy including previous medications will be recorded.
- Any adverse events (since consent, if applicable) will be recorded.
- Local urine pregnancy test (dipstick) if applicable.
- Complete physical examination including vital signs will be performed.
- Patient's menstruation calendar will be reviewed (if applicable).
- A resting 12-lead electrocardiogram using site's own equipment will be performed and evaluated (if possible prior to blood draw).
- Echocardiography (at least to be performed in patients with a history of pulmonary hypertension (time window V1 to V2) and after 1 year (time window V9 to V9a).
- FVC measurement will be conducted with the FlowScreen® spirometer.
- DLCO measurement will be conducted. Order of lung function and DLCO will always be 1. FVC measurement followed by patient's rest, followed by 2. DLCO measurement.
- Blood and urine samples (safety lab) will be collected and submitted to the central laboratory (for details refer to Section 5.3.3). Prior to blood draw, a pre-assessment of all in/exclusion criteria is highly recommended.
- Site personnel will check if a historical ATA status is available. If no ATA status is available, an additional blood sample will be taken and sent to central lab for determination.
- Local urine pregnancy test (dipstick) if applicable.
- Site personnel will send HRCT to central review (if not already done at time of informed consent).
- For patients qualified to enter the screening period, Visit 2 will be scheduled.
- Site personnel will perform a screening call in IRT (if not already done at time of informed consent).

6.2.2 Treatment phase

At the beginning of each visit during treatment phase, investigator and site personnel should ensure the well-being of the patient as well as prepare all requirements for conduct of the visits that are necessary.

The order of the different trial procedures should be planned taking into account the specific structure of the investigational site and following the mandatory needs outlined in the clinical trial protocol.

Mandatory needs / the following must be ensured during trial visits:

- **Patient reported outcome questionnaires have to be filled out always prior to any other procedures by the patient in a quiet area and in the following order:**
  1. **SGRQ**
  2. **FACIT**
  3. **SHAQ**
  4. **EQ-5D-5L**
  5. **Patient's visual analogue scale (VAS) on global impression of health**
- **Urine pregnancy test and any laboratory sample collection must be performed prior trial medication administration.**
- **Timing of FVC and DLCO measurement at the visits must be performed approximately the same time of the day with ± 90 min maximum difference to reference time point at Visit 2.**
- **Order of pulmonary function tests must always be**
  1. **FlowScreen® spirometry (FVC) followed by patient's rest**
  2. **DLCO with site's own equipment.**

Timing of FVC and DLCO measurement at Visit 2 is critical as this will be the reference measurement for future visits (approximately the same time of the day with ± 90 min maximum difference). It is therefore highly recommended to discuss with the performing unit and the patient and plan for future visits upfront to ensure that the allowed time window can be met in all following visits.

For Visit 2 (randomization), the following prerequisites must be available

- Eligibility confirmation of central HRCT review.
- ATA status (positive or negative).
- Safety laboratory results including haemoglobine and creatinine from Visit 1.

Baseline Visit 2 (randomization) procedures

- All patients will be asked to fill out the patient reported outcome questionnaires prior to any other visit procedure. The order of the questionnaires will always be: 1. SGRQ, 2. FACIT, 3. SHAQ, 4. EQ-5D-5L, 5. Patient's global impression of health visual analogue scale (VAS).
- Site personnel will review questionnaires for completeness.
- Physical examination including vital signs and HCRU interview will be performed.
- Patient's menstruation calendar will be reviewed (if applicable).
- Adverse events and concomitant therapy since last visit will be reviewed and recorded.
- Medical history will be reviewed.
- Repeated resting 12-lead electrocardiogram using site's own equipment will be performed and evaluated if ECG was abnormal at Visit 1 (if possible prior to blood draw).
- Echocardiography will be performed (if applicable and not already performed during screening period).
- The modified Rodnan Skin Score (mRSS) and digital ulcers will be assessed.
- SPO_2 (unaffected skin at earlobe or forehead) at rest will be recorded.
- FVC measurement will be conducted with the FlowScreen® spirometer.
- DLCO measurement with site's own equipment will be conducted.
- All in/exclusion criteria will be assessed based on Visit 1 laboratory and Visit 2 measures.
- Safety blood and urine samples will be collected and submitted to the central laboratory.
- Biomarker samples will be collected and submitted to the central laboratory.
- The time of blood collection for biomarker samples will be recorded in the eCRF. Note: blood samples will always be collected prior to drug administration.
- One blood sample for DNA banking will be collected in eligible patients and only after obtaining a separate informed consent.
- Local urine dipstick pregnancy test (if applicable).
- If a patient is eligible for the trial, randomization will be performed by using the IRT system (and entering the ATA status if not already done at Visit 1).

- Treatment will be dispensed.
- The next visit will be scheduled and prepared.
- Patient's menstruation calendar will be dispensed (if applicable).
- Physician will complete his/her physician's global impression of patient's overall health visual analogue scale (VAS).

Visit 7, Visit 9, and Visit 12/EOT ('big visits') procedures

At Visit 7, Visit 9 (primary endpoint visit) and Visit 12/EOT, the same procedures will be performed as done at baseline Visit 2. Exceptions are the typical randomisation measures, e.g. eligibility review, medical history assessment and randomization as well as DNA banking sample which is only taken once. For Visit 7, 9 and 12/EOT always refer to the Flowchart.

General rules

- Treatment compliance will be reviewed by site personal.
- Trial medication will be collected and/or dispensed according to Flowchart.
- Visit 12 and end of treatment visit (EOT) are identical visits. EOT is to be used in eCRF at any time a patient ends trial medication (scheduled or prematurely).
- Visit 12 is to be used if a patient prematurely discontinued trial medication but agreed and came to future visits as planned (e.g. patient discontinues trial medication prematurely at Visit 10, then he/she would complete Visit 11 and 12. If a patient does continue on trial medication until the end of the trial he/she would complete EOT instead).
- IRT should always be notified on end of treatment (EOT).
- Vital status will be collected for all patients at week 52 and 100 or at the timepoint when patient's last full visit would have been scheduled, whatever occurs earlier.
- PROs / Questionnaires will always be scheduled prior any other procedure and in the above described order and will be reviewed for completeness by site personal.
- Drug intake at visit days should always be performed at site and after blood and urine sample collection and pregnancy test.
- FlowScreen® spirometry (FVC) and DLCO measurements will always be in the allowed time window and the described order (reference visit = Visit 2).

Some measures are not scheduled for every 'big visit', these are:

- Resting 12-lead electrocardiogram using site's own equipment will be performed and evaluated at Visit 7 and 9 and V12/EOT (if possible prior to blood draw).
- Echocardiography (Visit 1 to 2 and Visit 9 to 9a, and not at Visit 7 and Visit 12/EOT).
- ATA assessment (Visit 2, 7, 9, and not at Visit 12/EOT).
- Biomarker blood sampling (Visit 2, 7, 9, and not at Visit 12/EOT).
- At Visit 7 (and 'medium Visit 4' see below), a pharmacokinetic (PK) sample will be collected. The patient needs to record exact date and clock time of medication intake the preceding three days (via PK card dispensed the visit before). The date and time of blood collection and drug administration at the site will be recorded in the eCRF.
- 2 to 3 take home pregnancy tests (dipsticks) at Visit 7 and 9

'Randomization' and 'big visit' procedures may be performed on more than one calendar days, adhering to the following rules:

- Patients Questionnaires are to be completed before any other procedure.
- FVC & DLCO are to be completed the same day
- PK and Biomarker samples are to be taken before drug administration

Visit 3, 4, 5, 6, 8, 10, and 11 ('medium visits') procedures

Please note that not all medium visits are drug dispensation visits (please always refer to Flowchart). However, compliance of patients regarding drug intake should always be reviewed (see also treatment compliance in Section 4.3).

- Physical examination including vital signs and HCRU interview will be performed.
- Patient's menstruation calendar will be reviewed (if applicable).
- Adverse events and concomitant therapy since last visit will be reviewed and recorded.
- Local dipstick pregnancy test (if applicable).
- Safety blood and urine samples will be collected and submitted to the central laboratory.
- At medium Visit 4, a PK sample and biomarker samples will be collected. The patient needs to record exact date and clock time of medication intake the preceding three days.

- At Visit 3 and 6 the patient will be provided with the PK card to support the record of the exact date and clock time of medication intake three days preceding Visits 4 and 7.
- The date and time of blood collection and drug administration at the site will be recorded.
- FlowScreen® spirometry (FVC) in the allowed time window will be performed.
- mRSS and digital ulcer assessment will be done at Visits 6, 8, 10 and 11.
- Patient's menstruation calendar will be dispensed (if applicable).
- 2 to 3 take home pregnancy tests (dipsticks) at Visit 8, 10 and 11
- Treatment compliance will be reviewed by site personal at every visit (except at randomisation visit and at 'a-Visits').
- Trial medication will be collected and/or dispensed according to Flowchart.

Intermediate 'a-Visit' procedures

- Safety blood and urine samples will be collected and submitted to the central laboratory.
- Local dipstick pregnancy test will be performed (if applicable).

6.2.3 Follow-up Visit and trial completion

A follow-up Visit has to be scheduled 28 days after End of treatment Visit (28 days safety follow-up after treatment discontinuation)

- Physical examination including vital signs.
- Adverse events and concomitant therapy will be assessment since last visit.
- Patient's menstruation calendar will be reviewed (if applicable).
- Local dipstick pregnancy test (if applicable).
- Safety blood and urine samples will be collected and submitted to the central laboratory.
- FlowScreen® spirometry (FVC) in the allowed time window will be performed.
- Patient's participation will be concluded (trial completion).

Trial completion

The trial completion eCRF page has to be filled-in when the patient has terminated the trial. The end of the trial is:

- At the end of the follow-up Visit for patients who have completed the trial on treatment as planned.
- After early discontinuation end of treatment (EOT) and follow-up Visit, if a patient did not accept to come to future visits planned.
- At the end of Visit 12 or at the end of the trial for patients who discontinued drug early but came to future visits as planned.

