Trial Statistical Analysis Plan

c08861098-02

BI Trial No.:	1199.214
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). Including Protocol Amendment 3 [c16778189], Protocol Amendment 4 [c03014699]
Investigational Product(s):	Nintedanib
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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse event
ALKP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BIcMQ	BI customised MedDRA Query
BRPM	Blinded report planning meeting
CDG	Customised Drug Grouping
CI	Confidence Interval
CT	Concomitant Therapy
CTC	Common Terminology Criteria
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CRISS	Combined Response Index in Systemic Sclerosis
DLCO	Carbon Monoxide Diffusion Capacity
DM&SM	Boehringer Ingelheim Data Management and Statistics Manual
DRA	Drug Regulatory Affairs
DMG	Dictionary Maintenance Group
EMA	European Medicines Agency
EQ5D-5L	EuroQol 5-Dimensionnal quality of life questionnaire (five-level version)
GLI	Global Lungs Initiative
HAQ-DI	Health Assessment Questionnaire Disability Index
Hb	Haemoglobin
FACIT	Functional Assessment of Chronic Illness Therapy
FAS	Full analysis set
FVC	Forced Vital Capacity
ICH	International Conference on Harmonisation
IPV	Important Protocol Violation
INR	International Normalized Ratio
LLN	Lower Limit of Normal

Term	Definition / description
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MQRM	Medical Quality Review Meeting
mRSS	Modified Rodnan Skin Score
O*C	Oracle Clinical
PK	Pharmacokinetics
PPS	Per protocol set
PSTAT	Project Statistician
PT	Preferred term
PV	Protocol violation
Q1	Lower quartile
Q3	Upper quartile
SA	Statistical analysis
SD	Standard deviation
SGRQ	Saint George Respiratory Questionnaire
SHAQ	Scleroderma Health Assessment Questionnaire
SMQ	Standardised MedDRA query
SpO2	Saturation of oxygen
SOC	System organ class
TCM	Trial Clinical Monitor
TESS	Treatment emergent signs and symptoms
ToC	Table of contents
TMW	Trial Medical Writer
TSAP	Trial statistical analysis plan
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale

3. INTRODUCTION

As per ICH E9 (3), the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This TSAP assumes familiarity with the Clinical Trial Protocol (CTP), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 7 “Statistical Methods and Determination of Sample Size”. Therefore, TSAP readers may consult the CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size, randomisation.

SAS® Version 9.4 or later will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

The methodology used in case of non-convergence of the models on the primary or key secondary endpoints has been updated in the TSAP, in order avoid a possible biased and over-precise estimates when using a simplified covariance matrix (see Section 7.4.1).

The combined response index in systemic sclerosis (CRISS) will not be analysed using a MMRM as the distribution of this endpoint is not normal (U-Shaped). It will be analysed as described in Section 7.5.2.5. For clarification, the wording of the endpoint related to CRISS was updated from “Absolute change from baseline at week 52 in CRISS to “CRISS at Week 52”.

In addition to the analyses planned in the CTP, for exploratory purposes, FVC rate of decline based on all data collected during the whole trial period will be analysed using a similar model as the primary model on the primary endpoint (see Section 7.6.3).
The absolute declines since baseline in FVC (% predicted) at week 52 of >5% or >10% will be added as further endpoints in order complement other analyses.

The “Time to first dose reduction or treatment interruption [days]” will be analysed as well in order to have a thorough description of dose reductions / treatment interruptions.

“Time to all-cause mortality” endpoint will be renamed “Time to death” for clarification purposes.

5. ENDPOINT(S)

In this Section, more details are given regarding endpoints whenever necessary. Note that for all endpoints and analyses, Section 6.7 should be consulted for the baseline value definition. Unless otherwise specified, all data up to 52 weeks (included – as defined in Section 6.7) will be taken into account, including follow-up visits (scheduled 4 weeks after End-Of-Treatment) before 52 weeks.

5.1 PRIMARY ENDPOINT(S)

The primary efficacy endpoint is the annual rate of decline in Forced Vital Capacity (FVC) over 52 weeks (expressed in mL).

5.2 SECONDARY ENDPOINT(S)

Endpoints will be used as defined in the CTP section 5.1.2. Additional specifications for some endpoints are given below.

5.2.1 Key secondary endpoint(s)

- Absolute change from baseline in the modified Rodnan Skin Score (mRSS) at week 52. The mRSS will be calculated as a sum of all its 17 areas and will have a range from 0 (no thickening) to 51 (severe thickening in all 17 areas). A high score corresponds to worse skin thickness.

- Absolute change from baseline in St George's Respiratory Questionnaire (SGRQ) total score at week 52. Specific rules of handling of missing / inconsistent SGRQ questions are detailed in Section 6.6. Please also refer to the SGRQ manual (13) for calculations of SGRQ scores. A high score corresponds to worse health.

5.2.2 (Other) Secondary endpoint(s)

5.2.2.1 Change from baseline endpoints

Refer to Section 6.6 for missing baseline assessment.

- FVC [%predicted]. The predicted values are calculated by the vendor using Global Lungs Initiative (GLI) 2012 equations (17).
- Carbon Monoxide Diffusion Capacity (DL_{CO}) [%predicted]. The DL_{CO} % predicted value will be calculated as the mean of the two valid measurements entered in the CRF (in case only one valid measurement is available then this one will be used).

  Then DL_{CO} %predicted will be corrected for Haemoglobin (Hb) and will always be presented after correction for Hb (see formulae in Appendix 10.1 of the CTP):

  In males (aged 15 years and above):

$$\text{DLCO \% predicted (corrected for Hb)} = \frac{\text{DLCO \%predicted (as reported in the CRF)x (10.22 + Hb)}}{\text{1.7 Hb}}$$

In females (aged 15 years and above):

$$\text{DLCO \% predicted (corrected for Hb)} = \frac{\text{DLCO \%predicted (as reported in the CRF)x (9.38 + Hb)}}{\text{1.7 Hb}}$$

(Hb being in g/dL)

- CRISS index score (18): It represents a probability of patient improvement and therefore ranges from 0 to 1.

Step 1: For patients who are considered as not improved over 52 weeks [1], CRISS index score is set to 0.
Step 2: For patients who are considered as improved over 52 weeks [1], CRISS index score is calculated as follows:

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

where:

Δ_{MRSS}, $\Delta_{FVC\%}$, $\Delta_{Pt\text{-}glob}$, $\Delta_{MD\text{-}glob}$ and $\Delta_{HAQ\text{-}DI}$ indicate respectively the absolute change from baseline to week 52 in mRSS, in FVC% predicted, in patient global assessment, in physician global assessment and in health assessment questionnaire disability index (HAQ-DI) score. Visual analogue scale VAS ranges from 0 to 10.

[1] Irrespective of improvements in other core items, a patient is considered as not improved over 52 weeks if he/she develops any of the following:

- He/she experiences a new scleroderma renal crisis over 52 weeks (according to reporting of AE preferred term coded “Scleroderma Renal Crisis”)
- Relative decline from baseline in FVC% predicted≥ 15% at week 52 and FVC% predicted <80% predicted at week 52
- New onset of left ventricular failure (based on reporting of AE preferred term coded “Left ventricular failure” or “Acute left ventricular failure”) or new onset of pulmonary arterial hypertension requiring treatment (based on reporting of AE preferred term coded “Pulmonary arterial hypertension” and with therapy required according to tick box in the AE page of the CRF)

- Digital ulcer net burden (see CTP Section 5.2.5 for the definition). It is calculated at a visit by counting the total number of fingertips with ulcers (i.e. number of fingers with presence of digital ulcer ticked “Yes” on the CRF) at the corresponding visit

- HAQ-DI (disability index) score (16). The score is calculated as follows:
Each question is scored 0–3 (where 0= “without difficulty” and 3= “unable to do”). There are 8 categories (Dressing and Grooming, Arising, Eating, Walking, Hygiene, Reach, Grip, Activities), each including 2 or 3 questions. The score for each category corresponds to the maximum question score within each category. In each category where devices and/or help from another person are checked as being used, the score

of that category is set to 2, except if the score is already at 2 (corresponding to "with much difficulty") or at 3 (corresponding to "unable to do") then the score cannot increase further. Finally, HAQ-DI score corresponds to the sum of the sub-scores of all 8 categories divided by the number of categories completed.
Please note that if there are fewer than 6 categories with responses, then a score cannot be calculated. The HAQ-DI score scale has 25 possible values (i.e., 0, 0.125, 0.250, 0.375 … 3). A high score corresponds to worse impairment.

- FACIT dyspnoea score. Two sub-scale scores are calculated from the FACIT-dyspnoea questionnaire: FACIT dyspnoea or functional limitations score (which is a further endpoint – please refer to Section 5.3.1). Each of them is scored so that a higher score value means worse dyspnoea (shortness of breath) or increased functional limitations.
    - All 10 dyspnoea items include a 4-point rating scale (no shortness of breath = 0; mildly short of breath = 1; moderately short of breath = 2; severely short of breath = 3). Those who report not doing the task (i.e. they ticked "I did not do this in the past 7 days") are asked to report whether it was attributable to dyspnoea or simply because they did not have an opportunity to do the task in the past week. If the response is because of dyspnoea (i.e., "stopped trying" or "knew could not do it because of shortness of breath"), the response is treated the same as the response "severely short of breath." (=3). Otherwise, the response is treated as missing (i.e., not included for scoring).
    - All 10 functional limitations items include a 4-point rating scale (no difficulty = 0; A little difficulty = 1; some difficulty = 2; much difficulty = 3).

  For each sub-scale of the FACIT scale, a raw score is calculated as: Sum individual item scores * 10 / number of items answered. When there are missing data, the calculation by sub-scale in this way is acceptable as long as more than 50% of the items were answered (i.e. a minimum of 5 out of 10 items) (15)
  Raw scores are then converted to scale scores using the table included in the FACIT-Dyspnoea Scale Short Form Scoring Guideline (14).

5.2.2.2 Time to death

Time to death (over the whole trial duration, including after 52 weeks) is defined with start date being the date of randomisation. Patients who did not die during the trial will be censored at the last contact date.

For this endpoint, the last contact date of a patient is defined as the latest date recorded in the Case Report Form (CRF) from the dates listed below:
Date of last visit, last reported Adverse Event (AE) (excluding censored dates), last reported concomitant treatment date, last laboratory sample date, last drug intake, last reported date in menstruation diary, last reported dose change / interruption date, date of trial completion, last known alive date or date of death.

Refer to Table 6.1:1 for details of the analysis periods used for time-to-event endpoints.

5.3 FURTHER ENDPOINT(S)

Further endpoints will be used as defined in the CTP section 5.1.3. Additional specifications for some endpoints are given below.

5.3.1 Absolute change from baseline endpoints

Refer to Section 6.6 for missing baseline assessment.

- SHAQ domain scores are the following six VAS:
    - Pain (How much pain have you had because of your illness in the past week?)
    - Gastrointestinal involvement (How much have your intestinal problems interfered with your daily activities in the past week?)
    - Lung involvement (How much have your breathing problems interfered with your daily activities in the past week?)
    - Vascular (How much has Raynaud's interfered with your daily activities in the past week?)
    - Digital ulcers (How much have your finger ulcers interfered with your daily activities in the past week?)
    - Patient global assessment (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?)

  For each of the six VAS (rated from 0 to 10), the score is calculated according to the following formulae: $\frac{10\ X\ distance\ measured\ from\ the\ left\ hand\ side\ to\ the\ mark}{Total\ length\ of\ the\ scale}$

  Each VAS is scored separately and the scores are not added together. Higher scores indicate more severe limitation.

- FACIT functional limitations scoring: please refer to Section 5.2.2.1.

- SGRQ domain scores: Specific rules of handling of missing / inconsistent SGRQ questions are detailed in Section 6.6. Please also refer to the SGRQ manual (13) for calculations of SGRQ scores.

- EQ-5D-5L VAS score indicating the self-rated patient's health state today (rated from 0 to 100). This does not take into account the first 5 descriptive questions of the questionnaire.

- Patient and physician global-VAS scores (rated from 0 to 10) are calculated as: $\frac{10\ X\ distance\ measured\ from\ the\ left\ hand\ side\ to\ the\ mark}{Total\ length\ of\ the\ scale}$

  Lower scores indicate worse overall health.

5.3.2 Categorical endpoints

- Proportion of patients with a relative decline since baseline in FVC (mL) at week 52 of >5% or >10%
- Proportion of patients with an absolute decline since baseline in FVC (% predicted) at week 52 of >5% or >10%
- Disease progression is defined in Section 5.2.7 of the CTP. Please refer to Section 6.6 for handling of missing data

5.3.3 Biomarkers

Biomarkers endpoints will be described in separate Statistical Analysis Plans.

5.4 OTHER VARIABLE(S)

5.4.1 Demographics and baseline characteristics

Demographics and other baseline characteristics will include the following.

5.4.1.1 Demographic data

- Gender
- Race:
- Single race respondents
- Multiple race respondents (all combinations ticked)
- All race categories, regardless of how many other races were also ticked in the CRF
- Ethnicity, overall and by race
- Age [years] will be calculated as : year of informed consent - year of birth
- Age in classes [years] (<30; >=30 and <45; >=45 and <60;>=60 and <75; >=75)
- Weight [kg] as continuous variable and in classes (<30; ≥30 and <60; ≥60 and <90; ≥90)
- Height [cm]
- Body mass index [kg/m2]: Weight[kg] / Height [m]*Height[m], as a continuous variable and in classes (< 18.5; >=18.5 and <25; >=25 and <30, >=30)

5.4.1.2 Trial indication

- Time elapsed since the first onset of non-Raynaud symptom [years] will be calculated as: (date of randomisation – date of onset of first non-Raynaud symptom) / 365.25
- Time elapsed since the first onset of non-Raynaud symptom will also be coded in classes (<= 1 year; > 1 year to ≤ 3 years; > 3 years to ≤ 5 years; > 5 years to ≤ 7 years; > 7 years)

- SSc Subtype (Diffuse cutaneous SSc, Limited cutaneous SSc)

- SSc related medical history as collected on the specific SSC related Medical History page of the CRF: history (Yes, No), symptoms still present at screening (Yes, No)

- Autoantibodies (as collected on the SSc related history page of the CRF):
  - Anti-topoisomerase antibodies (ATA) status (Positive, Negative)
  - Anti-Centromere antibodies (ACA) status (Positive, Negative)
  - Anti-RNA polymerase III antibodies ((anti-)RNA Pol III) status (Positive, Negative)
  - Antinuclear antibodies (ANA) status (Positive, Negative)

- HRCT assessment results:
  - Extent of fibrotic disease in the lung [%]
  - Ground Glass Opacities (Yes, No)
  - Honeycombing (Yes, No)
  - Reticulation (Yes, No)

5.4.1.3 Baseline characteristics for lung function and gas transfer characteristics

- FVC [mL]
- FVC [% predicted]
- Oxygen Saturation on Pulse Oximetry (SpO2) [%]
- DL_{CO} (corrected for Hb) [% predicted] as defined in Section 5.2.2.1

5.4.1.4 Baseline characteristics for questionnaires and derived outcomes

- Modified Rodnan Skin Score (mRSS)
- SGRQ Total, Symptoms, Activities and Impact scores
- Digital Ulcers count
- FACIT dyspnoea score and FACIT functional limitations score
- HAQ-DI score and SHAQ VAS scores (VAS scores include pain, assessment of limitation, vascular involvement, digital ulcers, lung involvement and gastrointestinal involvement).
- EQ-5D-5L patient´s self-rated health status
- Patient's global VAS
- Physician's global VAS

5.4.2 Compliance

Compliance will be calculated from baseline to Week 52, and over the duration of the study as:

$$\text{Compliance [\%]} = \frac{\text{Number of capsules actually taken over the treatment period}}{\text{Number of capsules which should have been taken over the treatment period}} \times 100$$

The number of capsules which should have been taken over the treatment period will be calculated as:

Number of capsules which should have been taken over the treatment period [capsules] = (date of last trial drug intake [1] – date of first trial drug intake + 1) [days] × 2 [2]

[1] For compliance over 52 weeks, the earliest of (Day 373 as defined in Section 6.7, or date of last trial drug intake) will be used.