Patients who prematurely discontinued trial medication

In case a patient has to permanently discontinue trial medication, for whatever reason, he/she will be encouraged to attend all future visits up ~~to Visit 12~~ as originally planned (except for the laboratory 'a-Visits').

- During these visits, the patient will undergo all planned examinations and especially FlowScreen® spirometry (FVC); however he/she will not have to do the ECG, safety laboratory, biomarker laboratory and PK blood draw.
- These visits will be regarded as part of the trial despite the patient having discontinued trial medication.
- For the substudy assessments after early discontinuation of trial medication refer to Substudy Flowchart and respective footnotes.

The need for coming to future visits in case of prematurely discontinuation of trial medication will be explained to patients prior to their participation in the trial.

If the patient refuses to attend all future visits as originally planned, but agrees with vital status assessment, the latter will be conducted twice; 52 weeks and 100 weeks after randomization or at the timepoint when patient's last full visit would have been scheduled, whatever occurs earlier. Details are described below.

Vital status information

In case of early discontinuation of trial medication, if the patient does not agree to come to future visits as originally planned, every attempt will be made to get information on vital status at 52 weeks and at 100 weeks after his/her randomization or at the timepoint when patient's last full visit would have been scheduled, whatever occurs earlier.

Patients will be asked to agree to be contacted by the site personnel, which could be by telephone calls, to allow collection of this information.

If death occurs, the investigator will review the circumstances, including the relevant medical records to ascertain the most likely primary and secondary causes of death.

Collection of vital status will be performed in accordance with national ethical and regulatory guidelines.

The need for vital status information will be explained to patients prior to their participation in the trial.

Extension trial

All patients who have completed the trial on trial medication will be offered to enter an open label extension trial. The main objective of the open label extension trial is to follow up long term safety and lung function parameters.

A maximum of 12 weeks drug-free interval before rolling over will be allowed. The extension trial is a separate trial and a specific consent will be sought before participation. A separate ISF and clinical trial protocol will be issued.

Procedures will be put in place so that the blind of the parent trial will be maintained for the trial team, investigator and patient (until database lock of the parent trial).

6.2.4 Dose reduction visit / dose increase visit

If a patient experiences a drug related adverse event, the dose can be reduced and the dose can be re-increased after recovery as described in Section 4.2.1. In both cases, the patient will have to come back to a visit where the following will be performed:

- Physical examination including vital signs.
- Adverse events and concomitant therapy will be assessment since last visit.
- Local dipstick pregnancy test (if applicable).
- Safety blood and urine samples will be collected and submitted to the central laboratory.
- FlowScreen® spirometry (FVC) in the allowed time window will be performed.
- Trial medication will be collected and treatment compliance will be reviewed.
- IRT call for reduction or increase of the dose and trial medication dispensation.

6.2.5 Optional substudies

Substudies will be performed at selected, highly specialized and experienced sites. Patients at these dedicated sites will be invited to optionally participate in one or several substudies and give their consent by a separate patient information / informed consent (PI / IC). Participation in the main trial must not be affected if a patient withdraws from a substudy participation.

Participation in the substudies is voluntary and not a prerequisite for participation in the main trial.

Scheduling of optional substudy procedures is specified in the Substudy Flowchart and corresponding footnotes.

Substudy information for respective sites will be provided in the ISF.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This is a multi-centre, multi-national, prospective, randomised, placebo-controlled, double blind clinical trial to investigate the efficacy and safety of nintedanib at a dose of 150 mg bid, in patients with Systemic Sclerosis associated Interstitial Lung Disease.

The primary endpoint is the annual rate of decline in FVC in mL, estimated from readings taken over 52 weeks. The primary endpoint will be analysed using a random coefficient regression model (i.e. a random slope and intercept) as detailed in Section 7.3.1.

The key secondary endpoints are the absolute change from baseline in the mRSS at week 52, and the absolute change from baseline in the SGRQ total score at week 52. These will be analysed using a Mixed Model Repeated Measures (MMRM) approach as detailed in Section 7.3.2.

7.2 NULL AND ALTERNATIVE HYPOTHESES

A hierarchical testing procedure will be used to test the primary and key secondary endpoints in order to protect the type I error rate. The primary objective is to establish the superiority of nintedanib over placebo. The following hypotheses for the primary endpoint will be tested first (based on a two-sided test):

> H_{01}: There is no difference in the annual rate of decline in FVC in mL between nintedanib 150 mg bid and placebo.
>
> H_{a1}: There is a difference in the annual rate of decline in mean FVC in mL between nintedanib 150 mg bid and placebo.

If the null hypothesis H_{01} is rejected at the 5% significance level in favour of nintedanib 150 mg bid, then the following hypotheses for the first key secondary endpoint will be tested (based on a two-sided test):

> H_{02}: There is no difference in the mean absolute change from baseline in the mRSS at week 52 between nintedanib 150 mg bid and placebo.
>
> H_{a2}: There is a difference in the mean absolute change from baseline in the mRSS at week 52 between nintedanib 150 mg bid and placebo.

If the null hypothesis H_{02} is rejected at the 5% significance level in favour of nintedanib 150 mg bid, then the following hypotheses for the second key secondary endpoint will be tested:

> H_{03}: There is no difference in the mean absolute change from baseline in the SGRQ total score at week 52 between nintedanib 150 mg bid and placebo.

H_{a3}: There is a difference in the mean absolute change from baseline in the SGRQ total score at week 52 between nintedanib 150 mg bid and placebo.

Each step will only be considered confirmatory providing all the previous steps were successful. If any of the previous steps were not successful (i.e. the null hypothesis was not rejected), then the procedure stops and the current endpoint (and any subsequent endpoints) will be analysed for exploratory purposes only.

7.3 PLANNED ANALYSES

The efficacy and safety analyses will be conducted on the treated set, which consists of patients who are randomised to a treatment group and receive at least one dose of trial medication. For efficacy analyses, all measurements performed within the first 52 weeks will be used, even if a patient prematurely discontinues treatment (i.e. using an intent-to-treat principle).

For efficacy and safety analyses, patients will be analysed according to their planned treatment group.

7.3.1 Primary endpoint analyses

The primary endpoint is the annual rate of decline in FVC in mL estimated from measurements taken over 52 weeks. ATA status (positive or negative), age, height, gender and baseline FVC in mL will be included as explanatory variables in the model. Baseline FVC is defined as the FVC result recorded at Visit 2, unless missing in which case the screening result will be used. The decrease in FVC is assumed to be linear within each subject over the 52 weeks; this was also assumed in the idiopathic pulmonary fibrosis trials INPULSIS-1 and INPULSIS-2 (P14-07514). The intercepts and slopes will be assumed to be normally distributed with arbitrary covariance matrix. The within patient error will be assumed to be independent and normally distributed with mean zero and a common variance. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$, and an intent-to-treat principle will be used (i.e. all available data up to 52 weeks will be used, including baseline and data for patients who prematurely discontinue randomised treatment). Analyses will be implemented using SAS® version 9.4 or higher.

The assumptions for the primary analysis of decline in FVC will be tested as described in the trial statistical analysis plan (TSAP). The primary analysis will be based on observed data and will assume data are missing at random. The effect of missing data will be investigated using multiple imputation methods which assume that patients who discontinue treatment will no longer benefit from it in the future. See Section 7.5.1 for further details of these sensitivity analyses.

Subgroup analyses (for example, by gender, age, ATA status, SSc subtype and subgroups reflecting disease severity) will be specified in the TSAP.

A cumulative distribution plot will be provided, showing the percentage of patients by the change from baseline in FVC in mL at week 52.

FVC data collected beyond week 52 will be analysed in a descriptive manner only. Data will be summarised graphically and using summary statistics.

7.3.2 Secondary endpoint analyses

7.3.2.1 Analyses of the key secondary endpoints

The key secondary endpoints of the absolute change from baseline in mRSS at week 52, and the absolute change from baseline in the SGRQ total score at week 52, will be analysed using a restricted maximum likelihood (REML) based repeated measures approach. Analyses will include the fixed, categorical effects of treatment, ATA status, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline and baseline-by-visit interaction. An unstructured (co)variance structure will be used to model the within patient measurements.

If this analysis fails to converge, the following covariance structures will be tested in order: heterogenous toeplitz, toeplitz and autoregressive 1 (AR[1]). The first model to converge will be used. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$ (two-sided 95% confidence intervals [CIs]). In case the model fails to converge under PROC MIXED, the “singular” option will be considered. The treatment comparisons will be the contrast between treatments at week 52. An intent-to-treat principle will be used (i.e. all available data up to 52 weeks will be used, including data for patients who prematurely discontinue randomised treatment).

The effect of missing data will be investigated using multiple imputation methods which assume that patients who discontinue treatment will no longer benefit from it in the future. See Section 7.5.1 for further details. Additional sensitivity analyses and subgroup analyses may be done and will be described in the TSAP.

A cumulative distribution plot will be provided, showing the percentage of patients by the change from baseline in mRSS at week 52.

7.3.2.2 Analyses of the other secondary endpoints

The rate of decline in FVC in percent predicted will be analysed in the same way as the primary endpoint including ATA status and baseline FVC% predicted as covariates. All other continuous secondary endpoints will be analysed in the same way as the key secondary endpoints using a MMRM approach.

If the percentage of deaths during the trial is less than 2% in total, then the number and percentage of deaths will be presented by treatment group. Otherwise, a Cox proportional hazards model stratified by ATA status will be used to estimate and test (based on a Wald test) the hazard ratio of nintedanib vs placebo for the time to all-cause mortality endpoint. A Kaplan-Meier plot by treatment group will also be presented. Note that the endpoint will be based on all available data collected up to trial completion.

Any p-values presented for the secondary endpoints (with the exception of the key secondary endpoints) will be considered nominal in nature and no adjustment for multiplicity will be made.

7.3.3 Further endpoint analyses

All further endpoints will be summarized descriptively and will be considered exploratory in nature.

Baseline levels and changes from baseline in serum and plasma protein biomarkers will be summarized descriptively over time by treatment group. Correlations between change from baseline in clinical measures (FVC, mRSS) and serum/plasma and RNA biomarker levels will be explored. In addition, the relationships between drug concentrations, clinical efficacy and selected biomarkers will be explored. The results may be included in a separate biomarker analysis plan and report.

7.3.4 Safety analyses

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Standard BI summary tables and listings will be produced. All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events. To this end, all adverse events occurring between start of treatment and end of the residual effect period will be considered ‘treatment-emergent’. The residual effect period is the 28 days after the date of the last dose of trial medication. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as ‘treatment-emergent’. Based on the half-life of the study drug, adverse events that occur between the start of treatment and up to 7 days after the date of the last dose of trial medication will be analysed in addition.

Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of the MedDRA.

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be highlighted in the

listings. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

Vital signs, physical examinations, or other safety-relevant data observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

7.3.5 Pharmacokinetic analyses

In the CTR, pre-dose plasma concentrations (Cpre,ss) of nintedanib and its two metabolites (BIBF 1202 and BIBF 1202-glucuronide) will be tabulated with descriptive statistics.

For pharmacokinetic analysis and displays, concentrations will be used in the same format as reported in the bio-analytical report. Only concentrations within the validated concentration range and actual sampling times will be used. See Appendix 10.6.1 for further details.

7.4 INTERIM ANALYSES

Safety data will be reviewed on a regular basis by a DMC (see the DMC charter for further details). A blinded assessment of variability and/or rate of FVC decline may be performed in order to check and re-estimate the sample size assumptions. More details regarding the timing and the recalculation strategy will be provided in the TSAP and will be available by the time of first patient in. No unblinded interim analyses are planned.

7.5 HANDLING OF MISSING DATA

7.5.1 Efficacy endpoints

The effect of missing data on the primary endpoint will be investigated using multiple imputation techniques.

For the primary endpoint, the following subsets of patients will be defined:

1) Patients with an FVC result at week 52 who received trial medication until week 52.
2) Patients with an FVC result at week 52 who prematurely discontinued trial medication prior to week 52.
3) Patients without an FVC result at week 52 who were alive at week 52.
4) Patients without an FVC result at week 52 who died prior to week 52.

These four subsets of patients will be used in sensitivity analyses to estimate the treatment effect under differing assumptions around the persistence of efficacy after withdrawal of trial medication. Table 7.5.1: 1 describes the planned sensitivity analyses for handling missing primary endpoint data. Sensitivity analyses 1 and 2 will only be performed if there are at least 10 patients included in patient subset 2 in each treatment group.

Table 7.5.1: 1 Sensitivity analyses for handling missing primary endpoint data

Analysis	**Patient subset 3: No FVC result but alive at Week 52**		**Patient subset 4: No FVC result and died prior to Week 52**	
	Handling of missing FVC result	**Underlying assumption**	**Handling of missing FVC result**	**Underlying assumption**
Primary analysis	Missing data handled by model.	Assumes missing at random. Discontinued patients would have behaved similarly to patients who did not discontinue.	Missing data handled by model.	Assumes missing at random. Discontinued patients would have behaved similarly to patients who did not discontinue.
Sensitivity analysis 1	Based on the slope estimates for drug and placebo in patient subset 2.	Patients without a result would have behaved similarly to discontinued patients with a result who are in the same treatment group.	Based on the slope estimates for placebo patients in patient subset 2, but truncated so that those who died are more severe.	Patients who died before week 52 would have behaved in a similar or worse way to a placebo patient who prematurely discontinued.
Sensitivity analysis 2	Based on the slope estimates for placebo in patient subset 2.	Patients without a result would have behaved similarly to discontinued placebo patients with a result.		
Sensitivity analysis 3	Based on the slope estimates for placebo in patient subsets 1 and 2.	Patients without a result would have behaved similarly to placebo patients with a result regardless of whether they prematurely discontinued treatment or not.	Based on slope estimates for placebo patients in subsets 1 and 2, but truncated so those who died are more severe.	Patients who died before week 52 would have behaved in a similar or worse way to a placebo patient regardless of whether they prematurely discontinued treatment or not.

Further sensitivity analyses will be described in detail in the TSAP. Similar sensitivity analyses will be performed for the key secondary endpoints. In the analysis of all other continuous secondary endpoints, missing data will not be imputed. The mixed effect model will handle missing data based on a likelihood method under the "missing at random assumption". Following the intention-to-treat (ITT) principle, every randomised patient with at least one data point (at baseline or after randomization) will be included in this analysis. In the analysis of time to all-cause mortality, missing or incomplete data will be handled using censoring as detailed in the TSAP.

7.5.2 Safety endpoints

Missing or incomplete AE dates will be imputed according to BI standards. Other missing safety data will not be imputed.

7.5.3 Plasma concentrations

Descriptive statistics of concentrations at specific time points will be calculated only when at least 2/3 of the individuals have concentrations within the validated concentration range. The overall sample size to decide whether the “2/3 rule” is fulfilled will be based on the total number of samples intended to be drawn for that time point (i.e. BLQ, NOR, NOS, NOA are included).

7.6 RANDOMISATION

Patients will be randomised in blocks to double-blind treatment. The randomization will be stratified by ATA status (positive or negative) within the IRT system. Approximately equal numbers of patients will be randomised to each treatment group (i.e. a 1:1 randomisation will be used). BI will arrange for the randomization and the packaging and labelling of trial medication. The randomisation list will be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment will be both reproducible and non-predictable. The block size will be documented in the clinical trial report. Access to the codes will be controlled and documented. All members of the clinical trial team will remain blinded to the randomization schedule until the final database is locked. The independent DMC will at any time have the possibility to look at unblinded data according to the DMC charter.

7.7 DETERMINATION OF SAMPLE SIZE

The estimated treatment difference in the absolute change in FVC in mL over 52 weeks is assumed to be between 70 and 110 mL, based on the cyclophosphamide trial in scleroderma lung disease (R14-5407), and on the idiopathic pulmonary fibrosis (IPF) trials INPULSIS-1 and INPULSIS-2 (P14-07514). Note that FVC percent predicted has been converted to mL using the approximate relationship of 1% = 35 mL based on the IPF results which were

presented in both percent predicted and mL. An equal standard deviation across treatment groups of 245 mL (based on the cyclophosphamide trial) and a 1:1 randomization is assumed. The sample size calculations in Table 7.7:1 have been performed based on a two-sided, two-sample superiority t-test, with a significance level of 5% and power of either 80% or 90%.

Table 7.7: 1 Primary endpoint: Sample size calculations based on a two-sided, two-sample t-test with a significance level of 5% and various assumptions

Mean treatment difference in absolute change in FVC in mL	50	50	**70**	70	110	110
Standard deviation of FVC in mL	245	245	**245**	245	245	245
Power (%)	90	80	**90**	80	90	80
Sample size per treatment group	506	378	**259**	194	106	79

The first key secondary endpoint of the absolute change from baseline in the mRSS at week 52 is also considered. Based on skin thickness results from the cyclophosphamide trial in scleroderma lung disease (R14-5407), the estimated treatment difference is assumed to be between 2 and 3 points. An equal standard deviation across treatment groups of 9 (based on the same reference) and a 1:1 randomization is assumed. The sample size calculations in Table 7.7: 2 have been performed based on a two-sided, two-sample superiority t-test, with a significance level of 5% and power of either 80% or 90%.

Table 7.7: 2 First key secondary endpoint: Sample size calculations based on a two-sided, two-sample t-test with a significance level of 5% and various assumptions

Mean treatment difference in absolute change in mRSS	**3**	3	2	2	2.2	2.6
Standard deviation of mRSS	**9**	9	9	9	9	9
Power (%)	**90**	80	90	80	80	90
Sample size per treatment group	**191**	143	427	319	260	260

Finally, the second key secondary endpoint of the absolute change from baseline in the SGRQ total score at week 52 is considered. As a minimum clinically important difference is yet to be established in SSc-ILD, the minimum clinically important difference in COPD patients of 4 points will be assumed (P12-11232). An equal standard deviation across treatment groups of 13 will be assumed based on the pooled analysis of the IPF trials INPULSIS-1 and INPULSIS-2 (P14-07514). The sample size calculations in Table 7.7: 3

have been performed based on a two-sided, two-sample superiority t-test, with a significance level of 5% and power of either 80% or 90%.

Table 7.7: 3 Second key secondary endpoint: Sample size calculations based on a two-sided, two-sample t-test with a significance level of 5% and various assumptions

Mean treatment difference in absolute change in SGRQ total score	-4	**-4**	-3	-3	-3.2	-3.7
Standard deviation of SGRQ total score	13	**13**	13	13	13	13
Power (%)	80	**90**	80	90	80	90
Power (%)	167	**223**	296	396	260	260

A hierarchical testing procedure will be used to test the primary and key secondary endpoints, as discussed in Section 7.2.

Assuming a small number of non-analysable patients (i.e. patients who do not provide at least one post-baseline result), a sample size of 260 patients per treatment group will achieve 90% power when detecting a treatment difference of 70 mL in the primary endpoint. There is also sufficient power to test the key secondary endpoints if the hierarchy testing procedure allows.

It should be noted that the sample size calculation for the primary endpoint is based on the treatment difference at 52 weeks using a two-sample t-test, although this endpoint will be analysed using a rate of decline model. This model is more powerful. Basing the sample size calculations on simulations of such a rate of decline model (applying the method by Chen et al., R15-3192) provides reassurance that a sample size of 260 will achieve at least 90% power and is robust to small changes in assumptions.

Calculations for the sample sizes shown in the tables were performed using nQuery Advisor® 7.0 statistical package by Statistical Solutions Ltd.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP) and relevant BI Standard Operating Procedures (SOPs) and the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997).

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The Investigator will inform the Sponsor immediately of any urgent safety measures taken to protect the trial subjects against any immediate hazard, and also of any serious breaches of the protocol or of ICH GCP and the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997).

The rights of the Investigator and of the Sponsor with regard to publication of the results of this trial are described in the Investigator contract. As a rule, no trial results should be published prior to finalization of the Clinical Trial Report.