[2]The time of first administration are taken into account, so only one capsule may be expected to be taken on some days (if time is after 14:30 then the calculation is then adapted accordingly).

In case of dose reduction to 100 mg bid, the number of capsules taken per day is still 2, so the calculation of compliance remains the same. Only treatment interruptions not due to AE will be considered as a compliance issue and will be taken into account in the calculation (duration of interruptions due to AE will be subtracted from the duration of the treatment period, as defined in Section 6.1).

Compliance will also be categorised into classes: <50%, >=50% to <80%, >=80% to <= 120%, > 120%.

5.4.3 Exposure

The date of first trial drug intake is recorded at visit 2.

5.4.3.1 Exposure over 52 weeks

Duration of exposure [months] = [Earliest of (date of last trial drug intake, Day 373 as defined in Section 6.7) – date of first trial drug intake +1 day] / 30.5

Duration of exposure in categories: <=3 months (91 days); >3 months (91 days) to <= 6 months (182 days); > 6 months (182 days) to <=12 months (365 days); > 12 months (365 days) to <= 14 months (426 days); > 14 months (426 days).

Treatment interruptions will not be subtracted from the duration of exposure.

Duration on each actual dose (100 or 150 mg bid): For each dose, sum of each continuous duration of exposure to dose effectively taken [days] up to Day 373 /30.5. By definition, this duration of exposure will be adjusted for treatment interruptions, dose reductions and dose

increases. This will be summarised in months and in categories (<= 2 months, > 2 months to <= 6 months, > 6 months)

Total dose [g]: Duration of exposure [days] * actual dose [g] (0.1 or 0.15 based on dose actually administered, twice a day)

Dose intensity [%]: amount of drug actually administered over the first 52 weeks (dose 100mg and 150mg) divided by the amount of drug that would have been administered had dose 150mg bid been administered over the first 52 weeks (from date of first trial drug intake to Day 373 as defined as Section 6.7, whether or not trial drug was prematurely discontinued). Dose intensity will be summarised in percent and in categories (<= 30 %, >30% - <=50%, >50% - <=90%, >90% - <100%, >=100%)

5.4.3.2 Exposure over all the trial

Similarly, duration of exposure, duration on actual dose, total dose and dose intensity will be summarised over the whole trial period (as defined in Section 6.7).

Dose intensity [%] over the whole trial period is defined as: amount of drug actually administered over the whole trial (dose 100mg and 150mg bid) divided by the amount of drug that would have been administered had dose 150mg bid been administered over the whole trial (from date of first trial drug intake to date of last trial drug intake).

Over this period, the categories for the duration of exposure will be: <=3 months (91 days); >3 months (91 days) to <= 6 months (182 days); > 6 months (182 days) to <=12 months (365 days); > 12 months (365 days) to <= 18 months (547 days); > 18 months (547 days) to <=24 months (730 days); > 24 months (730 days).

Treatment interruptions will not be subtracted from the duration of exposure.

5.4.4 Liver enzyme and bilirubin elevations

Liver enzyme and bilirubin elevations will be reported using the three following definitions:

- (ALT and/or AST ≥ 3 fold ULN) AND bilirubin ≥ 2 fold ULN[1]
    - And ALKP >= 2xULN
    - And ALKP < 2xULN
- ALT ≥ 5 fold ULN and/or AST ≥ 5 fold ULN
- ALT ≥ 3 fold ULN and/or AST ≥ 3 fold ULN

[1] These elevations are defined within a time window of 30 days i.e. the elevation of bilirubin should appear within 30 days after the elevation of AST and/or ALT.

The proportion of patients presenting signs of hepatic injury will be summarised, based on the following definition for signs of hepatic injury:

- ALT and/or AST ≥8 fold ULN
- ALT and/or AST ≥ 3 fold ULN and total bilirubin ≥ 2 fold ULN in the same sample
- ALT and/or AST ≥3 fold ULN and unexplained INR > 1.5 in the same sample
- ALT and/or AST ≥3 fold ULN and unexplained eosinophilia (>5%) in the same sample
- ALT and/or AST ≥3 fold ULN and appearance of fatigue, nausea, vomiting, right upper abdominal quadrant pain or tenderness, fever and/or rash within +/- 7 days of the abnormal ALT and/or AST laboratory test result (please refer to Section 9.6 for the list of relevant MedDRA preferred terms to support the derivation of a potential hepatic injury)

In addition, maximum individual elevations based on worst value on treatment will be defined as:

- ≥3 fold ULN; ≥5 fold ULN; ≥8 fold ULN for AST and ALT
- ≥1.5 fold ULN; ≥2 fold ULN for bilirubin
- ≥1.5 fold ULN; ≥2 fold ULN for ALKP
- ≥ 1 fold ULN; ≥ 3 fold ULN for GGT

5.4.5 Marked changes in vital signs

A marked increase is defined as:

- Systolic Blood Pressure >150 mmHg and increase >=25 mmHg above baseline
- Diastolic Blood Pressure >90 mmHg and increase >10 mmHg above baseline
- Pulse Rate >100 bpm and increase >10 bpm above baseline

A marked decrease is defined as:

- Systolic Blood Pressure <100 mmHg and decrease >10 mmHg below baseline
- Diastolic Blood Pressure <60 mmHg and decrease >10 mmHg below baseline
- Pulse Rate <60 bpm and decrease >10 bpm below baseline

5.4.6 Safety time-to-event analyses

- Time to first dose reduction [days]
- Time to first treatment interruption [days]
- Time to premature treatment discontinuation [days]
- Time to first dose reduction or treatment interruption [days]

The above variables will also be described in categories : <= 1 month (30 days), > 1 month (30 days) to <= 2 months (61 days), > 2 months (61days) to <= 3 months (91 days); > 3 months (91 days) to <= 6 months (182 days); > 6 months (182 days).

- Time to first liver enzyme elevation (ALT and/or AST > =3xULN)

In addition, the following two variables will be reported in section 16.1.13.1 of the CTR.

- Time to first liver enzyme elevation in conjunction with bilirubin elevation (ALT and/or AST > =3x ULN and bilirubin >= 2xULN)
- Time to first liver enzyme elevation (ALT and/or AST > =5xULN)

Safety time-to-event variables are defined with start date of time at risk being randomisation date. Censoring will be applied at Day 373 for the analysis over 52 weeks and on the date of last trial drug intake + 28 days for the analysis over the entire trial period (as defined in Table 6.7: 1).

Refer to Table 6.1:1 for details of the analysis periods used for time-to-event endpoints.

For these endpoints, the last contact date of a patient is defined as the latest date recorded in the Case Report Form (CRF) from the dates listed below:

Date of last visit, last reported Adverse Event (AE) (excluding censored dates), last reported concomitant treatment date, last laboratory sample date, last drug intake, last reported date in menstruation diary, last reported dose change / interruption date, date of trial completion.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

For the definition of treatment administered during the trial, see section 4 of CTP.

Note: the last day of each of the following periods is excluded from the respective period. It defines the first day of the subsequent period.

- Screening: from informed consent to randomisation
- Post-randomisation (optional[a]): from randomisation to first trial drug intake in treatment period.
- Treatment period: from first trial drug intake (or re-start of treatment if interruption) to last trial drug intake (or the day before start date of interruption if interruption) plus one day
- Off-treatment (optional[a]): from start date of interruption to re-start of treatment
- Residual effect period([b]): from the last trial drug intake plus one day to last trial drug intake plus 28 days plus one day or to date of first trial drug intake in extension trial, whichever occurs earlier
- Follow-up (optional[a] [b]): from last trial drug intake plus 29 days up to the beginning of post-study period. This period is only created if last trial drug intake took place more than 28 days before trial completion, or for patients having prematurely discontinued the treatment and still continuing the trial
- Post-study(optional[a] [b]): from the latest between last trial drug intake plus 29 days, 'date of trial completion' (from the trial completion part of the eCRF) plus one day, and 'date of Informed Consent in extension trial' (if applicable). This period is not created if date of first trial drug intake in extension trial is before last trial drug intake plus 28 days

[a] This period is optional insofar as it does not necessarily exist for all patients.

[b] In addition, a residual effect period of 7 days will be used for adverse event analyses to more closely reflect the period of time after the last trial drug intake when measureable drug levels or pharmacodynamics effects are still likely to be present.

As a summary:

- For efficacy analyses, data from randomisation date up to week 52 data will be considered (please see Section 7.4, Section 7.5 and Section 7.6). For efficacy descriptive analyses over the whole trial period, all data collected after randomisation date will be considered.

- For safety analyses, data from the treatment period, possible off-treatment periods and residual effect period will be considered as on-treatment.

All analyses will be based on the planned treatment group (Placebo or Nintedanib 150mg bid) as randomised by IXRS.

Table 6.1: 1 Summary of analysed periods according to the type of endpoint

		Studied period	
Type of analysis	**Analyses / Endpoints**	**Start date**	**End date** [1]
Efficacy analyses over 52 Weeks	Analyses on all endpoints listed in Section 5.1 of the CTP, except for time to death	Date of randomisation	Date of last measurement up to 52 Weeks (included - Day 373 as defined in Section 6.7)
On-treatment efficacy analyses over 52 Weeks	- Annual rate of decline in FVC in mL over 52 weeks, including only on-treatment data - Absolute change from baseline in the mRSS at week 52, including only on-treatment data - Absolute change from baseline in SGRQ total score at week 52, including only on-treatment data	Date of randomisation Off-treatment periods not excluded	Last trial drug intake (included) OR Week 52 time-point (Day 373 as defined in Section 6.7), whichever occurs first
Descriptive analyses over the trial period	Absolute change from baseline in: - FVC (mL) - FVC (% of predicted) - mRSS - SGRQ (Total score and Symptoms, Activities and Impact scores) - DLCO (% of predicted) - Digital ulcer net burden - HAQ-DI score - SHAQ domain scores (VAS scores) - FACIT dyspnoea and functional limitations score - EQ-5D-5L VAS score - Patient global VAS score - Physician global VAS score - SpO2(%) - Vital signs	Date of randomisation	Date of last measurement up to follow-up visit (included)

Table 6.1: 1 Summary of analysed periods according to the type of endpoint (cont'd)

		Studied period	
Type of analysis	**Analyses / Endpoints**	**Start date**	**End date [1]**
Descriptive analyses over the trial period	Relative change from baseline in : - FVC (mL) - mRSS	Date of randomisation	Date of last measurement up to follow-up visit (included)
Efficacy survival analysis[2]	Time to death (over the trial period)	Date of randomisation	Last contact date (as defined in Section 5.2.2.2)
Extent of exposure	See Section 5.4.3	Date of first trial drug intake	Last drug intake
Safety survival analysis[2]	Time to first liver enzyme elevation (for all definitions mentioned in Section 5.4.4)	Date of randomisation	Last trial drug intake + 28 days
	Time to - first dose reduction - first treatment interruption - premature treatment discontinuation	Date of randomisation	Last trial drug intake + 28 days
Safety survival analysis over 52 weeks[2]	Time to - first dose reduction - first treatment interruption - premature treatment discontinuation	Date of first trial drug intake	- If last drug intake < Day 373: Last drug intake - Else, if last drug intake ≥ Day 373: Day 373
On-treatment safety analyses over 52 weeks	- Adverse events - Laboratory data - Vital signs	Date of first trial drug intake	- If last drug intake < Day 373: Last drug intake + 28 days - Else, if last drug intake ≥ Day 373: Day 373
On-treatment safety analyses (over the whole trial)	- Adverse events - Laboratory data - Vital signs	Date of first trial drug intake	Last trial drug intake + 28 days Off-treatment periods not excluded. However, for safety listings, anything happening during a treatment interruption will be flagged as occurring during the off-treatment period

[1] End date is included. End date will always be checked against the date of first trial drug intake in 1199.225. For safety endpoints, if date of first trial drug intake in 1199.225 is earlier than end date calculated as mentioned in this table, then the end date of the studied period will be substituted by the date of first trial drug intake in 1199.225
[2] For time-to-event endpoint, if a patient does not have an event during the studied period then [redacted] will be censored on the day corresponding to the end date of the studied period

6.2 IMPORTANT PROTOCOL VIOLATIONS

The following table defines the different categories of important PVs (7). As there is no Per Protocol Set planned in this trial, none of the IPVs will lead to exclusion from a patient set. However the proportion of patients with IPVs will be presented for completeness purposes and to demonstrate the adherence to the CTP.

Unless otherwise specified, the following IPVs in Table 6.2: 1 have been defined over 52 weeks as this is the primary timepoint of interest in this trial. IPVs detected over the whole trial period will be reported in Section 16.1.13.1 of the CTR and the derivation will be adapted accordingly.

Table 6.2: 1 Important protocol violations over 52 weeks

Category/Code		**Description**	**Requirements**	**Excluded from**
A		**Entrance Criteria Not Met**		
	A1	**Inclusion criteria not met**		
	A1.1	Patient aged <18 years when signing his/her informed consent	Inclusion criteria 2 not met (Age <18 at the date of Informed Consent – Or other age restriction specified as per a local amendment) *Automatic IPV*	None
	A1.2	2013 ACR / EULAR classification criteria for SSc not fulfilled OR no chest HRCT performed demonstrating SSc related Interstitial Lung Disease pattern or extent of fibrotic disease in the lung <10% on HRCT	Inclusion criteria 3 or 5 not met; or extent of fibrotic disease <10% according to database *Automatic IPV*	None
	A1.3	SSc disease onset (defined by first non-Raynaud symptom) > 7 years of Visit 1.	CRF date of onset (defined by first non-Raynaud symptom) > 7 years before date of Visit 1, according to database *Automatic IPV*	None
	A1.4	FVC < 40% of predicted value at Visit 2	FVC < 35% (5% tolerance) at visit 2 according to database *Automatic IPV*	None
	A1.5	Single breath DL_{CO} (corrected for Hb) < 30% of predicted value at Visit 2	DLCO <25% (5% tolerance) at visit 2 according to database *Automatic IPV*	None
	A2	**Exclusion criteria met**		
	A2.1	Patient has laboratory values that indicate additional risk at Visit 1: a) >1.5xULN for AST or ALT b) >1.5xULN for Bilirubin c) Creatinine clearance < 30 mL /min (Cockcroft-Gault formula)	Laboratory values out of range at visit 1 according to the database *Automatic IPV*	None

Table 6.2: 1 Important protocol violations over 52 weeks (cont'd)

Category/Code		Description	Requirements	Excluded from
	A2.2	Patient with other disease(s) which are excluded as per exclusion criteria	Exclusion criteria 6-7-8-9-10-11-12-13-14-20-25-26 met *Automatic IPV*	None
	A2.3	Forbidden previous therapy	Exclusion criteria 15-16-17-18-19 met *Manual IPV based on exclusion criteria and / or to be identified at the site level on the manual PV log / issue log*	None
	A2.4	Potential risk related to fetotoxicity	Exclusion criteria 21-22 met *Automatic IPV*	None
B		**Informed Consent**		
	B1	Informed consent not given	Inclusion criteria 1 not met *Automatic IPV*	None
	B2	Informed consent given too late	CRF date of informed consent is after date of Visit 1. Signature of the wrong IC version, and later signature of the correct one will also be part of this IPV category *Manual IPV / issue log*	None
	B3	Informed consent not given or withdrawn for one of the substudies (HRCT, Skin Biopsy) but procedure done	*To be identified at the site level on the manual PV log/ issue log*	None
C		**Trial medication and randomisation**		
	C1	Incorrect trial medication taken	Medication kit taken (between Baseline - excluded - and Week 52) which does not match the treatment which the patient was randomised to (to be determined after unblinding). *Review of MQRM listings and / or to be identified at the site level on the manual PV log / issue log*	None
	C2	Randomisation not followed	Wrong stratification factor at time of randomisation. OR Wrong medication kit given leading to the patient taking treatment different from the one randomised by IXRS at time of randomisation (Visit 2). This is an IPV only if the medication error leads to an actual treatment switch (to be determined after unblinding). *Review of MQRM listings and / or to be identified at the site level on the manual PV log/ issue log*	None

Table 6.2: 1 Important protocol violations over 52 weeks (cont'd)

Category/Code		Description	Requirements	Excluded from
	C3	Overall Compliance (between baseline and Week 52) not between 80% and 120% inclusive (or non-compliance based on investigator assessment)	In case calculated overall between baseline and Week 52 compliance is missing: If the answer to the question "Did the patient take trial medication as instructed?" of the CRF is "No" at at least one of the visits where the compliance cannot be calculated, then an IPV will be flagged. Otherwise no IPV although calculated overall compliance between baseline and Week 52 is missing. *Automatic IPV with review of MQRM listings*	None
	C4	Trial medication not interrupted when ALT or AST ≥ 5 fold ULN	Based on liver enzyme elevation and interruptions reported between baseline and Week 52 *Automatic IPV*	None
	C5	Trial medication not permanently discontinued after signs of liver enzyme elevations were observed that a) are indicative of hepatic injury as defined in Section 5.3.7.1 of the CTP b) correspond to ALT or AST ≥ 3 fold ULN despite dose reduction or treatment interruption for 2 weeks or more	All patients where signs of liver enzyme elevations (between baseline and Week 52) are not dealt with according to the requirements of the CTP. *Manual IPV based on review of MQRM listings*	None
	C6	Medication code broken inappropriately	Reason for medication code broken is inappropriate (e.g. not emergency) and data collected after unblinding between baseline and Week 52 *Review of MQRM listings and / or to be identified at the site level on the manual PV log / issue log.*	None
D		**Concomitant Medication**		
	D1	Patient received prohibited concomitant therapies between baseline and Week 52 (see Section 4.2.2.1 of the CTP)	Based on concomitant therapies reported between baseline and Week 52 *Review of MQRM listings and / or to be identified at the site level on the manual PV log/ issue log*	None

Table 6.2: 1 Important protocol violations over 52 weeks (cont'd)

Category/Code		Description	Requirements	Excluded from
E		**Missing data**		
	E1	Patient without any physical assessment for more than 6 months, although under study medication	Missing results for physical assessment for more than 6 months during the trial *Automatic IPV*	None
	E2	No baseline or post-baseline FVC assessments up to Week 52	*Automatic IPV*	None
	E3	No baseline or post-baseline mRSS up to Week 52	*Automatic IPV*	None
	E4	No reliable[1] baseline or post-baseline SGRQ total score up to Week 52 [1] As per exclusion criteria 24	No baseline or post-baseline value or exclusion criteria 24 met *Automatic IPV*	None

Automatic PVs are those detected via an automated programming process using SAS.
Note: IPVs E2, E3 and E4 will be not be reported over the whole trial period.

A summary of IPV decisions will be provided in the final BRPM minutes.

6.3 PATIENT SETS ANALYSED

- Screened set
  This patient set includes all patients having signed informed consent and performed visit 1.

- Randomised set (RS)
  This patient set includes all randomised patients, whether treated or not.

- Treated set (TS)
  This patient set includes all randomised patients who received at least one dose of trial medication.

- PK set (PKS)
  This patient set includes those in the Treated Set with at least one valid plasma concentration available

6.4 SUBGROUPS

The subgroups listed in Table 6.4: 1 will be investigated. Selected variables as defined in Section 5.4 will be used to characterize the study population in all subgroups. Selected safety analyses as well as efficacy analyses on the primary and both key secondary endpoints will be done on some selected subgroups only (only in subgroups with more than 20 patients over both treatment groups within each category of the subgroup)

For more details on the planned analysis, please refer to Section 7.4.3.

Table 6.4: 1 Subgroup analyses – List of subgroups

	Description of study population[1]	**Efficacy analyses on the primary and both key secondary endpoints[2]**	**Safety analyses[3]**	**Rationale for subgroup analysis**
ATA status (Positive / Negative)	X	X	X	ATA is the stratification factor for randomisation in the trial
Gender (Male / Female)	X	X	X	SSc differences in males vs females have been described (Clin Exp Rheumatol. 2017 Sep-Oct;35 Suppl 106(4):89-97)
Age (<65 / ≥65)	X	X	X	Regulatory requirement
Race (White / Asian / Black or African American)[4]	X	X	X	Regulatory requirement
Region (Asia / Europe / Canada and United States / Rest of the World)	X	X	X	Assessing the homogeneity of treatment effect across region
Mycophenolate mofetil /sodium use at baseline (Yes / No)	X	X	X	Evaluation of influence of effect of stable background immunosuppressive therapy to study treatment as allowed per CTP
Methotrexate use at baseline (Yes / No)	X			Evaluation of influence of effect of stable background immunosuppressive therapy to study treatment as allowed per CTP
SSc subtype (Diffuse cutaneous SSc / Limited cutaneous SSc)	X	X	X	Evaluation of efficacy and safety in different SSc subtypes as manifestation and course of disease is described as being significantly different

Table 6.4: 1 Subgroup analyses – List of subgroups (cont'd)

	Description of study population[1]	**Efficacy analyses on the primary and both key secondary endpoints[2]**	**Safety analyses[3]**	**Rationale for subgroup analysis**
Baseline bodyweight (≤65kg, >65kg)	X		X	Based upon safety profile of Nintedanib- "Patients with low body weight (< 65 kg), Asian and female patients have a higher risk of elevations in liver enzymes."

[1] [2] [3] For more details, please refer to Table 7.4.3:1
[4] Only single race respondents are taken into account. In case more than 20% of patients ticked multiple races in the CRF, then a category "Multiple or missing' will be added for subgroup analyses by race

In addition, US / non-US subgroup analyses will also be done and will be included in Section 16.1.13.1 (efficacy and safety analyses).

6.5 POOLING OF CENTRES

This section is not applicable because centre/country is not included in the statistical model.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Missing data will not be imputed, except for some sensitivity analyses on the primary and key secondary endpoints.

6.6.1 Primary endpoint

The statistical model used for primary analysis (see Section 7.4.1) allows for missing data, assuming they are missing at random. Even patients with only one post-baseline assessment can be included in the model and can therefore participate in variance estimation. The statistical model assumes that patients who dropout would have behaved similarly to those who remained in the study.

Several sensitivity analyses will be conducted to investigate the potential effect of missing data on the results of the primary analysis (see Section 7.4.2).

6.6.2 Secondary endpoints

6.6.2.1 Change from baseline endpoints

The statistical model Mixed effect Model for Repeated Measures (MMRM) used for the analysis of continuous secondary endpoints allows for missing data, assuming they are missing at random.

For the two key secondary endpoints, several sensitivity analyses will be conducted to investigate the potential effect of missing data on the results of the main analysis.

6.6.2.1.1 Modified Rodnan Skin Score

In case of missing score for an area, mRSS total score will be missing.

6.6.2.1.2 Saint George's Respiratory Questionnaire

As the SGRQ manual (13) allows for 25% of missing data per component (i.e., 2 questions for symptoms, 6 questions for impacts and 4 questions for activities) the rules defined in the SGRQ manual will be used to derive the SGRQ.

Additionally the responses to questions 5 and 6 will be made consistent to the extent that if the answer to question 5 is 5 (none of the time) and the answer to question 6 is non-missing (i.e., length of worst attack specified), then question 6 will be set to missing. Therefore scores will be calculated ignoring that item. In this case, the missing response to question 6 will not be included in the count of missing questions for the symptoms component.

If the patient did not receive any respiratory treatment, then Part 2 Section 5 of the SGRQ should be skipped to go directly to Section 6. In this case, based on SGRQ manual instructions, responses will be considered as zero (and thus will not be included in the count of missing questions for the impact component).

Missing questions from Part1 Section 1 ("If you ever held a job…") will be left as missing (and counted as missing).

6.6.2.1.3 Digital ulcer net burden

If the presence of a digital ulcer is missing for a finger, digital ulcer net burden will be set to missing.

6.6.2.1.4 HAQ-DI

According to HAQ-DI scaling and scoring manual, if there are fewer than 6 categories with responses, an index score cannot be calculated and will be set to missing (no imputation planned).

6.6.2.1.5 FACIT dyspnoea or functional limitations score

If there are missing items, subscale scores can be calculated by multiplying the sum of the subscale by the number of items in the subscale, then dividing by the number of items actually answered. However this is only acceptable if more than 50% of the items were answered (FACIT Administration and Scoring Guidelines). No imputation planned in case of missing score.

6.6.2.1.6 EQ-5D-5L (EuroQol 5-Dimensionnal quality of life questionnaire)

No imputation planned. No score will be derived.

6.6.2.1.7 CRISS

Index score calculation:

For patients who are considered as improved over 52 weeks, in case the absolute change from baseline to week 52 in mRSS, FVC %predicted, patient global assessment, physician global assessment or HAQ-DI score is missing, then CRISS index score will be considered as missing.

In the multiple imputations step, after transformation into a binary responder variable, missing values will be imputed using the worst case (i.e. as Non-responder in all the imputations).

6.6.2.1.8 Disease progression

The handling of missing data is summarised in the table below:

Table 6.6.2.1.8: 1 Handling of missing data for disease progression

Absolute change from baseline in FVC %predicted at 52 weeks	Change from baseline in mRSS (absolute and relative) at 52 weeks	Death	Disease progression	Missing data rule
Missing	Missing or no mRSS worsening	Alive	Yes	Worst case
Missing or no FVC worsening	Missing	Alive	Yes	Worst case
Missing or FVC worsening or no FVC worsening	Missing or mRSS worsening or no mRSS worsening	Death	Yes	None
Missing or FVC worsening or no FVC worsening	mRSS worsening	Alive	Yes	None
FVC worsening	Missing or mRSS worsening or no mRSS worsening	Alive	Yes	None
No FVC worsening	No mRSS worsening	Alive	No	None

FVC worsening means absolute decline since baseline in FVC percent predicted >10%

mRSS worsening means relative change from baseline in mRSS of >25% and absolute change from baseline of >5 points. In case baseline mRSS is 0 (and relative change can therefore not be calculcated), then it will only be checked if the absolute change from baseline in mRSS is >5 points.

6.6.2.2 Categorical endpoints

In the analysis of the binary endpoints, patients with missing data will be considered as non-responders (i.e. worst case analysis).

6.6.2.3 Time-to-event endpoints

In the analyses of the time-to-event endpoints, missing or incomplete data will be managed by standard survival analysis techniques (i.e. censoring).

6.6.3 Other endpoints

6.6.3.1 Concomitant therapies

In case of (partially) missing start and end dates of concomitant therapies, the dates will be imputed so that the extent of exposure to the concomitant therapy is maximal, i.e. the first

day (month) of the month (year) for incomplete start dates and the last day (month) of the month (year) for incomplete end dates.

6.6.3.2 Safety endpoints

Missing or incomplete AE dates will be imputed according to BI standards (see "Handling of missing and incomplete AE dates") (8).

6.6.3.3 Trial diagnosis date / Date of onset of Raynaud / Date of onset of first non-Raynaud symptom

In case of partially missing date of trial diagnosis or date of onset of Raynaud or date of onset of first non-Raynaud symptom, the following imputation will be done:

- If day is missing, then imputed day will be the 1st of the month
- If day and month are missing, then imputed date will be the 1st of January of the (non-missing) year
- If year is missing, date will not be imputed

6.6.3.4 Pharmacokinetic endpoints

Handling of missing PK data will be performed according to the BI standard procedure "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies" (001-MCS-36-472_RD-01) (6).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

As a general rule, the last assessment/measurement before the date of first trial drug intake (included) will be used as baseline (possibly last screening assessment if no further available value).

Endpoints which are censored at Week 52 will be cut on Day 373 which is calculated as: Date of first trial drug intake (i.e. Day 1) + 372 (=365+7 day window per the CTP flow chart). All references to Day 373 throughout this document refer to this date which is 372 days after the date of first trial drug intake.

Visit windowing will be performed as described in Tables 6.7: 1, 6.7: 2 and 6.7: 3, in order to assign data to the relevant study visit based on the actual day of the assessment. Data will be analysed using the re-calculated visits in the statistical tables. However, in the listings, all

visits performed will be displayed (even if outside time-window), along with the re-calculated visit.

Table 6.7: 1 Time windowing rules for spirometry, physical exam, vital signs, HCRU, mRSS, Digital ulcer, menstruation calendar

Time window of actual day [1]			**Allocated to**		
Start day	End day (included)	Length of the time-window [days]	Visit number	Visit name	Planned day of the visit
Last assessment before the date of first trial drug intake	1	1	1 or 2[2]	Baseline	1
2	22	21	3	2 weeks	15
23	36	14	4	4 weeks	29
37	64	28	5	6 weeks	43
65	127	63	6	12 weeks	85

Table 6.7: 1 Time windowing rules for spirometry, physical exam, vital signs, HCRU, mRSS, Digital ulcer, menstruation calendar (cont'd)

Time window of actual day [1]			**Allocated to**		
128	211	84	7	24 weeks	169
212	309	98	8	36 weeks	253
310	373	63	9	52 weeks	365
374	533	161	10	68 weeks	477
534	645	112	11	84 weeks	589
646	708	63	12	100 weeks	701
709	Last trial drug intake + 27 [3]	Variable	NA	Between 100 weeks and follow-up visit	NA
Last trial drug intake + 28	Last trial drug intake + 35 [3]	7	FU	Follow-up	NA

Note: mRSS and Digital ulcer not measured at visits 3, 4, 5 and follow-up

[1] First trial drug intake date is taken into account as a reference to calculate time windows
[2] Depending on the last assessment before first trial drug intake (included), refer to Section 6.7 for baseline definition
[3] These two periods only exist if follow-up visit occurs after 709 days (included)

Table 6.7: 2 Time windowing rules for SGRQ, FACIT-dyspnoea, SHAQ, EQ-5D-5L, patient global VAS, DLCO, SpO2, antoantibody assessment, Physician global VAS

Time window of actual day [1]			**Allocated to**		
Start day	End day (included)	Length of the time-window [days]	Visit number	Visit name	Planned day of the visit
Last assessment before the date of first trial drug intake	1	1	1 or 2[2]	Baseline	1
2	253	252	7	24 weeks	169
254	373	280	9	52 weeks	365
374	708	175	12	100 weeks	701
709	Last trial drug intake + 27 [3]	Variable	NA	Between 100 weeks and follow-up visit	NA
Last trial drug intake + 28	Last trial drug intake + 35 [3]	7	FU	Follow-up	NA

[1] First trial drug intake date is taken into account as a reference to calculate time windows
[2] Depending on the last assessment before first trial drug intake (included), refer to Section 6.7 for baseline definition
[3] These two periods only exist if follow-up visit occurs after 709 days (included)

Table 6.7: 3 Time windowing rules for laboratory measurements (and pregnancy test)

Time window of actual day [1]			**Allocated to**		
Start day	End day (included)	Length of the time-window [days]	Visit number	Visit name	Planned day of the visit
Last assessment before the date of first trial drug intake	1	1	1 or 2[2]	Baseline	1
2	22	21	3	2 weeks	15
23	36	14	4	4 weeks	29
37	64	28	5	6 weeks	43
65	106	42	6	12 weeks	85
107	148	42	6a	18 weeks	127
149	190	42	7	24 weeks	169
191	232	42	7a	30 weeks	211
233	281	49	8	36 weeks	253
282	337	56	8a	44 weeks	309
338	373	56	9	52 weeks	365
374	449	56	9a	60 weeks	421
450	505	56	10	68 weeks	477
506	561	56	10a	76 weeks	533

Table 6.7: 3 Time windowing rules for laboratory measurements (and pregnancy test) (cont'd)

Time window of actual day [1]			**Allocated to**		
Start day	End day (included)	Length of the time-window [days]	Visit number	Visit name	Planned day of the visit
562	617	56	11	84 weeks	589
618	673	56	11a	92 weeks	645
674	708	35	12	100 weeks	701
709	Last trial drug intake + 27 [3]	Variable	NA	Between 100 weeks and follow-up visit	NA
Last trial drug intake + 28	Last trial drug intake + 35 [3]	7	FU	Follow-up	NA

[1] First trial drug intake date is taken into account as a reference to calculate time windows
[2] Depending on the last assessment before first trial drug intake (included), refer to Section 6.7 for baseline definition
[3] These two periods only exist if follow-up visit occurs after 709 days (included)

If after windowing of visits at baseline, two values fall within the same baseline interval, then the last value will be taken into account. If after windowing of post-baseline visits, two visits fall in the same interval, then the measurement closest to the planned visit will be taken into account. In case two measurements are equidistant from the planned visit, then the last one will be picked.