Additional information for Japan:

The rights of the investigator / trial site and of the sponsor with regard to publication of the results of this trial are described in the investigator contract / trial site's contract. As a general rule, no trial results should be published prior to finalisation of the Clinical Trial Report.

The certificate of insurance cover is made available to the Investigator and the patients, and is stored in the ISF (Investigator Site File)."

8.1 TRIAL APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH / GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the Investigator as part of the trial records. A signed copy of the

informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative."

Additional information for Japan:

The Investigator must give a full explanation to trial patients by using the patient information form, which is prepared avoiding the use of technical terms and expressions. The patient is given sufficient time to consider participation in the trial. The Investigator obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The Investigator must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the Sponsor, Sponsor's designees, or by IRB / IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the Investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3 RECORDS

eCRF for individual patients will be provided by the Sponsor. See Section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on the eCRF must be consistent with the source data or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the trial; current medical records must also be available.

8.3.2 Direct access to source data and documents

The Investigator / institution will permit trial-related monitoring, audits, IRB / IEC review and regulatory inspection, providing direct access to all related source data / documents. eCRF and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the Sponsor's clinical trial monitor, auditor and inspection by health authorities (e.g. FDA). The Clinical Research Associate (CRA) on site monitor and auditor may review all eCRF, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 8.3.1.

8.3.3 Storage period of records

For Japan:

Trial site(s):

The trial site(s) must retain the source documents and essential documents for a period defined by the Japanese GCP regulation and trial site's contract with the sponsor.

Sponsor:

The Sponsor must retain the essential documents according to the Sponsor's SOPs.

8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

8.4.1 Listedness

To fulfil the regulatory requirements for expedited safety reporting, the Sponsor evaluates whether a particular adverse event is "listed", i.e. is a known side effect of the drug or not. Therefore, a unique reference document for the evaluation of listedness needs to be provided. For nintedanib this is the current version of the Investigator's Brochure for more details.

8.4.2 Expedited reporting to health authorities and IEC / IRB

Expedited reporting of serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSAR) to health authorities and IEC / IRB, will be done according to local regulatory requirements.

8.5 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers.

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the trial need to be available for inspection on request by the participating physicians, the Sponsor's representatives, by the IRB / IEC and the regulatory authorities.

8.6 END OF TRIAL

The end of the trial is defined as last patient out.

For EU member states.

The IEC / competent authority in each participating EU member state needs to be notified about the end of the trial or early termination of the trial.

For Japan:

When the trial is completed, the Investigator should inform the head of the trial site of the completion in writing, and the head of the trial site should promptly inform the IRB and Sponsor of the completion in writing.

8.7 PROTOCOL VIOLATIONS

For Japan:

The investigator should document any deviation from the protocol regardless of their reasons. Only when the protocol was not followed in order to avoid an immediate hazard to trial subjects or for other medically compelling reason, the principal investigator should prepare and submit the records explaining the reasons thereof to the sponsor, and retain a copy of the records.

8.8 COMPENSATION AVAILABLE TO THE PATIENT IN THE EVENT OF TRIAL RELATED INJURY

For Japan:

In the event of health injury associated with this trial, the Sponsor is responsible for compensation based on the contract signed by the trial site.

9. REFERENCES

9.1 PUBLISHED REFERENCES

P05-12782 Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, Grinten CPM van der, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J. Standardisation of spirometry. Eur Respir J 2005. 26(2):319-338.

P11-11216 Richeldi L, Costabel U, Selman M, Kim DS, Hansell DM, Nicholson AG, Brown KK, Flaherty KR, Noble PW, Raghu G, Brun M, Gupta A, Juhel N, Klueglich M, Bois RM du. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. N Engl J Med 2011. 365(12):1079-1087.

P12-11232 Jones PW. St.George's Respiratory Questionnaire: MCID. COPD J Chronic Obstruct Pulm Dis 2005. 2:75-79.

P14-07514 Richeldi L, et al, INPULSIS Trial Investigators. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. New England Journal of Medicine, published on May 18, 2014, doi: 10.1056/NEJMoa1402584 N Engl J Med 2014. 370(22):2071-2082.

P14-07919 Herzog EL, Mathur A, Tager AM, Feghali-Bostwick C, Schneider F, Varga J. Interstitial lung disease associated with systemic sclerosis and idiopathic pulmonary fibrosis: how similar and distinct? Arthritis and Rheumatology, Accepted Article, Accepted: May 08, 2014, doi: 10.1002/art.38702 Arthritis Rheumatol 2014. 66(8):1967-1978.

P14-16916 Pope J. Measures of systemic sclerosis (scleroderma): Health Assessment Questionnaire (HAQ) and Scleroderma HAQ (SHAQ), physician- and patient-rated global assessments, Symptom Burden Index (SBI), University of California, Los Angeles, Scleroderma Clinical Trials Consortium Gastrointestinal Scale (UCLA SCTC GIT) 2.0, Baseline Dyspnea Index (BDI) and Transition Dyspnea Index (TDI) (Mahler's Index), Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR), and Raynaud's Condition Score (RCS). Arthritis Care Res (Hoboken) 2011. 63(Suppl 11):S98-S111.

P14-16917 Steen VD, Medsger TA. The value of the Health Assessment Questionnaire and special patient-generated scales to demonstrate change in systemic sclerosis patients over time. Arthritis Rheum 1997. 40(11):1984-1991.

P15-00879 Kowal-Bielecka O, et al, EUSTAR Co-Authors. EULAR recommendations for the treatment of systemic sclerosis: a report from the EULAR Scleroderma Trials and Research group (EUSTAR). Ann Rheum Dis 2009. 68(5):620-628.

R06-2002 Macintyre N, Crapo RO, Viegi G, Johnson DC, Grinten CPM van der, Brusasco V, Burgos F, Casaburi R, Coates A, Enright P, Gustafsson P, Hankinson J, Jensen R, McKay R, Miller MR, Navajas D, Pedersen OF, Pellegrino R, Wanger J. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J 2005. 26(4):720-735.

R10-4848 Common terminology criteria for adverse events (CTCAE): version 4.0 (NIH publication no. 09-5410, published: May 28, 2009 (v4.03: June 14, 2010), revised June 2010, reprinted June 2010). http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pd f 2010.

R11-1366 Choi SW, Victorson DE, Yount S, Anton S, Cella D. Development of a conceptual framework and calibrated item banks to measure patient-reported dyspnea severity and related functional limitations. Value Health 2011. 14:291-306.

R14-4918 Barnes J, Mayes MD. Epidemiology of systemic sclerosis: incidence, prevalence, survival, risk factors, malignancy, and environmental triggers. Curr Opin Rheumatol 2012. 24(2):165-170.

R14-4927 Gabrielli A, Avvedimento EV, Krieg T. Scleroderma. N Engl J Med 2009. 360(19):1989-2003.

R14-5045 Hinchcliff ME, Beaumont JL, Carns MA, Podlusky S, Thavarajah K, Varga J, Cella D, Chang RW. Longitudinal evaluation of PROMIS-29 and FACIT-dyspnea short forms in systemic sclerosis. Journal of Rheumatology, Published online before print November 1, 2014, doi: 10.3899/jrheum.140143 J Rheumatol 2014.

R14-5055 Hoogen F van den, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. Arthritis Rheum 2013. 65(11):2737-2747.

R14-5056 Hinchcliff M, Beaumont JL, Thavarajah K, Varga J, Chung A, Podlusky S, Carns M, Chang RW, Cella D. Validity of two new patient-reported outcome measures in systemic sclerosis: Patient-Reported Outcomes Measurement Information System 29-item Health Profile and Functional Assessment of Chronic Illness Therapy-Dyspnea short form. Arthritis Care Res (Hoboken) 2011. 63(11):1620-1628.

R14-5058 Bruce B, Fries JF. The Health Assessment Questionnaire (HAQ). Clin Exp Rheumatol 2005. 23(Suppl 39):S14-S18.

R14-5407 Tashkin DP, et al. Cyclophosphamide versus placebo in scleroderma lung disease. N Engl J Med 2006. 354(25):2655-2666.

R14-5409 Assassi S, Sharif R, Lasky RE, McNearney TA, Estrada-Y-Martin RM, Draeger H, Nair DK, Fritzler MJ, Reveille JD, Arnett FC, Mayes MD, GENISOS Study Group. Predictors of interstitial lung disease in early

systemic sclerosis: a prospective longitudinal study of the GENISOS cohort. Arthritis Res Ther 2010. 12(5):R166.

R15-0845 Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, Enright PL, Hankinson JL, Ip MSM, Zheng J, Janet Stocks on behalf of the ERS Global Lung Function Initiative. Multi-ethnic reference values for spirometry for the 3 - 95 year age range: the global lung function 2012 equations: report of the Global Lung Function Initiative (GLI), ERS task force to establish improved lung function reference values. Eur Respir J 2012. 40(6):1324-1343.

R15-1205 Clements PJ, et al. Skin thickness score in systemic sclerosis: an assessment of interobserver variability in 3 independent studies. J Rheumatol 1993. 20(11):1892-1896.

R15-1207 Khana D, et al, Investigators in CRISS and EPOSS. Measures of response in clinical trials of systemic sclerosis: the combined response index for systemic sclerosis (CRISS) and outcome measures in pulmonary arterial hypertension related to systemic sclerosis (EPOSS). J Rheumatol 2009. 36(10):2356-2361.

R15-2010 Ferraz MB, Quaresma MR, Aquino LRL, Atra E, Tugwell P, Goldsmith CH. Reliability of pain scales in the assessment of literate and illiterate patients with rheumatoid arthritis. J Rheumatol 1990. 17(8):1022-1024.

R15-2073 Kubota M, Kobayashi H, Quanjer PH, Omori H, Tatsumi K, Kanazawa M, Clinical Pulmonary Functions Committee of the Japanese Respiratory Society. Reference values for spirometry, including vital capacity, in Japanese adults calculated with the LMS method and compared with previous values. Respir Invest 2014. 52(4):242-250.

R15-3192 Chen J, Stock S, Deng C. Sample size estimation through simulation of a random coefficient model by using SAS. http://www.lexjansen.com/pharmasug/2008/sp/SP03.pdf (access date: 22 June 2015) ; PharmaSUG 2008.

R96-0690 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976. 16(1):31-41.

R96-2382 EuroQol - a new facility for the measurement of health-related quality of life. Health Policy 1990. 16:199-208.

R98-0966 Jones PW, Quirk FH, Baveystock CM. The St.George's respiratory questionnaire. Respir Med 1991. 85(Suppl B):25-31.

9.2 UNPUBLISHED REFERENCES

c01783972-11 Investigator’s Brochure nintedanib (BIBF 1120)

c09412738 Influence of bosentan on the pharmacokinetics of nintedanib in healthy male
subjects, Study 1199.239, 10 November 2016

c09712613 Investigation of drug-drug interaction between nintedanib and pirfenidone in patients with IPF (an open label, multiple-dose, Study 1199.229, 31 July 2017 two group study)

10. APPENDICES

10.1 LUNG FUNCTION CRITERIA

At Visit 2, FVC must fulfil the following criteria:

- ≥ 40% of predicted normal

Predicted normal values will be calculated according to GLI (Global Lung Initiative) (R15-0845, R15-2073) at the site level, using the Flowscreen. FVC percent predicted is a key inclusion criterion and a secondary endpoint using the following demographic information: race, age, gender and height.

At Visit 2, DLCO must fulfil the following criteria:

- Within range 30% - 89% predicted of normal; corrected for Hb

For predicted normal values, different sites may use different prediction formulas, based on the method used to measure DLCO. In any case, the method used must be in compliance with the ATS/ERS guideline on DLCO measurements (R06-2002), and the prediction formula appropriate for that method. Raw data (gas mixture, equation used for prediction of normal, further adjustments made if so) must be traced.

Predicted DLCO corrected for haemoglobin (Hb) expressed in g·dL-1 (R06-2002) can be calculated as:

- Predicted DLCO corrected for Hb = Predicted DLCO x (1.7Hb/(10.22+Hb)) for males aged 15 years or above
- Predicted DLCO corrected for Hb = Predicted DLCO x (1.7Hb/(9.38+Hb)) for females and children aged less than 15 years

For decision on inclusion / exclusion, DLCO results from Visit 2 will be corrected for haemoglobin (value obtained at Visit 1) by the site.

For analysis of the trial data, DLCO results will be corrected for haemoglobin by central data management. This means that the site has to enter the DLCO results without haemoglobin correction in the eCRF, at all visits.

There should be at least two acceptable tests that meet the repeatability requirement of either being within 3 mL CO (Standard Temperature and Pressure, Dry - STPD)•min-1 •mmHg-1 (or 1 mmol•min-1•kPa-1) of each other or within 10% of the highest value.

10.2 CREATININE CLEARANCE

Creatinine clearance calculation is done according to Cockroft and Gault (R96-0690).

- Creatinine clearance = (140 - age) x (Weight in kg) x (0.85 if female) / (72 x serum creatinine in mg/dL)

10.3 PATIENT REPORTED OUTCOME QUESTIONNAIRES

10.3.1 SGRQ

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ)
ENGLISH FOR THE U.S.A.

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

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

Before completing the rest of the questionnaire:

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

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

[redacted] PhD FRCP
Professor of Respiratory Medicine,
St. George's University of London,
Jenner Wing,
Cranmer Terrace,
London SW17 ORE, UK.

Tel. [redacted]
Fax

continued…

St. George's Respiratory Questionnaire
PART 1

Please describe how often your respiratory problems have affected you over the past 4 weeks.

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

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

5. How many times during the past 4 weeks have you suffered from severe or very unpleasant respiratory attacks?

Please check (✓) *one*:
- more than 3 times ☐
- 3 times ☐
- 2 times ☐
- 1 time ☐
- none of the time ☐

6. How long did the worst respiratory attack last?
(Go to Question 7 if you did not have a severe attack)

Please check (✓) *one*:
- a week or more ☐
- 3 or more days ☐
- 1 or 2 days ☐
- less than a day ☐

7. Over the past 4 weeks, in a typical week, how many good days (with few respiratory problems) have you had?

Please check (✓) *one*:
- No good days ☐
- 1 or 2 good days ☐
- 3 or 4 good days ☐
- nearly every day was good ☐
- every day was good ☐

8. If you wheeze, is it worse when you get up in the morning?

Please check (✓) *one*:
- No ☐
- Yes ☐

St. George's Respiratory Questionnaire
PART 2

Section 1

How would you describe your respiratory condition?

Please check (✓) *one*:

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

If you have ever held a job:

Please check (✓) *one*:

- My respiratory problems made me stop working altogether ☐
- My respiratory problems interfere with my job or made me change my job ☐
- My respiratory problems do not affect my job ☐

Section 2

These are questions about what activities usually make you feel short of breath <u>these days.</u>

For each statement please check (✓) *the box* that applies to you *these days*:	True	False
Sitting or lying still	☐	☐
Washing or dressing yourself	☐	☐
Walking around the house	☐	☐
Walking outside on level ground	☐	☐
Walking up a flight of stairs	☐	☐
Walking up hills	☐	☐
Playing sports or other physical activities	☐	☐

St. George's Respiratory Questionnaire
PART 2

Section 3

These are more questions about your cough and shortness of breath these days.

	For each statement please check (✓) *the box* that applies to you *these days*: True	False
Coughing hurts	☐	☐
Coughing makes me tired	☐	☐
I am short of breath when I talk	☐	☐
I am short of breath when I bend over	☐	☐
My coughing or breathing disturbs my sleep	☐	☐
I get exhausted easily	☐	☐

Section 4

These are questions about other effects that your respiratory problems may have on you these days.

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

Section 5

These are questions about your respiratory treatment. If you are not receiving treatment go to section 6.

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

continued…

St. George's Respiratory Questionnaire
PART 2

Section 6

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

	For each statement, please check (✓) *the box* that applies to you *because of your respiratory problems*: True	False
I take a long time to get washed or dressed	☐	☐
I cannot take a bath or shower, or I take a long time to do it	☐	☐
I walk slower than other people my age, or I stop to rest	☐	☐
Jobs such as household chores take a long time, or I have to stop to rest	☐	☐
If I walk up one flight of stairs, I have to go slowly or stop	☐	☐
If I hurry or walk fast, I have to stop or slow down	☐	☐
My breathing makes it difficult to do things such as walk up hills, carry things up stairs, light gardening such as weeding, dance, bowl or play golf	☐	☐
My breathing makes it difficult to do things such as carry heavy loads, dig in the garden or shovel snow, jog or walk briskly (5 miles per hour), play tennis or swim	☐	☐
My breathing makes it difficult to do things such as very heavy manual work, ride a bike, run, swim fast, or play competitive sports	☐	☐

Section 7

We would like to know how your respiratory problems <u>usually</u> affect your daily life.

	For each statement, please check (✓) *the box* that applies to you *because of your respiratory problems*: True	False
I cannot play sports or do other physical activities	☐	☐
I cannot go out for entertainment or recreation	☐	☐
I cannot go out of the house to do the shopping	☐	☐
I cannot do household chores	☐	☐
I cannot move far from my bed or chair	☐	☐

St. George's Respiratory Questionnaire

Here is a list of other activities that your respiratory problems may prevent you from doing. (You do not have to check these, they are just to remind you of ways your shortness of breath may affect you):

Going for walks or walking the dog
Doing activities or chores at home or in the garden
Sexual intercourse
Going to a place of worship, or a place of entertainment
Going out in bad weather or into smoky rooms
Visiting family or friends or playing with children

Please write in any other important activities that your respiratory problems may stop you from doing:

. . . . . .
. . . . . .
. . . . . .
. . . . . .

Now please check the box (one only) that you think best describes how your respiratory problems affect you:

They do not stop me from doing anything I would like to do ☐
They stop me from doing one or two things I would like to do ☐
They stop me from doing most of the things I would like to do ☐
They stop me from doing everything I would like to do ☐

Thank you for completing this questionnaire. Before you finish would you please make sure that you have answered all the questions.

10.3.2 Functional Assessment of Chronic Illness Therapy (FACIT-dyspnoea)

FACIT-Dyspnea (Dyspnoea) 10 Item Short Form

Part I. Over the past 7 days, how short of breath did you get with each of these activities?
Please mark one box per line to indicate your response.

	No shortness of breath	Mildly short of breath	Moderately short of breath	Severely short of breath	I did not do this in the past 7 days
1. Dressing yourself without help	☐	☐	☐	☐	☐

Please indicate why you did not do this in the past 7 days:

(Mark one)

☐ I have stopped trying, or knew I could not do this activity because of my shortness of breath.

☐ I did not do this activity for some other reason (including not having a chance to do it, other health issues etc).

	No shortness of breath	Mildly short of breath	Moderately short of breath	Severely short of breath	I did not do this in the past 7 days
2. Walking 50 steps/paces on flat ground at a normal speed without stopping.....	☐	☐	☐	☐	☐

Please indicate why you did not do this in the past 7 days:

(Mark one)

☐ I have stopped trying, or knew I could not do this activity because of my shortness of breath.

☐ I did not do this activity for some other reason (including not having a chance to do it, other health issues etc).

FACIT-dyspnea (dyspnoea)-short form
Page 1 of 6 – R 01 October 2012

Data Entry Initials _____
Data Entry Date _____

FACIT-Dyspnea (Dyspnoea) 10 Item Short Form

	No shortness of breath	Mildly short of breath	Moderately short of breath	Severely short of breath	I did not do this in the past 7 days
3. Walking up 20 stairs (2 flights) without stopping.....	☐	☐	☐	☐	☐

Please indicate why you did not do this in the past 7 days:

(Mark one)

☐ I have stopped trying, or knew I could not do this activity because of my shortness of breath.

☐ I did not do this activity for some other reason (including not having a chance to do it, other health issues etc).