7. PLANNED ANALYSIS

For End-Of-Text (EoT) tables (1,2,5), the set of summary statistics is: N / Mean / SD / Min / Median / Max. In descriptive statistics tables, mean, SD and median will be rounded to one additional digit than the raw individual value.

In case some endpoints show some extreme data, median, quartiles and percentiles will be presented additionally.

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective treatment group (unless otherwise specified, all patients in the respective patient set whether they have non-missing values or not). Percentages will be rounded to one decimal place. The category missing will be displayed only if there are actually missing values.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report.

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the report.

7.2.1 Baseline conditions

A summary of baseline conditions will be provided by treatment group, System Organ Class (SOC) and Preferred Term (PT). SOC and PT will be sorted by descending frequency over both treatment arms.

7.2.2 Concomitant therapies

Concomitant therapies will be described over several study periods:

- Previous therapies will be defined as treatments with an end date before first trial drug intake.
- Baseline therapies will be defined as treatments with a start date before first trial drug intake and a stop date after or on the day of the first trial drug intake (or ongoing after first trial drug intake).
- On-treatment concomitant therapies are defined as treatments with a start date after or on the day of first trial drug intake and before or on the day of last trial drug intake.
- Post-study drug discontinuation therapies are defined as treatments with a start date after last trial drug intake and before trial completion. This aims at flagging

concomitant treatments taken by patients having prematurely discontinued study medication but followed-up up to the end of the study.

Concomitant therapies will be described over the first 52 weeks, as well as over the entire duration of the study. Concomitant therapies over 52 weeks will be defined as follows:

- On-treatment concomitant therapies over 52 weeks are defined as treatments with a start date after or on the day of first trial drug intake and before or on either:
    - the day of last trial drug intake for patients having prematurely discontinued study medication before 52 weeks
    - the Week 52 time-point (Day 373 as defined in Section 6.7) for other patients.
- Post-study drug discontinuation concomitant therapies over 52 weeks are defined as treatments with a start date after last trial drug intake (for patients having prematurely discontinued study medication before 52 weeks) and before Week 52 time-point (Day 373 as defined in Section 6.7).

Table 7.2.2:1 summarises the concomitant therapy outputs which will be provided for each category of concomitant therapy created.

Summaries by ATC and preferred name (PN) will use the ATC3 code, and will be sorted by alphabetical ATC class and decreasing frequency of PN in the Nintedanib treatment arm within ATC class.

Summaries by Customised Drug Grouping (CDG) will be sorted alphabetically by the name of the CDG and by decreasing frequency of PN in the Nintedanib treatment arm within a CDG. CDGs are built using WHO-DD Standardised Drug Groupings (SDG), Sub-SDGs and ATC4 levels. CDGs are listed in Section 9.4.

Table 7.2.2:1 Concomitant therapy outputs and position in the CTR

	By ATC and PN		**By CDG and PN**	
	Over 52 weeks	**Entire trial duration**	**Over 52 weeks**	**Entire trial duration**
Previous therapies	16.1.13.1	Not applicable	Not required	Not applicable
Baseline therapies	16.1.13.1	Not applicable	15.1	Not applicable
On-treatment concomitant therapies	16.1.13.1	16.1.13.1	16.1.13.1	16.1.13.1

Table 7.2.2:1 Concomitant therapy outputs and position in the CT (cont'd)

	By ATC and PN		By CDG and PN	
	Over 52 weeks	**Entire trial duration**	**Over 52 weeks**	**Entire trial duration**
All on-treatment concomitant therapies* with a frequency >2% in at least one treatment arm	16.1.13.1	Not required	Not required	Not required
All on-treatment concomitant therapies*	16.1.13.1	16.1.13.1	16.1.13.1	16.1.13.1
All concomitant therapies**	16.1.13.1	16.1.13.1	15.1	16.1.13.1
All concomitant therapies** in patients who prem. disc. treatment	Not required	Not required	16.1.13.1	Not required
Post-study drug discontinuation therapies	Not required	Not required	16.1.13.1	Not required

* including baseline therapies.
** including baseline, on-treatment and post-study drug discontinuation therapies.

7.3 TREATMENT COMPLIANCE

Only descriptive statistics are planned for this section of the report.

7.4 PRIMARY ENDPOINT(S)

All analyses will be performed on the Treated Set.

Refer to Section 7.3.1 of the CTP.

7.4.1 Primary analysis

The primary analysis will be performed on the TS (according to randomised treatment), using all available data from baseline (excluded) up to Week 52 (after time-windowing), including visits done after premature treatment withdrawal, EOT visits and follow-up visits done before Week 52. Patients will be analysed according to the ATA status stratum to which they belong to (as reported in the CRF), regardless of any mis-assignment to treatment based on identification of the wrong stratum in IXRS.

The primary analysis is a restricted maximum likelihood (REML) based approach using a random slope and intercept model.

The analysis will include the fixed, categorical effects of treatment, ATA status and gender, fixed continuous effects of time and baseline FVC (mL), age and height as well as the treatment-by-time and baseline-by-time interactions. Random effects will be included for patient response for both time and intercept.

The statistical model can be written as follows:

$$y_{ijkmg} = \left(\alpha + a_i + \phi_m + \vartheta_g + \vartheta_a Age_i + \vartheta_h Height_i + \beta_0 S_i + \tau_k\right) + \left(\gamma + g_i + \beta_s S_i + \varphi_k\right) t_{ij} + e_{ij}$$

$$(a_i, g_i) \sim N_2\ (\mathbf{0}, \boldsymbol{\Sigma})$$

$$e_{ij} \overset{iid}{\sim} N\ (0, \sigma^2)$$

The components of the model are as follows:

y_{ijkmg} = FVC value (mL) for patient i in ATA status stratum m with gender g at Week j receiving treatment k,

α = mean patient intercept

a_i = random intercept effect for patient i, i=1,2,…

ϕ_m= the effect of ATA status stratum m, m=1,2. ATA status is used as reported in the CRF ("Positive" as the class of reference, regardless of any mis-assignment to treatment based on identification of the wrong stratum in IXRS)

ϑ_g = intercept coefficient of Gender covariate ("Male" as the class of reference)

ϑ_a = intercept coefficient of Age covariate

Age_i = Age covariate value [years] for patient i

ϑ_h = intercept coefficient of Height covariate

$Height_i$ = Height covariate value [cm] for patient i

β_0= intercept coefficient of baseline effect

S_i= FVC baseline measurement [mL] of patient i

τ_k= intercept coefficient of the effect of treatment k, k=1,2

γ = mean patient slope

g_i = random slope effect for patient i

β_s= slope coefficient of baseline effect

φ_k= slope coefficient of the effect of treatment k

t_{ij} = time of measurement j for patient i, j= 1,2,… J

e_{ij} = the random error associated with the j^{th} Week of patient i. Measurement errors are independent and normally distributed with mean 0 and variance σ^2, and uncorrelated with a_i and g_i.

$\boldsymbol{\Sigma}$ = a 2x2 unstructured covariance matrix

Within patient errors are assumed to follow a random coefficient regression model with random effect for intercept and slope. An unstructured variance-covariance structure will be

used to model these random slope and intercept. The variance-covariance matrix modeled to estimate the inter-individual variability is considered to have a Variance-Components structure. In the event of non-convergence, the following methods will be attempted (in order) to overcome it:

1. Add the 'singular=1e-10' option in the model statement – This raises the threshold at which columns are declared linearly dependent (from typically 1e-12).

2. Set 'maxiter=100' in the Proc Mixed statement – This increases the number of convergence iterations used from a default of 50.

3. Set 'scoring=4' to specify use of the Fisher scoring algorithm in the first 4 iterations.

4. Include the statement 'performance nothread' – this removes multi-threading from the calculations.

The first model to converge will be used as the primary analysis on the FVC rate of decline at week 52. If convergence does not achieved based on above approach, more simplified model can be used.

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$ (two-sided 95% confidence intervals).The primary treatment comparison of slopes will be assessed through the treatment-by-time interaction coefficient.

Please refer to Section 9.2 for more details concerning the statistical model and SAS code specifications.

7.4.2 Sensitivity analyses

Sensitivity analyses using different assumptions will be conducted to investigate the potential effect of data handling and the analysis model on the results of the main analysis.

For all sensitivity analyses to data handling assumptions the estimate, two-sided 95% Confidence Interval and p-value of the treatment effect will be represented on the same Forest plot. Tables presenting the results of the sensitivity analyses will be included in Section 16.1.13.1 of the CTR.

Interpretation of sensitivity analyses:

Separate Forest-plots will be produced for the primary and each key secondary endpoint (in Section 15 of the CTR). The consistency of the results of the sensitivity analyses with the primary analysis result will be assessed by checking if the treatment effect estimate of a sensitivity analysis lies inside the confidence interval of the treatment effect of the primary analysis.
The tables corresponding to the Forest-plots will also be performed as part of Section 16.1.13.1 of the CTR.

7.4.2.1 Sensitivity to data handling assumptions

7.4.2.1.1 Statistical model using on-treatment measurements only

A sensitivity analysis including only on-treatment measurements of FVC (mL) will be presented. The same model as for the primary analysis will be used (see Section 7.4.1). This model which implies that data are assumed to be missing at random and it is implicitly supposed that patients who dropout would have behaved similarly to those who remained in the study.

This analysis is considered of principal importance amongst the planned sensitivity analyses since it most closely reflects the expected biologic effect of nintedanib in the treatment of patients with SSc-ILD.

7.4.2.1.2 Sensitivity to missing data handling

To investigate the potential impact of missing data on the treatment effect, patients will be classified into different patterns depending on the availability of data:

- Patients with a 52 week FVC value (see Table 6.1: 1 for further information regarding the analysis period):

    1. those who received trial drug until 52 weeks (defined as patients who did not prematurely discontinue the trial medication before 52 weeks as according to the "end of trial medication" page of the CRF) (pattern 1)

    2. those who prematurely discontinued trial drug before 52 weeks (as per information given on the "end of trial medication" page of the CRF) but who were followed up until week 52 (pattern 2)

- Patients without a 52 week FVC value:

    3. those who were alive at 52 weeks (based on "vital status" page of the CRF, and no fatal AE recorded on the "adverse event" page of the CRF) (pattern 3)

    4. those who died before 52 weeks (based on "vital status" page of the CRF, or fatal AEs recorded on the "adverse event" page of the CRF) (pattern 4)

These four patterns will be used in sensitivity analyses to estimate the treatment effect under differing assumptions regarding the persistence of efficacy post withdrawal of randomised treatment. As described hereafter, three resulting alternative analyses will be defined.

Multiple imputation will be used to handle missing data at week 52. Non-monotone missing data and/or missing data at visits before week 52 will not be imputed. The imputation model will be similar to the statistical model of the primary analysis (see Section 7.4.1).

The number of imputations will be set to 1000 in order to ensure adequate efficiency for the estimation of missing data. For each imputed dataset, the same statistical model as defined for the primary analysis will be used for the analysis. See Section 7.4.1 for a description of the primary analysis model. The results will be pooled following the standard multiple imputation procedure (20). See also Section 9.2 for further technical information on the implementation of the multiple imputation approach.

Table 7.4.2.1.2: 1 Primary and sensitivity analyses for handling of missing data

Analysis	Pattern 3: Missing week 52 data in patients still alive at 52 weeks		Pattern 4: Missing week 52 data in patients who died before 52 weeks	
	Handling of missing week 52 data	**Underlying assumption regarding persistence of efficacy post-withdrawal**	**Handling of missing week 52 data**	**Underlying assumption regarding persistence of efficacy after death**
Primary	no imputation	assumes MAR	no imputation	assumes MAR
Sensitivity 1[1]	based upon the slope (SE) estimates in Drug and Placebo in patients of pattern 2, multiple imputation of missing week 52 data in the respective treatment group	rate of decline in patients with missing week 52 data is similar to rate of decline in patients of pattern 2 in the respective treatment group (e.g. treatment effect persists in same manner as for pattern 2 patients after trial drug discontinuation)	multiple imputation of missing 52 week data due to death based on the same slope (SE) estimates in Placebo patients of pattern 2, but truncated[3] to force the slope in patients who died to be more severe than in those who survived	Assuming that deaths observed in the trial will likely be related to worsening of SSc, it seems reasonable to assume that the unobserved FVC values should on average be lower than those in patients who did not die prior to week 52 Rate of decline in patients who died before week 52 is similar to rate of decline in the Placebo patients of pattern 2 with most severe slopes
Sensitivity 2[1]	based upon the slope (SE) estimates in Placebo patients of pattern 2: multiple imputation of missing week 52 data in all patients regardless of treatment group	rate of decline in all patients with missing week 52 data is similar to rate of decline in Placebo patients of pattern 2 (e.g. treatment effect does not persist after trial drug discontinuation)		

Table 7.4.2.1.2: 1 Primary and sensitivity analyses for handling of missing data (cont'd)

Analysis	Pattern 3: Missing week 52 data in patients still alive at 52 weeks		Pattern 4: Missing week 52 data in patients who died before 52 weeks	
	Handling of missing week 52 data	**Underlying assumption regarding persistence of efficacy post-withdrawal**	**Handling of missing week 52 data**	**Underlying assumption regarding persistence of efficacy after death**
Sensitivity 3[2]	based upon the slope (SE) estimates in Placebo patients from the primary analysis model, i.e. in patients from pattern 1 or 2: multiple imputation of missing week 52 data in all patients regardless of treatment group	rate of decline in all patients with missing week 52 data is similar to rate of decline estimated in all Placebo patients (e.g. treatment effect does not persist after trial drug discontinuation)	multiple imputation of missing 52 week data due to death based on the same slope (SE) estimates in all Placebo patients (i.e. in patients from pattern 1 or 2), but truncated[3] to force the slope in patients who died to be more severe than in those who survived	Assuming that deaths observed in the trial will likely be related to worsening of SSc, it seems reasonable to assume that the unobserved FVC values should on average be lower than those in patients who did not die prior to week 52 Rate of decline in patients who died before week 52 is similar to rate of decline in the Placebo patients with most severe slopes

[1] Sensitivity analyses 1 and 2 will only be performed if the number of patients in pattern 2 is greater than 10 (from both Nintedanib and Placebo group together for sensitivity analysis 1 and from placebo group for sensitivity analysis 2)

[2] Patients falling into pattern 2 are used as the basis for multiple imputations in sensitivity analyses 1 and 2 but since the number of patients in that pattern may be small, a third sensitivity analysis will be performed to confirm the robustness of the primary analysis results.

[3] If β represents the true slope with $f(\beta) \sim N(\hat{\beta}, \hat{\sigma}^2)$ where $\hat{\beta}$ and $\hat{\sigma}$ are the placebo slope and SE estimates from either patients in pattern 2 or all placebo patients, then sampling for patients who died prior to 52 weeks is restricted to the interval $(-\infty, \hat{\beta}]$ of the truncated distribution $f(\beta)/2$. In this way, it is guaranteed that, on average, the imputed FVC slope for patients who died is steeper than the average slope in patients who survived to week 52.

In addition to the patterns defined in the scope of the multiple imputation, the number (and percentage) of patients in each possible pattern of FVC data will be explored and presented in Appendix 16.1.13.1 of the CTR. Graphs showing FVC data over time in each pattern of monotonic missing data will also be provided in Appendix 16.1.13.1 of the CTR.

7.4.2.2 Sensitivity to the analysis model

7.4.2.2.1 Sensitivity to linearity assumption

The linearity assumption for the decline in FVC [mL/yr] will be explored graphically. The following graphical displays will be provided:

- the mean (± Standard Error of the Mean (SEM)) observed FVC [mL] for each treatment group over time
- the mean (± SEM) observed FVC change from baseline [mL] for each treatment group over time
- the mean (± SEM) estimated FVC [mL] for each treatment group over time (as estimated in the primary analysis)

The following alternative models will also be performed and a graphical display only will be provided:

- A polynomial time model (quadratic form in t) will be explored
- An exponential model (of the form: a + b exp(-c*t)) will be explored as well

For each model, a plot will be provided representing both the mean (± SEM) estimated FVC [mL] over time and the mean (± SEM) estimated FVC [mL] over time using the linear form (by treatment group).