	No shortness of breath	Mildly short of breath	Moderately short of breath	Severely short of breath	I did not do this in the past 7 days
4. Preparing meals.....	☐	☐	☐	☐	☐

Please indicate why you did not do this in the past 7 days:

(Mark one)

☐ I have stopped trying, or knew I could not do this activity because of my shortness of breath.

☐ I did not do this activity for some other reason (including not having a chance to do it, other health issues etc).

FACIT-dyspnea (dyspnoea)-short form
Page 2 of 6 – R 01 October 2012

Data Entry Initials _____
Data Entry Date _____

FACIT-Dyspnea (Dyspnoea) 10 Item Short Form

	No shortness of breath	Mildly short of breath	Moderately short of breath	Severely short of breath	I did not do this in the past 7 days
5. Washing dishes	☐	☐	☐	☐	☐

Please indicate why you did not do this in the past 7 days:

(Mark one)

☐ I have stopped trying, or knew I could not do this activity because of my shortness of breath.

☐ I did not do this activity for some other reason (including not having a chance to do it, other health issues etc).

	No shortness of breath	Mildly short of breath	Moderately short of breath	Severely short of breath	I did not do this in the past 7 days
6. Sweeping or mopping	☐	☐	☐	☐	☐

Please indicate why you did not do this in the past 7 days:

(Mark one)

☐ I have stopped trying, or knew I could not do this activity because of my shortness of breath.

☐ I did not do this activity for some other reason (including not having a chance to do it, other health issues etc).

FACIT-dyspnea (dyspnoea)-short form
Page 3 of 6 – R 01 October 2012

Data Entry Initials _____
Data Entry Date _____

FACIT-Dyspnea (Dyspnoea) 10 Item Short Form

	No shortness of breath	Mildly short of breath	Moderately short of breath	Severely short of breath	I did not do this in the past 7 days
7. Making a bed.....	☐	☐	☐	☐	☐

Please indicate why you did not do this in the past 7 days:

(Mark one)

☐ I have stopped trying, or knew I could not do this activity because of my shortness of breath.

☐ I did not do this activity for some other reason (including not having a chance to do it, other health issues etc).

	No shortness of breath	Mildly short of breath	Moderately short of breath	Severely short of breath	I did not do this in the past 7 days
8. Lifting something weighing 10-20 lbs (about 4.5-9kg, like a large bag of groceries).....	☐	☐	☐	☐	☐

Please indicate why you did not do this in the past 7 days:

(Mark one)

☐ I have stopped trying, or knew I could not do this activity because of my shortness of breath.

☐ I did not do this activity for some other reason (including not having a chance to do it, other health issues etc).

FACIT-dyspnea (dyspnoea)-short form
Page 4 of 6 – R 01 October 2012

Data Entry Initials _____
Data Entry Date _____

FACIT-Dyspnea (Dyspnoea) 10 Item Short Form

	No shortness of breath	Mildly short of breath	Moderately short of breath	Severely short of breath	I did not do this in the past 7 days
9. Carrying something weighing 10-20 lbs (about 4.5-9kg, like a large bag of groceries) from one room to another.....	☐	☐	☐	☐	☐

Please indicate why you did not do this in the past 7 days:

(Mark one)

☐ I have stopped trying, or knew I could not do this activity because of my shortness of breath.

☐ I did not do this activity for some other reason (including not having a chance to do it, other health issues etc).

	No shortness of breath	Mildly short of breath	Moderately short of breath	Severely short of breath	I did not do this in the past 7 days
10. Walking (faster than your usual speed) for ½ mile (almost 1 km) without stopping.....	☐	☐	☐	☐	☐

Please indicate why you did not do this in the past 7 days:

(Mark one)

☐ I have stopped trying, or knew I could not do this activity because of my shortness of breath.

☐ I did not do this activity for some other reason (including not having a chance to do it, other health issues etc).

FACIT-dyspnea (dyspnoea)-short form
Page 5 of 6 – R 01 October 2012

Data Entry Initials _____
Data Entry Date _____

FACIT-Dyspnea (Dyspnoea) 10 Item Short Form

Part II: Functional Limitation. Considering your shortness of breath over the past 7 days, rate the amount of difficulty you had when doing the following activities:

		No difficulty	A little difficulty	Some difficulty	Much difficulty
1.	Dressing yourself without help	☐	☐	☐	☐
2.	Walking 50 steps/paces on flat ground at a normal speed without stopping	☐	☐	☐	☐
3.	Walking up 20 stairs (2 flights) without stopping	☐	☐	☐	☐
4.	Preparing meals	☐	☐	☐	☐
5.	Washing dishes	☐	☐	☐	☐
6.	Sweeping or mopping	☐	☐	☐	☐
7.	Making a bed	☐	☐	☐	☐
8.	Lifting something weighing 10-20 lbs (about 4.5-9kg, like a large bag of groceries)	☐	☐	☐	☐
9.	Carrying something weighing 10-20 lbs (about 4.5-9kg, like a large bag of groceries) from one room to another	☐	☐	☐	☐
10.	Walking (faster than your usual speed) for ½ mile (almost 1 km) without stopping	☐	☐	☐	☐

FACIT-dyspnea (dyspnoea)-short form
Page 6 of 6 – R 01 October 2012

Data Entry Initials _____
Data Entry Date _____

10.3.3 Scleroderma health assessment questionnaire (SHAQ)

HEALTH ASSESSMENT QUESTIONNAIRE

PATKEY#_____
QUESTDAT_____

Name_____ **Date**_____

In this section we are interested in learning how your illness affects your ability to function in daily life. Please feel free to add any comments on the back of this page.

HAQADMIN_____

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

QUESTYPE_____

PMSVIS_____
RASTUDY_____
QUESTNUM_____

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

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

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

DRSGASST_____
RISEASST_____

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

_____ Dressing and Grooming
_____ Arising
_____ Eating
_____ Walking

EATASST_____
WALKASST_____

STANFORD-RA (MAY99 - Phase 31) – English, USA -1- ©Stanford University
HAQ-DI - United States/English
f:\institut\cultadap\project\5008\study5008\questionnaire\original\forproject\haq-di_au1.0-eng-usori.doc-10/12/2006-co

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

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

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

_____Raised toilet seat _____Bathtub bar
_____Bathtub seat _____Long-handled appliances for reach
_____Jar opener (for jars previously opened) _____Long-handled appliances in bathroom
_____Other (Specify: _____)

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

_____Hygiene _____Gripping and opening things
_____Reach _____Errands and chores

HYGNASST_____
RCHASST_____
GRIPASST_____
ACTVASST_____

STANFORD-RA (MAY99 - Phase 31) – English, USA -2- ©Stanford University
HAQ-DI - United States/English
f:\institut\cultadap\project\5008\study5008\questionnaire\original\forproject\haq-di_au1.0-eng-usor\.doc-10/12/2008-co

We are also interested in learning whether or not you are affected by pain because of your illness.
How much pain have you had because of your illness **IN THE PAST WEEK** ?
PLACE A MARK ON THE LINE TO INDICATE THE SEVERITY OF THE PAIN.

NO PAIN — VERY SEVERE PAIN
0 — 100

IN THE PAST WEEK, how much have your intestinal problems interfered with your daily activities?
PLACE A MARK ON THE LINE TO INDICATE THE LIMITATION OF ACTIVITY.

INTESTINAL PROBLEMS DO NOT LIMIT ACTIVITIES — VERY SEVERE LIMITATION
0 — 100

IN THE PAST WEEK, how much have your breathing problems interfered with your daily activities?
PLACE A MARK ON THE LINE TO INDICATE THE LIMITATION OF ACTIVITY.

BREATHING PROBLEMS DO NOT LIMIT ACTIVITIES — VERY SEVERE LIMITATION
0 — 100

IN THE PAST WEEK, how much has Raynaud's interfered with your daily activities?
PLACE A MARK ON THE LINE TO INDICATE THE LIMITATION OF ACTIVITY.

RAYNAUD'S DOES NOT LIMIT ACTIVITIES — VERY SEVERE LIMITATION
0 — 100

IN THE PAST WEEK, how much have your finger ulcers interfered with your daily activities?
PLACE A MARK ON THE LINE TO INDICATE THE LIMITATION OF ACTIVITY.

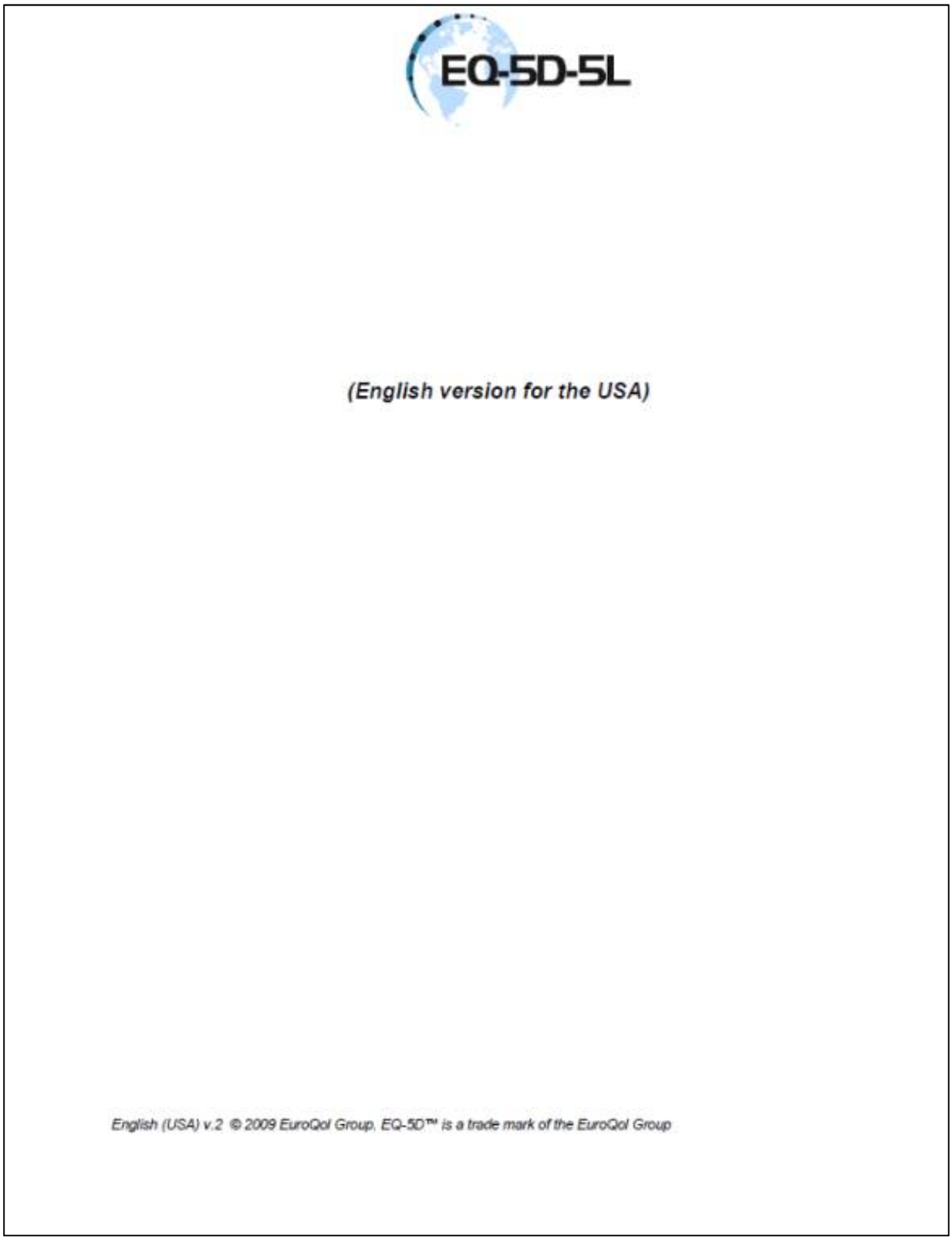
FINGER ULCERS DO NOT LIMIT ACTIVITIES — VERY SEVERE LIMITATION
0 — 100

Overall, considering how much pain, discomfort, limitations in your daily life and other changes in your body and life, how severe would you rate your disease today?
PLACE A MARK ON THE LINE TO INDICATE THE LIMITATION OF ACTIVITY.

NO DISEASE — VERY SEVERE LIMITATION
0 — 100

ID4145

10.3.4 EQ-5D-5L



Under each heading, please check the ONE box that best describes your health TODAY

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

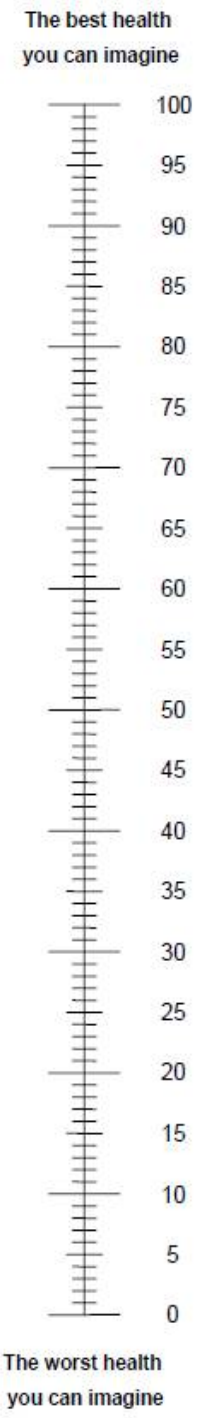
I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

2

USA (English) © 2009 EuroQol Group. EQ-5D™ is a trade mark of the EuroQol Group

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



3

USA (English) © 2009 EuroQol Group. EQ-5D™ is a trade mark of the EuroQol Group

10.4 PATIENTS GLOBAL IMPRESSION OF HEALTH

Boehringer Ingelheim

BI Trial No. 1199.214

Country _____

Visit No. _____ Site No. _____

Visit Date _____ Patient No. _____

Patient's Global Impression of Overall Health

Visual Analog Scale

How was your overall health during the last week?

Please mark on the scale below a vertical line anywhere between the two ends corresponding to your overall health during the last week.

Extremely Poor **Excellent**

1199.214 VAS Patient's overall health: Version 1.0 dated 28 Apr 2015 Page 1 of 1

10.5 PHYSICIAN'S GLOBAL IMPRESSION OF PATIENTS'S HEALTH

Boehringer Ingelheim
BI Trial No. 1199.214
Country _____

Visit No. _____ Site No. _____

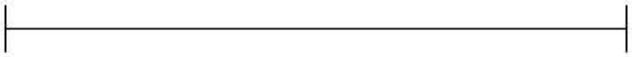
Visit Date _____ Patient No. _____

Physician's Global Impression of Patient's Overall Health

Visual Analog Scale

How was your patient's overall health during the last week?

Please mark on the scale below a vertical line anywhere between the two ends corresponding to your patient's overall health during the last week.



Extremely Poor **Excellent**

1199.214 Physician's VAS on Patient's overall health: Version 1.0 dated 28 Apr 2015 Page 1 of 1

10.6 HANDLING AND DERIVATION OF PHARMACOKINETIC PARAMETERS

10.6.1 Pharmacokinetic Methods

Concentrations will be used for calculations in the format that is reported in the bioanalytical report. The data format for descriptive statistics of concentrations will be identical with the data format of the respective concentrations. For the calculation of PK parameters, only concentrations within the validated concentration range will be used. The descriptive statistics of PK parameters will be calculated using the individual values with the number of decimal places as provided by the evaluation program. Then the individual values as well as the descriptive statistics will be reported with three significant digits in the clinical trial report. The actual sampling times will be used. For pre-dose samples, the actual sampling time will be set to zero. Noncompartmental PK parameters will be determined using WinNonlin or another validated program.

Analyte plasma concentrations will be plotted graphically versus time for all subjects as listed in the analyte plasma concentration-time tables. For the presentation of the mean profiles, the geometric mean and the planned blood sampling times will be used.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1.0
Date of CTP revision		02 Mar 2016
EudraCT number		2015-000392-28
BI Trial number		1199.214 (SENSCIS™)
BI Investigational Product(s)		Nintedanib
Title of protocol		A double blind, randomised, placebo-controlled trial evaluating efficacy and safety of oral nintedanib treatment for at least 52 weeks in patients with 'Systemic Sclerosis associated Interstitial Lung Disease'(SSc-ILD).
To be implemented only after approval of the IRB / IEC / Competent Authorities	x	
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		Synopsis
Description of change		Administrative changes, corrections and clarification.
Rationale for change		Add clarification and correction, add trial name 'SENSCIS™'.
Section to be changed	I II	Flowchart (Footnotes) Section 6 (Investigational Plan)
Description of change		Women of childbearing potential will have to perform a pregnancy test every 4-6 weeks. Once intervals between site visits are > 6 weeks, these will be centrally provided and performed at home.
Rationale for change		To ensure regular pregnancy testing as requested by health authorities.
Section to be changed		Flowchart – optional substudies

Description of change		Administrative changes, corrections and clarification.
Rationale for change		Clarification that the informed consent forms for substudy participation are to be signed before performing the respective substudy procedure. Depending on the substudy, the latest possibility would be at Visit 2.
Section to be changed		Abbreviations
Description of change		Administrative changes, corrections and clarifications.
Rationale for change		Abbreviation for 'QT' added
Section to be changed	I II III IV V	Section 1.1 (Medical Background) Section 2.3 (Benefit Risk Assessment) Section 3.2 (Discussion of Trial Design) Section 3.3.3 (Exclusion Criteria) Section 4.2.2 (Restrictions)
Description of change		Administrative changes, corrections and clarification
Rationale for change		Addition of mycophenolate sodium for clarification as for 'mycophenolate' two possible salt forms are available.
Section to be changed		Section 1.2 (Drug Profile)
Description of change		Addition of a cautionary statement for patients at risk to develop QT prolongation according to the IB.
Rationale for change		Clarification of inconsistency between IB and CTP.
Section to be changed		Section 3.1 (Overall Trial Design and Plan)
Description of change		Administrative changes, corrections and clarification.
Rationale for change		Clarification of 'early discontinuation of trial medication' through rewording.
Section to be changed		Section 3.3.2 (Inclusion Criteria)
Description of change		Change reference time point for historical HRCT within 12 month to Visit 1.
Rationale for change		Visit 1 is presenting the better predictable time point compared to Visit 2.
Section to be changed		Section 3.3.3 (Exclusion Criteria)
Description of change		At discretion of the investigator, not only digital ulcers but also severe other ulcers could lead to

		exclusion of a patient. The same holds true for severe GI symptoms due to SSc. As described in the patient information, double contraception is a requirement for women of childbearing potential participating in the trial.
Rationale for change		The respective wording was added to increase awareness for investigators for safety reasons.
Section to be changed		Section 3.3.3 (Exclusion Criteria)
Description of change		Patients with underlying chronic liver disease (Child Pugh A, B, C hepatic impairment) are to be excluded
Rationale for change		Based on interactions with regulatory authorities including the FDA, the recommended dosage of nintedanib for patients with Child Pugh A hepatic impairment is 100 mg bid which has been recently included into the US Prescribing Information. As in the current protocol all patients should initiate treatment with the same starting dose of nintedanib 150 mg bid, patients with Child Pugh A will be excluded. In addition patients with Child Pugh B and C hepatic impairment will also be excluded to again be in line with the information stated in the US Prescribing Information that treatment with nintedanib in these patients is not recommended.
Section to be changed		Section 4.2.2 (Restrictions regarding concomitant treatment)
Description of change		Low dose prednisone stabilization requirement removed
Rationale for change		Corrected for consistency with Exclusion Criterion No. 17
Section to be changed		Section 5.2.3 (Assessment of DLCO)
Description of change		DLCO adjustment for altitude and COHb removed
Rationale for change		Corrected for consistency with section 10.1

Number of global amendment		2.0
Date of CTP revision		26 Jan 2017
EudraCT number		2015-000392-28
BI Trial number		1199.214 (SENSCIS™)
BI Investigational Product(s)		Nintedanib
Title of protocol		A double blind, randomised, placebo-controlled trial evaluating efficacy and safety of oral nintedanib treatment for at least 52 weeks in patients with 'Systemic Sclerosis associated Interstitial Lung Disease'(SSc-ILD).
To be implemented only after approval of the IRB / IEC / Competent Authorities	x	
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve l3ogistical or administrative aspects only		
Section to be changed		Flowchart – Main Trial
Description of change		Administrative changes, corrections and clarification.
Rationale for change		Add clarification and correction
Section to be changed	I	Flowchart – Main Trial (Footnotes)
Description of change		Compliance / drug accountability at Visit 3 and Visit 5 to be performed only in case of dose reduction/increase
Rationale for change		Clarification what needs to be documented at Visit 3 and Visit 5 in regards of compliance / drug accountability
Section to be changed	I II III	Flowchart – Main Trial (Footnotes), Abbreviations 5.5 (Assessment of exploratory biomarker(s))
Description of change		Administrative changes, corrections and clarification.