In these models, data are assumed to be missing at random, which implies that patients who dropout would have behaved similarly to those who remained in the study.

7.4.2.2.2 Sensitivity to covariates

A statistical model similar to the primary analysis will be done, including the fixed, categorical effects of treatment, ATA status (Positive / Negative), fixed continuous effects of time and baseline FVC (mL), the treatment-by-time and baseline-by-time interactions. Random effects will be included for patient response for both time and intercept.

A statistical model similar to the primary analysis will be done, the fixed, categorical effects of treatment, ATA status (Positive / Negative), gender and mycophenolate mofetil /sodium background therapy use (Yes / No), fixed continuous effects of time, age , height and baseline FVC (mL), the treatment-by-time and baseline-by-time interactions. Random effects will be included for patient response for both time and intercept.

7.4.2.3 Overall summary of sensitivity analyses

Table 7.4.2.3: 1 Summary of planned sensitivity analyses according to the endpoint

	Sensitivity analysis	**Scope of sensitivity analysis**	**Primary endpoint**	**Key secondary endpoints**	
			Rate of FVC decline	**Change from baseline in mRSS score**	**Change from baseline in SGRQ total score**
Sensitivity to data handling assumptions	Analysis including only on-treatment data	To assess the direct effect of the trial drug and the impact of data measured post trial drug discontinuation.	X	X	X
	Multiple imputation approaches	To estimate the treatment effect under differing assumptions regarding the persistence of efficacy post withdrawal of randomised treatment	X	X	X
Sensitivity to the analysis model	Polynomial / Exponential time models	To verify the linear assumption of the primary model of the primary endpoint	X		
	Use of different covariates	To verify the impact of the choice of covariates in the primary model	X		

7.4.3 Subgroup analyses

For each subgroup analysis (refer to Section 6.4) of the primary endpoint, the heterogeneity of the treatment effect on the slope across subgroups will be estimated: A random slope and intercept mixed model will be fitted based upon the statistical model for the primary analysis considering the treatment-by-subgroup and treatment-by-subgroup-by-time interaction terms. A contrast statement, with appropriate contrasts, will be used to conduct an F-test of heterogeneity across all levels of the subgrouping at Week 52. The level at which p-values will be considered nominally significant is 5%. Nominally significant results will be discussed and may be explored further.

It can be shown that the following simplified, saturated model is equivalent to the fully specified model and will therefore be used for the analysis of subgroups:

$$y_{ijkmgu} = \left(\alpha + a_i + \phi_m + \vartheta_g + \vartheta_a Age_i + \vartheta_h Height_i + \beta_0 S_i + \tau_k \delta_{ku}\right) + \left(\gamma + g_i + \beta_s S_i + \theta_{ku}\varphi_k * sg_i\right)t_{ij} + e_{ij}$$

$$e_{ij} \overset{iid}{\sim} N(0, \sigma^2)$$

The components of the model are identical to the primary model (see Section 7.4.1 for explanation of notions) only adding the subgroup covariate:

- δ_{ku} = intercept coefficient for the effect of treatment k in subgroup category u for patient i and k = 1,2, u = 1,2,…
- θ_{ku} = slope coefficient for the effect of treatment k in subgroup category u for patient i and k = 1,2, u = 1,2,…

In the event of non-convergence, the same methods than the ones described in Section 7.4.1 will be used to overcome the issue.

Table 7.4.3: 1 Subgroup analyses – List of analyses

Description of study population	- Disposition of patients - Demographic data - Trial indication characteristics - Baseline pulmonary efficacy variables - Baseline SGRQ scores and mRSS - Baseline conditions
Efficacy analyses on the primary and both key secondary endpoints	Primary endpoint analyses - Forest-plot for rate of decline in FVC (mL/yr) over 52 weeks in all subgroups: representation on the same graph of the estimate, 95% Confidence Interval for each subgroup and subgroup interaction p-value value of F-test for heterogeneity across all levels of the subgrouping - Rate of decline in FVC (mL/yr) over 52 weeks by subgroup - Graphical representation of the mean (SEM) observed FVC change from baseline (mL) over time by subgroup - Graphical representation of the mean (SEM) estimated FVC change from baseline (mL) over time by subgroup

Table 7.4.3: 1 Subgroup analyses – List of analyses (cont'd)

Efficacy analyses on the primary and both key secondary endpoints	Key secondary endpoint analyses - Forest-plot for adjusted mean (SE) for absolute change from baseline in mRSS at 52 weeks in all subgroups: representation on the same graph of the estimate, 95% Confidence Interval for each subgroup and subgroup interaction p-value of F-test for heterogeneity across all levels of the subgrouping - Adjusted mean (SE) for absolute change from baseline in mRSS at 52 weeks by subgroup - Graphical representation of the mean (SEM) observed mRSS change from baseline over time by subgroup - Graphical representation of the mean (SEM) estimated mRSS change from baseline over time by subgroup - Forest-plot for adjusted mean (SE) for absolute change from baseline in SGRQ total score at 52 weeks in all subgroups: representation on the same graph of the estimate, 95% Confidence Interval for each subgroup and subgroup interaction p-value of F-test for heterogeneity across all levels of the subgrouping - Adjusted mean (SE) for absolute change from baseline in SGRQ total score at 52 weeks by subgroup - Graphical representation of the mean (SEM) observed SGRQ total score change from baseline over time by subgroup - Graphical representation of the mean (SEM) estimated SGRQ total score change from baseline over time by subgroup
Safety analyses	Over 52 weeks and over the whole trial: - Exposure to study drug - Exposure to actual treatment dose received - Adverse event overall summary - Frequency of patients with adverse events occurring with incidence in preferred term > 1% in at least one treatment arm by SOC and PT - Frequency of patients with adverse events by SOC and PT - Frequency of patients with serious adverse events by SOC and PT - Frequency of patients with adverse events leading to permanent drug discontinuation by SOC and PT - Frequency of patients with investigator defined drug-related adverse events by SOC and PT - Frequency of patients with adverse events by safety topic - Frequency of patients with serious adverse events by safety topic

7.5 SECONDARY ENDPOINT(S)

The statistical analyses for secondary endpoints will be based on the TS (according to randomised treatment), using data from baseline (excluded) up to Week 52 (after time-windowing), including visits done after premature treatment withdrawal, EOT visits and follow-up visits done before Week 52.

7.5.1 Key secondary endpoint(s)

7.5.1.1 Absolute change from baseline in the mRSS at week 52

Absolute change from baseline in the mRSS at week 52 will be analysed in the TS using a restricted maximum likelihood (REML) based repeated measures approach , as described in the CTP Section 7.3.2.1. Analyses will include the fixed, categorical effects of ATA status, and treatment-by-visit interaction, as well as the continuous fixed covariate of baseline-by-visit interaction. Visit will be treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements.

In the event of non-convergence, the same methods than the ones described in Section 7.4.1 will be used to overcome the issue, including in addition the following one: 5. Provide starting values for covariance parameters using a 'parms' statement. Estimates will be obtained from a simpler covariance matrix.

A cumulative distribution plot of the absolute change from baseline in the mRSS at week 52 will be provided, showing the cumulated frequencies for all possible absolute change from baseline in the mRSS values.

Several sensitivity analysis will be lead in order to assess the potential effect of data handling and the analysis model on the results of the main analysis.

The thorough list of sensitivity analyses planned is listed in Table 7.4.2.3: 1.

Note that for the imputation of mRSS total score missing values, imputed values will be truncated if needed so that they are comprised between 0 and 51.

A graph of the mean mRSS absolute change from baseline (± SEM) over time for each treatment group will be displayed. The same graph will be performed on adjusted mean changes from baseline.

In the subgroup analysis of the key secondary endpoints using MMRM models, a similar approach as for the primary endpoint will be used: A single MMRM model will be fitted involving all model terms from the primary analysis model except replacing the treatment-by-visit term by treatment-by-subgroup-by-visit. A Lsmestimate statement, with appropriate contrasts, will be used to conduct an F-test of heterogeneity across all levels of the subgrouping. The level at which p-values will be considered nominally significant is 5%. Nominally significant results will be discussed and may be explored further.

7.5.1.2 Absolute change from baseline in SGRQ total score at week 52

Similar analyses as for the first key secondary endpoint (Absolute change from baseline in the mRSS) will be performed for the absolute change in SGRQ total score, in the TS. Please refer to Section 7.5.1.1.

Note that for the imputation of SGRQ total score missing values, imputed values will be truncated if needed so that they are comprised between 0 and 100.

In addition, a cumulative distribution plot of the absolute change from baseline in SGRQ total score at week 52 will be provided.

7.5.2 (Other) Secondary endpoint(s)

No sensitivity or subgroup analyses will be performed on the following other secondary endpoints. These will be analysed on the TS.

7.5.2.1 Annual rate of decline in FVC in percent predicted over 52 weeks

A similar analysis as the primary model on the primary endpoint will be done, including baseline FVC% predicted and ATA status as a covariate. Please refer to Section 7.4.1.

7.5.2.2 Absolute change from baseline in FVC in mL at week 52

A similar analysis based on MMRM as for the key secondary endpoints will be performed for the absolute change in FVC. Please refer to Section 7.5.1.1.

In addition, a cumulative distribution plot of the absolute change from baseline in FVC in mL at week 52 will be provided.

7.5.2.3 Relative change from baseline (%) of mRSS at week 52

A similar analysis based on MMRM as for the key secondary endpoints will be performed for the relative change in mRSS. Please refer to Section 7.5.1.1.

7.5.2.4 Time to death

Please refer to CTP Section 7.3.2.2 for the summary of analyses and Section 5.2.2.2 for the definition of the censoring.

A Kaplan-Meier plot of time to death over the whole trial duration will be displayed. Time to death at Week 52 will also be displayed as additional information.

7.5.2.5 CRISS index score at week 52

For all analyses, please note that CRISS index represents a probability of improvement and ranges between 0 and 1.

Descriptive statistics summarizing CRISS value at 52 weeks will be provided by treatment group.

The cumulative proportion of patients whose probability of improving at week 52 with regard to their CRISS index will be shown by using a broad range of cut-offs for the CRISS value at 52 weeks (>=0, >=0.1, >=0.2, ... , >=0.9,1), in a cumulative proportion of responder analysis

graph (19). The proportion of patients showing improvement for CRISS based on each cut-off will also be tabulated.

In order to analyse CRISS index across both treatment groups, it will be transformed into a binary responder endpoint using multiple imputation. More specifically, the following steps will be applied:

- For each patient, 100 random uniform draws in the range from 0 to 1 will be taken
    - If the value of the draw > CRISS index value of the patient then the responder variable will be set to « No » for that patient
    - If the value of the draw ≤ CRISS index value of the patient then the responder variable will be set to « Yes » for that patient
- This results in 100 imputed datasets including a responder variable for each of the patients that indicates whether or not this patient is considered a responder or not, as derived from the actual CRISS index of the patient
- For each complete dataset of patients obtained by imputation as described above, the comparison between both treatment groups regarding the newly obtained binary will be performed using a Cochran-Mantel-Haenszel (CMH) model adjusting for ATA status. Adjusted Mantel-Haenszel odds ratio (OR) with 95% confidence intervals (CI) will be used to quantify the treatment effect between the Nintedanib group and Placebo.
- The OR and the 95% CI as obtained from all 100 imputations will then be combined using Rubin's rule (20): First, they will be log-transformed so that they are approximately normally-distributed. The SE on the log-scale will then be estimated by dividing the range of the CI on the log-scale by 2*1.96. Rubin's rules will then be applied to the log-scale point estimate and SE, and a nominal p-value calculated. The overall CI on the log-scale will be recalculated as the combined point estimate +/- 1.96 times the combined SE. For the purpose of interpretation and presentation, both the point estimate and 95% CI boundaries will be back transformed to the original scale.

7.5.2.6 Absolute change from baseline in DLCO in percent predicted at week 52

A similar analysis based on MMRM as for the key secondary endpoints will be performed for the absolute change in DLCO % predicted. Please refer to Section 7.5.1.1.

7.5.2.7 Absolute change from baseline in digital ulcer net burden at week 52

A similar analysis based on MMRM as for the key secondary endpoints will be performed for the absolute change in digital ulcer net burden. Please refer to Section 7.5.1.1.

7.5.2.8 Absolute change from baseline in HAQ-DI score at week 52

A similar analysis based on MMRM as for the key secondary endpoints will be performed for the absolute change in HAQ-DI score. Please refer to Section 7.5.1.1.

7.5.2.9 Absolute change from baseline in FACIT dyspnoea score at week 52

A similar analysis based on MMRM as for the key secondary endpoints will be performed for the absolute change in FACIT dyspnoea. Please refer to Section 7.5.1.1.

7.6 FURTHER ENDPOINT(S)

Further endpoints are listed in CTP section 5.1.3.

7.6.1 Categorical endpoints

Categorical endpoints representing proportion of patients (as defined in Section 5.3.2) will be summarised descriptively. Wilson 95% confidence interval and a nominal p-value will be calculated for each proportion of patients specified in Section 5.3.2.
The proportion of patients with an absolute change from baseline in SGRQ >= 4 points at week 52 will be analysed similarly.

The proportion of patients showing improvement based on CRISS will be summarised (improvement is defined based on CRISS value at 52 weeks and using a broad range of cut-offs) ([18]).

7.6.2 Change from baseline endpoints

Change from baseline endpoints at Week 52 (as defined in Section 5.3.1) will be summarised descriptively.

7.6.3 Analyses over the whole trial

Descriptive statistics by visit over the whole trial will be provided in the TS for endpoints listed in Table 6.1: 1. A graphical representation of the change from baseline over the whole trial may also be displayed.
In addition, for exploratory purposes, a similar analysis as the primary model on the primary endpoint will be done, based on all data collected during the whole trial period (up to 100 weeks). Only the treatment effect and associated confidence interval will be provided.

7.6.4 Pharmacokinetics

For PK analyses, data will be summarised descriptively according to the BI Standard procedures (6).

7.6.5 Biomarkers

Analyses on biomarkers will be described in a separate Statistical Analysis Plan and not included in the main CTR.

7.7 EXTENT OF EXPOSURE

Extent of exposure data will be summarised on the TS both over 52 weeks and over the whole trial (refer to Section 5.4.3.1 and Section 5.4.3.2).

A summary table showing the duration on treatment (both mean and frequency in classes, see Section 5.4.3) and dose intensity will be presented.

Besides, a summary table showing the duration on actual treatment dose (both mean and frequency in classes, see Section 5.4.3) and off-treatment duration will be performed. This will take into account the actual dose following dose reductions or increases.

A summary of treatment interruptions will be performed including number of patients with at least one interruption, number and reason of interruptions, as well as time to first interruption (both mean and frequency in classes, see Section 5.4.3). A similar summary will be performed for dose changes.

A table displaying the disposition of patients and the conclusion of patients' participation, and a table displaying the primary reason for non-inclusion/randomisation will be provided.

A Kaplan-Meier plot of time to premature treatment discontinuation will be produced. Similarly, Kaplan-Meier plots will be performed for time to first dose reduction and for time to first treatment interruption. No statistical tests will be performed.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS.

Safety analysis will primarily be based on data collected within the first 52 weeks. Additional safety analysis will also be presented for safety data collected overall including data collected beyond 52 weeks. See Section 6.1 of this document for further details of the treatment period specifications and refer to Table 6.1: 1 for the start and end dates for these analyses.

7.8.1 Adverse events

Unless otherwise specified, the analyses of adverse events will be descriptive in nature. All analyses of adverse events (AEs) will be based on the number of patients with AEs and NOT on the number of AEs (with the exception of AEs with additional information collection, see Section 7.8.1.3).

For analysis multiple AE occurrence data on the CRF will be collapsed into an AE event provided that all of the following applies:

- All AE attributes are identical (LLT, intensity, action taken, therapy required, seriousness, reason for seriousness, relationship [investigator defined drug-relatedness], outcome, AE of special interest)

- The occurrences were time-overlapping or time-adjacent (time-adjacency of 2 occurrences is given if the second occurrence started on the same day or on the day after the end of the first occurrence)

For further details on summarization of AE data, please refer to (8, 10).

The analysis of adverse events will be based on the concept of treatment emergent adverse events. That means that all adverse events occurring between first drug intake until last drug intake + 28 days will be assigned to the randomised treatment.

In addition, selected adverse events analyses will also be done considering a residual effect period of 7 days.

All adverse events occurring before first drug intake will be assigned either to 'screening' or 'post-randomisation' (for listings only).

For analyses based on a residual effect period of 28 days, adverse events occurring after last drug intake + 28 days will be assigned to 'follow-up' or 'post-study' (for listings only). All adverse events occurring between the start of an interruption of trial medication and the end of interruption of trial medication will be assigned to 'off-treatment' period in the listings. For details on the treatment definition, see Section 6.1.

According to ICH E3 (11), AEs classified as 'other significant' need to be reported and will include those non-serious and non-significant (i.e. not defined as protocol-specified AEs of special interest) adverse events with
(i) 'action taken = discontinuation' or 'action taken = reduced', or
(ii) marked haematological and other lab abnormalities or lead to significant concomitant therapy

Adverse events related to gastrointestinal perforation and hepatic injury will be considered as protocol pre-specified AEs of special interest (AESIs), and were collected as such in the eCRF.

An overall summary of adverse events will be presented.

The frequency of patients with AEs will be summarised by treatment, primary system organ class (SOC) and preferred term (PT). This will also be presented restricted to incidence in preferred term > 5% (in at least one treatment arm).

Separate tables will be provided for patients with other significant AEs according to ICH E3 (11), for patients with serious AEs (SAEs), for patients with severe AEs, for patients with AEs leading to permanent dose reduction, for patients with AEs leading to permanent drug discontinuation, for patients with investigator defined drug-related AEs and for patients with AEs leading to death. The frequency of patients with SAEs will also be presented restricted to incidence in preferred term > 1% (in at least one treatment arm).

In addition a table will be provided for patients with investigator defined drug-related SAEs. This will be based on the number of patients with AE that are both serious and investigator

defined drug-related. Similarly, a table will be provided for patients with investigator defined drug-related AEs leading to deaths.

The SOCs and PTs (within SOCs) will be sorted by descending frequency in Nintedanib treatment arm.

7.8.1.1 Pre-specified adverse events of special interest

Gastrointestinal perforations and hepatic injury are adverse events of special interest (AESI) pre-specified in the CTP Section 5.3.7.1. These are investigator reported on the eCRF and will be identified using this information for this analysis.
The frequency of patients with pre-specified AESI will be summarised by treatment, primary SOC and preferred term (PT).

7.8.1.2 Adverse events with additional information collection

Diarrhoea and bleeding are AEs with additional AE-specific information collected on the eCRF. These are investigator reported on the eCRF and will be identified using this information for this analysis. That is if the diarrhoea information has been completed for an adverse event then the adverse event will be considered as diarrhoea for this analysis regardless of subsequent MedDRA coding of the verbatim term. Likewise, if the bleeding information has been completed for an adverse event then the adverse event will be considered as bleeding for this analysis regardless of subsequent MedDRA coding of the verbatim term.
The frequency of patients with AEs with additional information collection will be summarised by treatment, primary SOC and PT separately for diarrhoea and bleeding. The additional information collected will also be summarised at the AE level rather than at the patient level separately for diarrhoea and bleeding.

7.8.1.3 Adjudicated adverse events

An independent adjudication committee will review all fatal cases and adjudicate cause of death to cardiovascular death, respiratory related death, non-cardiovascular/non-respiratory death, or undetermined cause of death on a per patient basis, e.g. one cause per patient. The adjudication committee will also review all AEs categorised as MACE according to the definition in the adjudication charter.

In addition to standard safety analyses, the frequency of patients with AEs leading to death will be summarised by treatment, adjudicated cause of death (Cardiac, Respiratory, Non-cardiac/non-respiratory or Undetermined), and PT.

The frequency of patients with AEs categorised as MACE (that is all AEs with trigger terms for MACE and therefore sent for adjudication) will be summarised by treatment and outcome of adjudication (adjudicated as MACE or adjudicated as not MACE). The frequency of patients with AEs adjudicated as MACE will also be summarised by treatment and PT.

7.8.1.4 Additional analysis of adverse event groupings by system

Further adverse event groupings by system have been defined outside the trial protocol as medically relevant to the clinical development program and are specified in Table 7.8.1.4: 1. The frequency of patients with AEs within these groupings will be summarised by treatment, safety topic and preferred term. Separate tables will be provided for patients with investigator defined drug-related AEs and serious AEs (SAEs).

Table 7.8.1.4:1 Adverse events by system and safety topic using aggregated terms

System	Safety Topic	Definition (selection criteria)
Gastrointestinal	Diarrhoea	PT Diarrhoea
	Nausea	PT Nausea
	Vomiting	PT Vomiting
	Abdominal pain	HLT 'Gastrointestinal and abdominal pains (excl oral and throat)
	Pancreatitis	SMQ Acute pancreatitis (narrow)
	Gastrointestinal perforation	SMQ Gastrointestinal perforation (narrow)
Hepatobiliary	Drug-induced liver injury (DILI)	PT Drug-induced liver injury
	Hepatic disorders combined Sub-categories: • Drug related hepatic disorders – comprehensive search (SMQ narrow) • Liver related investigations, signs and symptoms (SMQ broad) • Cholestasis and jaundice of hepatic origin (SMQ narrow) • Hepatitis, non-infectious (SMQ narrow)	Table to show cumulative row for all 4 SMQs below, followed by a cumulative row for each subSMQ, followed by all PTs driving that subSMQ SMQ Drug related hepatic disorders – comprehensive search (narrow) OR SMQ Liver related investigations, signs and symptoms (broad) OR SMQ Cholestasis and jaundice of hepatic origin (narrow) OR SMQ Hepatitis, non-infectious (narrow)
	Hepatic failure	SMQ Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (narrow)

Table 7.8.1.4:1 Adverse events by system and safety topic using aggregated terms (cont'd)

System	Safety Topic	Definition (selection criteria)
Cardiovascular	Arterial thromboembolism	SMQ Embolic and thrombotic events, arterial (narrow)
	Myocardial infarction	SMQ Myocardial infarction (narrow)
	Stroke	Pharmacovigilance Endpoint Stroke PTs (see Section 9.7) for included Preferred Terms)
	Stroke haemorrhagic	SMQ Haemorrhagic central nervous system vascular conditions (narrow)
	Stroke ischaemic	SMQ Ischaemic central nervous system vascular conditions (narrow)
	Stroke haemorrhagic and ischaemic	SMQ Haemorrhagic central nervous system vascular conditions (narrow) OR SMQ Ischaemic central nervous system vascular conditions (narrow)
	MACE Sub-categories: • Fatal events in SOC Cardiac disorders • Fatal events in SOC Vascular disorders • Any fatal or non-fatal events in SMQ Myocardial infarction (broad) • PTs Cardiac death, Sudden death, Sudden cardiac death • Any fatal or non-fatal stroke events	Fatal events in SOC Cardiac OR Fatal events in SOC Vascular OR Any fatal or nonfatal events in SMQ Myocardial infarction (broad) OR PTs Cardiac death, Sudden death, Sudden cardiac death OR Any fatal or nonfatal events as defined in Pharmacovigilance Endpoint Stroke PTs – updated to MedDRA 21.0

Table 7.8.1.4:1 Adverse events by system and safety topic using aggregated terms (cont'd)

System	Safety Topic	Definition (selection criteria)
Cardiovascular	Cardiac failure	SMQ Cardiac failure (narrow)
	QT prolongation	SMQ Torsade de pointes/QT prolongation (narrow)
	Venous thromboembolism	SMQ Embolic and thrombotic events, venous (narrow)
	Pulmonary embolism	PT Pulmonary embolism
	DVT	PT Deep vein thrombosis
	Hypertension	SMQ Hypertension (narrow)
Metabolic	Decreased appetite	PT Decreased appetite
	Weight decreased	PTs: Weight decreased, Abnormal loss of weight
Blood	Bleeding Subcategories: • GI bleeding – oral • GI bleeding – upper • GI bleeding – lower • GI bleeding – nonspecific • Skin bleeding • Respiratory bleeding • CNS bleeding • Urogenital bleeding • Other bleeding	SMQ Haemorrhage terms (excl laboratory terms) (narrow) displayed in total and then according to categories (attached spreadsheet): • Gastrointestinal – oral • Gastrointestinal – upper • Gastrointestinal – lower • Gastrointestinal – nonspecific • Skin • Respiratory • CNS • Urogenital • Other
	Thrombocytopenia	PTs: Thrombocytopenia, Platelet count decreased, Immune thrombocytopenic purpura
	Haematopoietic thrombocytopenia	SMQ Haematopoietic thrombocytopenia (broad)
	Neutropenia	SMQ Agranulocytosis (narrow) OR SMQ Haematopoietic leukopenia (narrow)
Renal	Renal failure	SMQ Acute renal failure (narrow)
	Proteinuria	SMQ Proteinuria (narrow)
	Glomerulonephritis (broad) Glomerulonephritis (narrow) Urinary tract infection	SMQ Chronic kidney disease (broad) HLT Glomerulonephritis and nephrotic syndrome BIcMQ Urinary tract infection (broad)

Table 7.8.1.4:1 Adverse events by system and safety topic using aggregated terms (cont'd)

System	Safety Topic	Definition (selection criteria)
Psychiatric	Depression	SMQ Depression (excl suicide and self-injury) (narrow)
	Suicide	SMQ Suicide/self-injury (narrow)
Cutaneous	Rash	BIcMQ Skin rash (narrow): Exfoliative rash Mucocutaneous rash Rash Rash erythematous Rash follicular Rash generalized Rash macular Rash maculo-papular Rash maculovesicular Rash morbilliform Rash neonatal Rash papular Rash papulosquamous Rash pruritic Rash pustular Rash rubelliform Rash scarlatiniform Rash vesicular Symmetrical drug-related itertriginous and flexural exanthema Vascular access site bruising
	Pruritus	PT Pruritus
	Severe skin reactions	SMQ Severe cutaneous adverse reactions (narrow)

Table 7.8.1.4:1 Adverse events by system and safety topic using aggregated terms (cont'd)

System	Safety Topic	Definition (selection criteria)
Liver laboratories	Hepatic enzyme increased	Alanine aminotransferase abnormal Alanine aminotransferase increased Aspartate aminotransferase abnormal Aspartate aminotransferase increased Hepatic enzyme abnormal Hepatic enzyme increased Hepatic function abnormal Hypertransaminasaemia Liver function test abnormal Transaminases abnormal Transaminases increased Blood alkaline phosphatase abnormal Blood alkaline phosphatase increased Gamma-glutamyltransferase abnormal Gamma-glutamyltransferase increased
	Hyperbilirubinaemia	Blood bilirubin abnormal Blood bilirubin increased Blood bilirubin unconjugated increased Hyperbilirubinaemia Icterus index increased Jaundice Jaundice hepatocellular Bilirubin conjugated abnormal Bilirubin conjugated increased
	Alanine aminotransferase increased	Alanine aminotransferase increased Alanine aminotransferase abnormal
	Aspartate aminotransferase increased	Aspartate aminotransferase increased Aspartate aminotransferase abnormal
	Gamma-glutamyl-transferase increased	Gamma-glutamyltransferase increased Gamma-glutamyltransferase abnormal
	Blood alkaline phosphatase increased	Blood alkaline phosphatase increased Blood alkaline phosphatase abnormal

These definitions are based on MedDRA Version 21.0. Note that changes to these definitions due to MedDRA updates will not trigger a TSAP update. Updated definitions are maintained in BIRDS under Human Pharma/nintedanib/Clinical/substance level/Project Data Management and Statistics/Section 4 Database.

The most recent version effective at DBL date will be used for trial reporting.

7.8.1.5 Adverse events of particular note

Gastro-intestinal adverse events (diarrhoea, nausea, vomiting, dehydration, weight decrease and decreased appetite) are considered as AEs of particular note.

Specific tables will be created in order to describe adverse events of particular note over 52 weeks:

- Summary of AEs including intensity, seriousness, clinical consequences (permanent dose reduction, drug discontinuation or drug interruption), drug relationship, therapy for event and outcome

- Summary of AEs including time to onset, number and duration of episodes

Depending on the number of patients having such AEs, a Kaplan-Meier plot of time to first adverse event of particular note may be drawn by treatment.

In addition, for pairs of selected adverse events (from diarrhoea, nausea, vomiting, decreased appetite, dehydration, weight decreased as defined in Table 7.8.1.4: 1) , the frequency of patients with concurrent AEs will be summarised by treatment where concurrence is defined as an overlap of at least one day.

7.8.1.6 Adverse event analyses over the whole trial

Time at risk analyses of AEs will be presented for the overall timeframe. Time at risk and incidence rates per 100 patient years will be calculated based on the first onset of an AE.

An overall summary of adverse events will be presented.

A summary by treatment, primary system organ class (SOC) and preferred term (PT) will be presented. This will also be presented restricted to incidence in preferred term > 5% (in at least one treatment arm).

Separate tables will be provided for patients with other significant AEs according to ICH E3 (11), for patients with serious AEs (SAEs), for patients with severe AEs, for patients with AEs leading to permanent dose reduction, for patients with AEs leading to permanent dose discontinuation, for patients with investigator defined drug-related AEs, for patients with AEs leading to death, for investigator defined drug-related SAEs, for investigator defined drug-related AEs leading to death. The summary of patients with SAEs will also be presented restricted to incidence in preferred term > 1% (in at least one treatment arm).

Time at risk analyses of AEs pre-specified AESI will be summarised by treatment, primary SOC and preferred term.

Time at risk analyses of AEs, investigator defined drug-related AEs and SAEs within groupings by system will be summarised by treatment, safety topic and preferred term.

Adjudicated AEs will be analysed similarly as planned in Section 7.8.1.3, except based on time at risk analyses.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (12). This will be performed for the safety analysis over 52 weeks and overall.

Please refer to Section 7.3.4 of the CTP for further details.

In addition a thorough description of liver enzymes and bilirubin elevations over the whole study period will be given, according to the definitions in Section 5.4.4, including a display of maximum individual elevation and a Kaplan-Meier plot of time to first liver enzyme elevation (if sufficient number of events).

A similar summary table of liver enzymes and bilirubin elevations over the first 52 weeks will also be provided (please refer to Table 6.7: 3 for time windowing definition).

The time to onset of first liver enzyme and bilirubin elevation [days] will be summarised by categories (<=21; >21-<=42; >42-<=63; >63).

For each patient having experienced a liver enzyme and bilirubin elevation, a graphical representation of AST, ALT and bilirubin over time will be provided.

7.8.3 Vital signs

Summary statistics will be presented for observed values and change from baseline by treatment and visit. This will be performed for the overall timeframe.

The frequency of patients with marked changes in vital signs over 52 weeks will also be summarised by treatment according to the definitions in Section 5.4.5 of this document.

7.8.4 ECG

Not applicable as ECG findings will be reported as adverse events.

7.8.5 Others

Clinically relevant findings after Doppler echocardiography will be reported as adverse events.

Any worsening of trial indication SSc-ILD will be reported and summarised as AEs.

In addition, information collected at Week 52 about relevant changes in echocardiography characteristics (based on Echocardiography eCRF page) will be summarised using descriptive statistics.