Rationale for change		Clarification that the Abbreviation for anti-RNA polymerase III antibodies is (anti-)RNA Pol III.
Section to be changed		Section 1.2 Drug Profile
Description of change		According to the changes in the recent IB Version 2.0 and Version 3.0 it was added pancreatitis and thrombocytopenia as well as drug-induced liver injury were infrequently reported in the IPF clinical trials and in the post-marketing period and are considered adverse drug reactions of nintedanib treatment in IPF. Patients with low body weight (<65 kg), Asian and female patients have a higher risk of elevations in liver enzymes.
Rationale for change		Clarification of inconsistency between IB and CTP.
Section to be changed	I	Section 3.3
Description of change		Added that enrolment will be generally competitive but restriction of recruitment of patients on stable dose of mycophenolate or methotrexate background medications may occur.
Rationale for change		To be able to adequately assess the treatment effect of nintedanib versus placebo in patients without background medication.
Section to be changed	I	Section 3.3
Description of change		Update of numbers of global country and site contribution
Rationale for change		Clarification and correction
Section to be changed	I	Section 3.3.2 Inclusion criteria
Description of change		Change the requested SSc disease onset (defined by first non-Raynaud symptom) from 5 years to 7 years of Visit 1.
Rationale for change		Ensure trial conduct feasibility without compromising characterization of study population.
Section to be changed	I	Section 3.3.3 (Exclusion Criteria)
Description of change		Change reference time point to assess eligibility in regards of airway obstruction (pre-bronchodilator FEV1/FVC <0.7) to Visit 2.
Rationale for change		Ensure consistency with all other Lung function criteria eligibility timepoints.

Section to be changed	I II	Section 3.3.3 (Exclusion Criteria) Section 4.2.2.1 (Restrictions regarding concomitant treatment)
Description of change		Add of washout requirements for mycophenolate mofetil / sodium or methotrexate.
Rationale for change		Clarification of washout requirements for mycophenolate mofetil / sodium or methotrexate.
Section to be changed	I	Section 3.3.3 (Exclusion Criteria)
Description of change		Deletion of tubal occlusion as an example for method of permanent sterilization.
Rationale for change		According to Clinical Trial Facilitation Group recommendations (2014), woman who underwent a tubal ligation are still to be considered 'of childbearing potential'.
Section to be changed	I	Section 3.3.3 (Exclusion Criteria)
Description of change		Additional Exclusion Criterion added. Patients with a history of SSc renal crisis are to be excluded.
Rationale for change		SSc renal crisis is a major complication in patients with systemic sclerosis (SSc) characterized by malignant hypertension and acute renal failure with a high risk for deterioration. As these patients may not automatically be captured by Ex 3, a new criterion was added.
Section to be changed	I	Section 4.1.4 (Drug assignment and administration of doses for each patient)
Description of change		Wording: 1 week treatment was changed to 5 days treatment following blister size.
Rationale for change		Correction for consistency.
Section to be changed	I	5.1 (Trial endpoints)
Description of change		Add absolute change from baseline at week 52 in CRISS index score to secondary endpoints and remove from further endpoints.
Rationale for change		As the Combined Response Index for Systemic Sclerosis is further evolving in use in clinical trials it should be elevated to secondary endpoints.
Section to be changed	I	5.3.7 (Assessment of adverse events)
Description of change		Remove additional note for Japan: The reason for the decision on causal relationship for unlisted

		AEs needs to be provided in the eCRF.
Rationale for change		Removed for consistency reasons.
Section to be changed	I	5.3.8 (Adverse event collection and reporting)
Description of change		Clarification that all primary causes of death will be reviewed by the independent adjudication. committee and process clarification regarding dataprotection measures
Rationale for change		Correction for clarification and consistency.
Section to be changed	I	5.5.2 (Analytical determinations)
Description of change		Clarification that autoantibody analysis from serum samples will be done in a central laboratory.
Rationale for change		Correction for clarification and consistency.
Section to be changed	I	5.5.3 (Biobanking)
Description of change		Clarification that DNA banking is not performed in all countries.
Rationale for change		Correction for clarification and consistency.
Section to be changed	I	6.1 (Screening)
Description of change		Clarification that rescreening is possible.
Rationale for change		Correction for clarification and consistency.
Section to be changed	I	6.1 (Screening)
Description of change		Referral to specific Visits removed
Rationale for change		Correction for clarification and consistency.
Section to be changed	I	6.2.1 (Screening)
Description of change		Correct reference time point for historical HRCT within 12 month to Visit 1.
Rationale for change		Correction for clarification and consistency with Inclusion criteria.
Section to be changed	I	6.2.2 (Treatment phase)
Description of change		Clarification that visit procedures may be performed on more than one calendar days.
Rationale for change		Correction for clarification and consistency.
Section to be changed	I	7.3.2 (Secondary endpoint analyses)
Description of change		Change test order of covariance structures.
Rationale for change		Correction for clarification.
Section to be changed	I	7.3.2 Secondary endpoint analyses

Description of change		Including ATA status and baseline FVC% predicted as covariates.
Rationale for change		Correction for clarification.
Section to be changed	I	10.1 (Lung function criteria)
Description of change		Clarification that at Visit 2 FVC % predicted will be calculated at the site level, by using the Flowscreen.
Rationale for change		Correction for clarification and consistency.

Number of global amendment		3.0
Date of CTP revision		15 Feb 2018
EudraCT number		2015-000392-28
BI Trial number		1199.214 (SENSCIS™)
BI Investigational Product(s)		Nintedanib
Title of protocol		A double blind, randomised, placebo-controlled trial evaluating efficacy and safety of oral nintedanib treatment for at least 52 weeks in patients with 'Systemic Sclerosis associated Interstitial Lung Disease'(SSc-ILD).
To be implemented only after approval of the IRB / IEC / Competent Authorities	x	
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve l3ogistical or administrative aspects only		
Section to be changed	I II III IV	Flowchart – Main Trial (Footnotes) 3.1 (Overall trial design and plan) 3.3.4 (Removal of patients from therapy or assessments) 6.2.2 (Treatment phase)
Description of change		Clarification of vital status assessment time points.
Rationale for change		Correction

Section to be changed	I	1.2. (Drug profile)
Description of change		It was added that based on results from a dedicated DDI study no clinically relevant PK interaction between nintedanib and pirfenidone when co-administered in patients with IPF was seen. In addition it was added that there was no clinically relevant pharmacokinetic effect of steady state bosentan treatment on nintedanib exposure detected in a dedicated DDI study in healthy volunteers. The new IB reference was added (combined IB for nintedanib in Idiopathic Pulmonary Fibrosis, Systemic Sclerosis, Progressive Fibrosing Interstitial Lung Disease).
Rationale for change		Correction for consistency between IB and CTP.
Section to be changed	I	2.3 (Benefit risk assessment)
Description of change		According to the changes in the recent IB it was clarified that cases of drug-induced liver injury (DILI) have been observed with nintedanib treatment. The majority of patients presented with mild to moderate liver enzyme elevation, which was in most cases transient upon dose reduction or treatment discontinuation. However, severe DILI with fatal outcome has also been reported
Rationale for change		Correction for consistency between IB and CTP.
Section to be changed	I II III	3.1 (Overall trial design and plan) 6.1 (Visit schedule) 6.2.2 (Treatment phase)
Description of change		Clarification that patients on treatment will have their end of treatment visit (EOT visit) at the same time or before the planned Visit 9 of the last randomised patient. The EOT visit will replace either Visit 9, 10, 11 or 12, whatever is the latest possible visit before or at the planned Visit 9 of the last randomised patient. For these patients, the trial ends with the completion of the follow-up visit 28 days after the EOT. All patients who have concluded the trial on treatment will be offered the opportunity to enter an open label extension trial. Clarification that for patients who discontinued

		treatment but agreed to come to further visits, the last visit will be either Visit 9, 10, 11 or 12, whatever is the latest possible visit before or at the planned Visit 9 of the last patient randomized. A follow up visit is not needed for patients who discontinued trial drug earlier.
Rationale for change		To clarify that not all patients will complete the trial at once and to specify the individual patient's end of the trial.
Section to be changed	I	4.2.2 (Restrictions)
Description of change		Clarification of clinically significant deterioration definition which could be related to organ systems other than skin and lung or in other clinical parameters than mRSS and FVC, at the discretion of the investigator.
Rationale for change		Clarification on definition.
Section to be changed	I	5.2.9 (HRCT substudy at dedicated sites only)
Description of change		It was added that the following assessments of structural change on HRCT may be determined on each scan: Gastrointestinal assessment / assessment of the oesophagus
Rationale for change		To add a possible exploratory assessment.
Section to be changed	I	5.5 (Assessment of exploratory biomarker)
Description of change		The list of biomarkers that might be evaluated was completed
Rationale for change		To clarify on possible biomarker panel.
Section to be changed	I	7.3.4 (Safety analyses)
Description of change		Clarification that based on the half-life of the trial drug, adverse events that occur between the start of treatment and up to 7 days after the date of the last dose of trial medication will be analysed in addition.
Rationale for change		Specification of an additional adverse event analyses to take the half-life of the trial drug into account.