8. REFERENCES

1	*001-MCG-159_RD-03:* "Standard table shells for inferential and descriptive End-of-Text tables (EoT-Catalogue)", current version; IDEA for CON.
2	*001-MCG-410*: "Structure, Derivation, and Documentation of Analysis Data Sets", current version; IDEA for CON.
3	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
4	*001-MCG-741*: "Clinical subgroup analyses for local and regional Populations in Asia - Clinical Bridging Study Waiver (BSW) and Descriptive Subgroup Analysis (SGA) Reports", current version; IDEA for CON.
5	*001-MCP-090:* "BI Style Guide", current version; IDEA for CON.
6	*001 MCS 36-472*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON.
7	*001-MCS-50-413*: "Handling of Protocol Violations in Clinical Trials and Projects", current version; group: Study Conduct; IDEA for CON.
8	*001-MCG-156_RD-01:* "Handling of missing and incomplete AE dates", current version; IDEA for CON.
9	*001-MCG-159*: "Reporting of Clinical Trials and Project Summaries", current version; IDEA for CON.
10	*001-MCG-156*: "Handling and summarization of adverse event data for clinical trial reports and integrated summaries", current version; IDEA for CON.
11	*CPMP/ICH/137/95*: "Structure and Content of Clinical Study Reports", ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version
12	*001-MCG-157*: "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON.
13	Jones PW, Forde Y. St George's Respiratory Questionnaire Manual. Version 2.3, 20.06.2009 [R12-2870]
14	FACIT-Dyspnoea Scale Short Form Scoring Guideline [R16-0894]
15	FACIT Administration and scoring guidelines [R10-5351]
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17	Philip H. Quanjer, Multi-ethnic reference values for spirometry for the 3–95 year age range: The global lung function 2012 equations [R15-0845]
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19	Farrar J, Dworkin R, Max M. Use of Cumulative Proportion of Responders Analysis Graph to Present Pain Data Over a Range of Cut-Offs points: Making Clinical Trial Data More Understandable. Journal of Pain and Symptom Management, Vol. 31 No. 4, 2006 [R11-4172]
20	Rubin, DB. Multiple Imputation for Nonresponse in Surveys. New York: Wiley, 1987. [R12-2378]
21	Japanese Ministry of Health, Labour and Welfare, Format for Preparing the Common Technical Document for Submission of New Drug Applications to Reduce Total Review Time, 2011 [R18-1356]

9. ADDITIONAL SECTIONS

9.1 HCRU (HEALTH CARE RESOURCE UTILISATION)

Descriptive statistics of HCRU over time will be provided in Section 16.1.13.1 of the CTR. Nevertheless, the economic modelling of the HCRU data will not be part of the clinical trial report but reported separately.

9.2 COMPLEMENTARY INFORMATION ON STATISTICAL MODEL AND SAS CODE

Primary endpoint model (and other rate of decline endpoints):

The key code is given below. Time is defined as duration since first trial drug intake divided by 365.25. Visit is the visit number.
Meanbase corresponds to the overall mean baseline for the endpoint.

```
proc MIXED data=FVC cl method=reml  order= formatted covtest;
      CLASS patient visit treatment gender ata;
      MODEL endpoint= gender age height ata fvcbaseline fvcbaseline*time
treatment treatment*time /solution CL ddfm=KR;
      RANDOM intercept time/ type=un subject=patient;

      ESTIMATE 'Nintedanib' fvcbaseline*time MEANBASE treatment*time  0 1 /
e CL;
      ESTIMATE 'Placebo' fvcbaseline*time MEANBASE treatment*time 1 0 / e
CL;
      ESTIMATE 'Nintedanib 150mg bid – Placebo' treatment*time -1 1 / e CL;
RUN;
```

Primary endpoint subgroup analysis model:

This is the case of subgroups wih 2 categories:

```
proc MIXED data=FVC cl method=reml  order= formatted covtest;
      CLASS patient visit treatment gender ata subgroup;
      MODEL endpoint= gender age height ata fvcbaseline fvcbaseline*time
treatment*subgroup treatment*subgroup*time /solution CL ddfm=KR;
      RANDOM intercept time/ type=un subject=patient;

 ESTIMATE 'Nintedanib – Subgroup A'  fvcbaseline*time MEANBASE treatment *
subgroup *time 0 0 1 0 / cl e;
 ESTIMATE 'Placebo - Subgroup A'   fvcbaseline*time MEANBASE treatment *
subgroup *time 1 0 0 0 / cl e;

 ESTIMATE 'Nintedanib - Subgroup B'   fvcbaseline*time MEANBASE treatment *
subgroup *time 0 0 0 1 / cl e;
 ESTIMATE 'Placebo - Subgroup B'   fvcbaseline*time MEANBASE treatment *
subgroup *time 0 1 0 0 / cl e;

 ESTIMATE 'Nintedanib – Placebo Subgroup A'  subgroup * treatment *time  -1
0 1 0 / e CL;
```

```
 ESTIMATE 'Nintedanib – Placebo Subgroup B'   subgroup * treatment *time  0
-1 0 1 / e CL;

 CONTRAST 'F-test of heterogeneity at 52 weeks' subgroup * treatment *time
-1 1  1 -1 / e;
RUN;
```

Model for key secondary endpoints (and other change from baseline endpoints):

The key code is given below.

```
proc MIXED data= MRSS cl order=internal covtest ;
      CLASS patient treatment visit ata;
      MODEL endpoint= ata baseline*visit treatment*visit /solution ddfm=KR;
      REPEATED visit/type=un subject =patient;
      LSMEANS treatment * visit / pdiff = control ("AM10PBO" "52")  om cl
alpha=0.05;RUN;
```

Change from baseline endpoints analysis by subgroup:

```
The LSMESTIMATE code depends on the number visits where the parameter was
measured and on the number of categories in the subgroup.
For FVC – in a subgroup with 4 categories:

ods output contrasts=ftest lsmeans=lsmeans diffs=diffs;
proc MIXED data= FVC cl method=reml order=formatted covtest ;
    CLASS patient visit treatment subgroup ata ;
      MODEL ept= ata baseline* visit visit*treatment*subgroup /solution
ddfm=KR;
      REPEATED visit/type=un subject =patient ;

 /* Within subgroup estimates : adj mean and adj mean difference*/
    LSMEANS visit* treatment *subgroup / pdiff = all om cl alpha=0.05 ;

/* Overall heterogeneity (F-test) */

    LSMESTIMATE visit*treatment*subgroup

    'Week 52, Subgroup 1'
    0 0 0 0 0 0 0 0
    0 0 0 0 0 0 0 0
    0 0 0 0 0 0 0 0
    0 0 0 0 0 0 0 0
    0 0 0 0 0 0 0 0
    0 0 0 0 0 0 0 0
    -3 1 1 1 3 -1 -1 -1,

    'Week 52, Subgroup 2'
    0 0 0 0 0 0 0 0
    0 0 0 0 0 0 0 0
    0 0 0 0 0 0 0 0
    0 0 0 0 0 0 0 0
    0 0 0 0 0 0 0 0
    0 0 0 0 0 0 0 0
   1 -3 1 1 -1 3 -1 -1,
```

```
    'Week 52, Subgroup 3'
    0 0 0 0 0 0 0 0
    0 0 0 0 0 0 0 0
    0 0 0 0 0 0 0 0
    0 0 0 0 0 0 0 0
    0 0 0 0 0 0 0 0
    0 0 0 0 0 0 0 0
   1 1 -3 1 -1 -1 3 -1,

    'Week 52, Subgroup 4'
    0 0 0 0 0 0 0 0
    0 0 0 0 0 0 0 0
    0 0 0 0 0 0 0 0
    0 0 0 0 0 0 0 0
    0 0 0 0 0 0 0 0
    0 0 0 0 0 0 0 0
   1 1 1 -3 -1 -1 -1 3

      /divisor=4  joint elsm cl alpha=0.05;
RUN;
```

For 2 subgroups, the LSMESTIMATE will write:

```
LSMESTIMATE visit*treatment*subgroup

    'Week 52, Subgroup 1'
    0 0 0 0
    0 0 0 0
    0 0 0 0
    0 0 0 0
    0 0 0 0
    0 0 0 0
    -1 1 1 -1,

    'Week 52, Subgroup 2'
    0 0 0 0
    0 0 0 0
    0 0 0 0
    0 0 0 0
    0 0 0 0
    0 0 0 0
    1 -1 -1 1
/divisor=2  joint elsm cl alpha=0.05;
```

Implementation of multiple imputation:

The following steps provide a guidance of how missing FVC data at week 52 will be implemented in patients of pattern 3 and 4 using multiple imputation. Refer to Table 7.4.2.1.2: 1 for the description of patterns and the different sensitivity analyses regarding handling of missing data.

1. Run the MMRM of the primary analysis (either including patients of pattern 2 only for sensitivity analyses 1 and 2 or on all patients for sensitivity analysis 3) to get the slope estimates (SE) by treatment group. Let $\hat{\beta}_D$ and $\hat{\sigma}_D$ denote the slope (SE) estimates in Nintedanib 150 mg and $\hat{\beta}_P$ and $\hat{\sigma}_P$ the slope (SE) estimates in placebo.

2. Let β_D and β_P represent the true slopes in drug and placebo respectively with $f(\beta_D) \sim N(\hat{\beta}_D, \hat{\sigma}^2{}_D)$ and with $f(\beta_P) \sim N(\hat{\beta}_P, \hat{\sigma}^2{}_P)$, using the slope (SE) estimates obtained in step 1.

3. Imputation of missing week 52 data in patients of pattern 3:

   Multiple impute missing values (1000 imputations per patient). To do so, draw random slopes from the distributions defined in step 2. Considering that the withdrawal of a patient leading to missing data can occur at any time during the study, the timepoint of the last available FVC value has to be taken into account to impute the missing FVC value at 52 weeks.

   FVC week 52 imputed_{ij} = last FVC value $\text{available}_i + \hat{\beta}_{ij}$(time between date of last FVC value available_i and planned 52 week timepoint [days])

   where i denotes the indicator of the i^{th} patient, j the indicator of the j^{th} imputation and $\hat{\beta}_{ij}$ denotes a random slope sampled from the distribution mentioned in step 3a for the i^{th} patient in the j^{th} imputation. Depending on the sensitivity analysis, use either random slopes drawn from $f(\beta_D)$ for patients randomised to Nintedanib 150 mg in sensitivity analysis 1 or $f(\beta_P)$ for all patients in sensitivity analyses 2 and 3.

4. Imputation of missing week 52 data in patients of pattern 4:

   Multiple impute missing values (1000 imputations per patient). To do so, draw random slopes from the truncated distribution $f(\beta_P)/2$ restricted to the interval $(-\infty, \hat{\beta}_P]$ defined in step 2.

   See step 3 for further details on how to use these slopes to impute the missing values at week 52.

5. Run the MMRM of the primary analysis on each imputed dataset, using a "by _IMPUTATION_ " statement.

6. Combine the estimates obtained in step 5 using PROC MIANALYZE.

9.3 ADDITIONAL ANALYSIS FOR REGIONAL SUBMISSIONS

For the Japanese submission, the analyses will be conducted according to "Format for Preparing the Common Technical Document for Submission of New Drug Applications to Reduce Total Review Time" (21).
For the analysis due to local regulatory submission, the following subsets are defined (4).

Some outputs from CTR Section 15 will be selected for the subsets defined in Table 9.3: 1. Due to small sample size of some subsets, some tables might be skipped. The same analyses models as defined for the overall population will be used (please refer to Section 7.4.1). In the event of non-convergence, the same methods than the ones described in Section 7.4.1 will be used to overcome the issue.

Table 9.3: 1 Patient subsets definition for local regulatory submission in Asia

Category	**Patient subset**
Local	· Japan · China The patients in each local site and Asian race will be included (e.g. Japan: Site in Japan and single race is Asian). If Asian race will be "Multiple" and multiple responder will be "Asian & xxx", the patient will be handled as "Asian". (e.g. Japan: Site in Japan and multiple race is Asian & White.)
East Asia	· East Asian countries The patients from East Asian countries or region (i.e. Japan and China) with Asian race. Asian race definition is same definition in local category.
India	· India The patients in any race from India sites will be included.

These subset analyses will not be produced as part of the CTR appendix and will not be described in the text of the CTR (9). The details will be handled in another document (cumulative SAP).

9.4 LIST OF BI CUSTOMISED DRUG GROUPINGS OF INTEREST

Customized drug groupings of interest for this trial are listed in Table 9.4: 1.

Table 9.4: 1 Customized drug grouping of interest

CT grouping name	**Type of grouping**
Antiarrhythmics	SDG
Antidiarrheal	ATC4 ('A07DA')
Antiemetics and antinauseants	SDG, excluding drugs from the Corticosteroids SDG
Antihypertensives	SDG
Anti-infectives	SDG
Antithrombotic drugs	SDG
Corticosteroids	SDG
Drugs interacting with CYP3A	SDG
Disease-modifying antirheumatic drugs (DMARDs)	SDG
Diuretics	SDG
Drugs for gastric acid related disorders	SDG
Drugs for obstructive airway diseases	SDG
Drugs used in pain therapies	SDG
Hormone replacement therapy	SDG
Immunosuppressant drugs	Sub-SDG (from Immunomodulators SDG)
Monoclonal antibodies	SDG
Nonsteroidal anti-inflammatory drugs (NSAIDs)	SDG
Drugs interacting with P-glycoprotein (P-gp)	SDG

Table 9.4: 1 Customized drug grouping of interest (cont'd)

CT grouping name	**Type of grouping**
Phosphodiesterase (PDE) inhibitors	SDG
Statins	SDG

WHO−DD version used: 18.MAR

9.5 SPECIFICATION OF RESTRICTED AND FORBIDDEN CONCOMITANT THERAPIES

Medications reviewed as potential IPVs were selected based on Table 9.5: 1

Table 9.5: 1 Restricted and forbidden concomitant therapies

Type of medication	Category of drugs	ATC/PN
Prohibited medications	Pirfenidone	PN=’Pirfenidone’
	Nintedanib (outside of the trial)	L01XE
	Other investigational drugs	PN=’Investigational drugs’
Restricted medications	Full dose therapeutic anticoagulation	B01AA, B01AB, B01AF, B01AE, B01AD, B01AX
	Antiplatelet therapies	B01AC, B01AX
	Mycophenolate mofetil/ sodium / MYCOPHENOLIC ACID	PN=’ Mycophenolate mofetil’ or PN=’ Mycophenolate sodium’ or PN=’ MYCOPHENOLIC ACID’
	Methotrexate	PN=’ Methotrexate’ or PN=’ Methotrexate sodium’
	Azathioprine, potassium para-aminobenzoate	L04AX
	Cyclophosphamide	PN=’ Cyclophosphamide’

Table 9.5: 1 Restricted and forbidden concomitant therapies (cont'd)

Type of medication	Category of drugs	ATC/PN
	Prednisone > 10mg /day	H02AB
	Hydroxychloroquine, colchizine, D-penicillamine, sulfasalazine	PN=' Hydroxychloroquine' or PN=' colchizine' or PN=' penicillamine' or PN=' sulfasalazine
	Rituximab, tocilizumab, abatacept,leflunomide, tacrolimus, newer anti-arthritic treatment like tofacitinib	L04AC, L04AA, D11AH, L04AD, L04AA

9.6 LIST OF POTENTIAL TERMS FOR HEPATIC INJURY DERIVATION

Table 9.6: 1 shows the list of potentially relevant MedDRA preferred terms to support the derivation of a potential hepatic injury:

Table 9.6: 1 List of potentially relevant MedDRA preferred terms

Symptom	MedDRA
Vomiting	PT Vomiting
Fatigue	PT Fatigue
Nausea	PT Nausea
Right upper abdominal quadrant pain or tenderness	HLT "Gastrointestinal and abdominal pains (excl oral and throat)"
Fever	PT Fever
Rash	BIcMQ skin rash (narrow)

9.7 LIST OF TERMS INCLUDED IN STROKE PHARMACOVIGILANCE ENDPOINT

This is list is based on MedDRA Version 21.0. Updates will be only maintained in BIRDS as specified in Section 7.8.1.4.
The following MedDRA Preferred Terms will be used to define stroke pharmacovigilance endpoint:

Amaurosis fugax
Amyloid related imaging abnormalities
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits
Amyloid related imaging abnormality-oedema/effusion
Basal ganglia haematoma
Basal ganglia haemorrhage
Basal ganglia stroke
Basilar artery occlusion
Basilar artery perforation
Basilar artery thrombosis
Brachiocephalic artery occlusion
Brain stem embolism
Brain stem haematoma
Brain stem haemorrhage
Brain stem infarction
Brain stem ischaemia
Brain stem stroke
Brain stem thrombosis
Brain stent insertion
Carotid aneurysm rupture
Carotid arterial embolus
Carotid artery occlusion
Carotid artery perforation
Carotid artery thrombosis
Central nervous system haemorrhage
Cerebellar artery occlusion
Cerebellar artery thrombosis
Cerebellar embolism
Cerebellar haematoma
Cerebellar haemorrhage
Cerebellar infarction
Cerebellar ischaemia
Cerebellar stroke
Cerebral aneurysm perforation
Cerebral arteriovenous malformation haemorrhagic
Cerebral artery embolism
Cerebral artery occlusion
Cerebral artery perforation
Cerebral artery restenosis

Cerebral artery thrombosis
Cerebral haematoma
Cerebral haemorrhage
Cerebral haemorrhage foetal
Cerebral haemorrhage neonatal
Cerebral infarction
Cerebral infarction foetal
Cerebral ischaemia
Cerebral microembolism
Cerebral thrombosis
Cerebral vascular occlusion
Cerebrovascular accident
Delayed ischaemic neurological deficit
Embolic cerebral infarction
Embolic stroke
Haemorrhage intracranial
Haemorrhagic cerebral infarction
Haemorrhagic stroke
Haemorrhagic transformation stroke
Intracranial haematoma
Intracranial tumour haemorrhage
Intraoperative cerebral artery occlusion
Intraventricular haemorrhage
Intraventricular haemorrhage neonatal
Ischaemic cerebral infarction
Ischaemic stroke
Lacunar infarction
Lacunar stroke
Lateral medullary syndrome
Perfusion brain scan abnormal
Perinatal stroke
Periventricular haemorrhage neonatal
Pituitary haemorrhage
Pituitary infarction
Post procedural stroke
Precerebral artery occlusion
Precerebral artery thrombosis
Pseudostroke
Putamen haemorrhage
Reversible ischaemic neurological deficit
Ruptured cerebral aneurysm
Stroke in evolution
Subarachnoid haematoma
Subarachnoid haemorrhage
Subarachnoid haemorrhage neonatal
Subdural haemorrhage neonatal

Thalamic infarction
Thalamus haemorrhage
Thrombotic cerebral infarction
Thrombotic stroke
Transient ischaemic attack
Vertebral artery occlusion
Vertebral artery perforation
Vertebral artery thrombosis

9.8 PREFERRED TERMS SELECTED FOR BLEEDING SUBCATEGORIES

This is list is based on MedDRA Version 21.0. Updates will be only maintained in BIRDS as specified in Section 7.8.1.4.

The following MedDRA Preferred Terms will be used to define bleeding subcategories:

CNS:

Acute haemorrhagic leukoencephalitis
Basal ganglia haematoma
Basal ganglia haemorrhage
Basilar artery perforation
Brain contusion
Brain stem haematoma
Brain stem haemorrhage
Brain stem microhaemorrhage
Carotid aneurysm rupture
Carotid artery perforation
Central nervous system haemorrhage
Cephalhaematoma
Cerebellar haematoma
Cerebellar haemorrhage
Cerebellar microhaemorrhage
Cerebral aneurysm perforation
Cerebral aneurysm ruptured syphilitic
Cerebral arteriovenous malformation haemorrhagic
Cerebral artery perforation
Cerebral haematoma
Cerebral haemorrhage
Cerebral haemorrhage foetal
Cerebral haemorrhage neonatal
Cerebral microhaemorrhage
Encephalitis haemorrhagic
Epidural haemorrhage
Extra-axial haemorrhage
Extradural haematoma
Haemorrhage intracranial
Haemorrhagic cerebral infarction
Haemorrhagic stroke
Haemorrhagic transformation stroke
Intracerebral haematoma evacuation
Intracranial haematoma
Intracranial tumour haemorrhage
Intraventricular haemorrhage
Intraventricular haemorrhage neonatal

Meningorrhagia
Periventricular haemorrhage neonatal
Pituitary haemorrhage
Putamen haemorrhage
Ruptured cerebral aneurysm
Spinal cord haematoma
Spinal cord haemorrhage
Spinal epidural haematoma
Spinal epidural haemorrhage
Spinal subarachnoid haemorrhage
Spinal subdural haematoma
Spinal subdural haemorrhage
Subarachnoid haematoma
Subarachnoid haemorrhage
Subarachnoid haemorrhage neonatal
Subdural haematoma
Subdural haematoma evacuation
Subdural haemorrhage
Subdural haemorrhage neonatal
Thalamus haemorrhage
Traumatic intracranial haematoma
Traumatic intracranial haemorrhage
Vertebral artery perforation

GI Lower:

Acute haemorrhagic ulcerative colitis
Anal fissure haemorrhage
Anal haemorrhage
Anal ulcer haemorrhage
Anorectal varices haemorrhage
Colonic haematoma
Diarrhoea haemorrhagic
Diverticulitis intestinal haemorrhagic
Diverticulum intestinal haemorrhagic
Enterocolitis haemorrhagic
Haematochezia
Haemorrhoidal haemorrhage
Intra-abdominal haematoma
Intra-abdominal haemorrhage
Large intestinal haemorrhage
Large intestinal ulcer haemorrhage
Lower gastrointestinal haemorrhage
Melaena
Melaena neonatal
Proctitis haemorrhagic

Rectal haemorrhage
Rectal ulcer haemorrhage

GI Nonspecific:

Anastomotic haemorrhage
Anastomotic ulcer haemorrhage
Bloody peritoneal effluent
Cullen's sign
Gastrointestinal vascular malformation haemorrhagic
Grey Turner's sign
Haemorrhagic ascites
Haemorrhagic hepatic cyst
Hepatic haematoma
Hepatic haemorrhage
Intestinal haematoma
Intestinal haemorrhage
Intestinal varices haemorrhage
Mesenteric haematoma
Mesenteric haemorrhage
Mucosal haemorrhage
Neonatal gastrointestinal haemorrhage
Peritoneal haematoma
Peritoneal haemorrhage

GI Oral:

Angina bullosa haemorrhagica
Gingival bleeding
Mouth haemorrhage
Oral contusion
Oral mucosa haematoma
Pharyngeal haematoma
Pharyngeal haemorrhage
Stomatitis haemorrhagic
Tongue haematoma
Tongue haemorrhage
Tonsillar haemorrhage
Tooth pulp haemorrhage
Tooth socket haemorrhage

GI Upper:

Chronic gastrointestinal bleeding

Duodenal ulcer haemorrhage
Duodenitis haemorrhagic
Gastric haemorrhage
Gastric ulcer haemorrhage
Gastric ulcer haemorrhage, obstructive
Gastric varices haemorrhage
Gastritis alcoholic haemorrhagic
Gastritis haemorrhagic
Gastroduodenal haemorrhage
Gastroduodenitis haemorrhagic
Gastrointestinal angiodysplasia haemorrhagic
Gastrointestinal haemorrhage
Gastrointestinal polyp haemorrhage
Gastrointestinal ulcer haemorrhage
Haematemesis
Haemorrhagic erosive gastritis
Haemorrhagic necrotic pancreatitis
Mallory-Weiss syndrome
Oesophageal haemorrhage
Oesophageal intramural haematoma
Oesophageal ulcer haemorrhage
Oesophageal varices haemorrhage
Oesophagitis haemorrhagic
Pancreatic haemorrhage
Pancreatitis haemorrhagic
Peptic ulcer haemorrhage
Small intestinal haemorrhage
Small intestinal ulcer haemorrhage
Ulcer haemorrhage
Upper gastrointestinal haemorrhage

Respiratory:

Bronchial haemorrhage
Bronchial varices haemorrhage
Epistaxis
Haemoptysis
Haemothorax
Laryngeal haematoma
Laryngeal haemorrhage
Nasal septum haematoma
Paranasal sinus haematoma
Paranasal sinus haemorrhage
Pulmonary alveolar haemorrhage
Pulmonary contusion
Pulmonary haematoma

Pulmonary haemorrhage
Respiratory tract haemorrhage
Respiratory tract haemorrhage neonatal
Thoracic haemorrhage
Tracheal haemorrhage
Traumatic haemothorax

Skin:

Abdominal wall haematoma
Abdominal wall haemorrhage
Achenbach syndrome
Administration site bruise
Administration site haematoma
Administration site haemorrhage
Application site bruise
Application site haematoma
Application site haemorrhage
Application site purpura
Bleeding varicose vein
Blood blister
Breast haematoma
Chest wall haematoma
Chronic pigmented purpura
Contusion
Ecchymosis
Eyelid bleeding
Eyelid contusion
Eyelid haematoma
Haemorrhage subcutaneous
Haemorrhage subepidermal
Haemorrhagic urticaria
Henoch-Schonlein purpura
Immune thrombocytopenic purpura
Implant site bruising
Implant site haematoma
Implant site haemorrhage
Incision site haematoma
Incision site haemorrhage
Increased tendency to bruise
Infusion site bruising
Infusion site haematoma
Infusion site haemorrhage
Injection site bruising
Injection site haematoma
Injection site haemorrhage

Instillation site bruise
Instillation site haematoma
Instillation site haemorrhage
Lip haematoma
Lip haemorrhage
Medical device site bruise
Medical device site haematoma
Medical device site haemorrhage
Mucocutaneous haemorrhage
Muscle contusion
Muscle haemorrhage
Naevus haemorrhage
Nail bed bleeding
Palpable purpura
Petechiae
Post procedural contusion
Post procedural haematoma
Post procedural haematuria
Post procedural haemorrhage
Post transfusion purpura
Post-traumatic punctate intraepidermal haemorrhage
Puncture site haemorrhage
Purpura
Purpura fulminans
Purpura neonatal
Purpura non-thrombocytopenic
Purpura senile
Skin haemorrhage
Skin neoplasm bleeding
Skin ulcer haemorrhage
Splinter haemorrhages
Subcutaneous haematoma
Thrombocytopenic purpura
Thrombotic thrombocytopenic purpura
Traumatic haematoma
Traumatic haemorrhage
Umbilical haematoma
Umbilical haemorrhage
Vaccination site bruising
Vaccination site haematoma
Vaccination site haemorrhage
Varicose vein ruptured
Vascular access site bruising
Vascular access site haematoma
Vascular access site haemorrhage
Vascular access site rupture

Vascular graft haemorrhage
Vascular pseudoaneurysm ruptured
Vascular purpura
Vessel puncture site bruise
Vessel puncture site haematoma
Vessel puncture site haemorrhage
Wound haematoma
Wound haemorrhage

Urogenital:

Bladder tamponade
Blood urine
Blood urine present
Broad ligament haematoma
Cervix haematoma uterine
Cervix haemorrhage uterine
Coital bleeding
Cystitis haemorrhagic
Dysfunctional uterine bleeding
Genital contusion
Genital haemorrhage
Haematosalpinx
Haematospermia
Haematuria
Haematuria traumatic
Haemorrhage urinary tract
Haemorrhagic ovarian cyst
Intrapartum haemorrhage
Kidney contusion
Menometrorrhagia
Menorrhagia
Metrorrhagia
Nephritis haemorrhagic
Ovarian haematoma
Ovarian haemorrhage
Pelvic haematoma
Pelvic haematoma obstetric
Pelvic haemorrhage
Penile contusion
Penile haematoma
Penile haemorrhage
Perineal haematoma
Peripartum haemorrhage
Perirenal haematoma
Polymenorrhagia

Post abortion haemorrhage
Postmenopausal haemorrhage
Postpartum haemorrhage
Premature separation of placenta
Prostatic haemorrhage
Renal artery perforation
Renal cyst haemorrhage
Renal haematoma
Renal haemorrhage
Retroplacental haematoma
Scrotal haematocoele
Scrotal haematoma
Spermatic cord haemorrhage
Subchorionic haematoma
Subchorionic haemorrhage
Testicular haemorrhage
Third stage postpartum haemorrhage
Ureteric haemorrhage
Urethral haemorrhage
Urinary bladder haemorrhage
Urogenital haemorrhage
Uterine haematoma
Uterine haemorrhage
Vaginal haematoma
Vaginal haemorrhage
Vulval haematoma
Vulval haematoma evacuation
Vulval haemorrhage

Other:

Abnormal withdrawal bleeding
Adrenal haematoma
Adrenal haemorrhage
Aneurysm ruptured
Aortic aneurysm rupture
Aortic dissection rupture
Aortic intramural haematoma
Aortic perforation
Aortic rupture
Aponeurosis contusion
Arterial haemorrhage
Arterial intramural haematoma
Arterial perforation
Arterial rupture
Arteriovenous fistula site haematoma

Arteriovenous fistula site haemorrhage
Arteriovenous graft site haematoma
Arteriovenous graft site haemorrhage
Astringent therapy
Atrial rupture
Auricular haematoma
Bloody discharge
Bone contusion
Bone marrow haemorrhage
Breast haemorrhage
Bursal haematoma
Cardiac contusion
Catheter site bruise
Catheter site haematoma
Catheter site haemorrhage
Choroidal haematoma
Choroidal haemorrhage
Ciliary body haemorrhage
Conjunctival haemorrhage
Corneal bleeding
Deep dissecting haematoma
Disseminated intravascular coagulation
Ear haemorrhage
Exsanguination
Extravasation blood
Eye contusion
Eye haematoma
Eye haemorrhage
Femoral artery perforation
Femoral vein perforation
Foetal-maternal haemorrhage
Graft haemorrhage
Haemarthrosis
Haematocoele
Haematoma
Haematoma evacuation
Haematoma infection
Haematotympanum
Haemobilia
Haemophilic arthropathy
Haemophilic pseudotumour
Haemorrhage
Haemorrhage coronary artery
Haemorrhage foetal
Haemorrhage in pregnancy
Haemorrhage neonatal

Haemorrhagic adrenal infarction
Haemorrhagic anaemia
Haemorrhagic arteriovenous malformation
Haemorrhagic breast cyst
Haemorrhagic cyst
Haemorrhagic diathesis
Haemorrhagic disease of newborn
Haemorrhagic disorder
Haemorrhagic infarction
Haemorrhagic thyroid cyst
Haemorrhagic tumour necrosis
Haemorrhagic vasculitis
Haemostasis
Hepatic haemangioma rupture
Hereditary haemorrhagic telangiectasia
Hyperfibrinolysis
Hyphaema
Iliac artery perforation
Iliac artery rupture
Iliac vein perforation
Induced abortion haemorrhage
Inferior vena cava perforation
Internal haemorrhage
Intraocular haematoma
Iris haemorrhage
Joint microhaemorrhage
Lacrimal haemorrhage
Liver contusion
Lower limb artery perforation
Lymph node haemorrhage
Mediastinal haematoma
Mediastinal haemorrhage
Myocardial haemorrhage
Myocardial rupture
Nipple exudate bloody
Ocular retrobulbar haemorrhage
Optic disc haemorrhage
Optic nerve sheath haemorrhage
Osteorrhagia
Papillary muscle haemorrhage
Parathyroid haemorrhage
Parotid gland haemorrhage
Pericardial haemorrhage
Periorbital haematoma
Periorbital haemorrhage
Periosteal haematoma

Peripheral artery aneurysm rupture
Peripheral artery haematoma
Placenta praevia haemorrhage
Procedural haemorrhage
Radiation associated haemorrhage
Retinal aneurysm rupture
Retinal haemorrhage
Retinopathy haemorrhagic
Retroperitoneal haematoma
Retroperitoneal haemorrhage
Scleral haemorrhage
Shock haemorrhagic
Soft tissue haemorrhage
Spleen contusion
Splenic artery perforation
Splenic haematoma
Splenic haemorrhage
Splenic varices haemorrhage
Spontaneous haematoma
Spontaneous haemorrhage
Stoma site haemorrhage
Subclavian artery perforation
Subclavian vein perforation
Subgaleal haematoma
Subgaleal haemorrhage
Subretinal haematoma
Superior vena cava perforation
Thyroid haemorrhage
Tumour haemorrhage
Umbilical cord haemorrhage
Vascular rupture
Vein rupture
Venous haemorrhage
Venous perforation
Ventricle rupture
Vitreous haematoma
Vitreous haemorrhage
Withdrawal bleed

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final version	**26-JUL-18**	[redacted]	None	This is the final TSAP.