TRIAL STATISTICAL ANALYSIS PLAN

c19924398-06

BI Trial No.:	1199.225 SENSCIS®- ON (Extension)
Title:	An open-label extension trial to assess the long term safety of nintedanib in patients with 'Systemic Sclerosis associated Interstitial Lung Disease' (SSc-ILD) Including Protocol Amendment 2 [c11787364-04]
Investigational Product(s):	OFEV®, Nintedanib
Responsible trial statistician(s):	[redacted] Phone: [redacted]
Date of statistical analysis plan:	09 JAN 2023 REVISED
Version:	4

1. TABLE OF CONTENTS

LIST OF TABLES

2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
ALK	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATA	Anti-Topoisomerase Antibodies
ATC	Anatomical Therapeutic Chemical Classification
BI	Boehringer Ingelheim
BIcMQ	BI customised MedDRA Query
CDG	Customised Drug Grouping
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CRF	Case Report Form
[redacted]	[redacted]
GGT	Gamma-Glutamyl-Transferase
GLI	Global Lungs Initiative
[redacted]	[redacted]
HLT	High Level Term
ICH	International Conference On Harmonisation
INR	International Normalized Ratio
IPD	Important Protocol Deviation
LLT	Low Level Term
MedDRA	Medical Dictionary For Regulatory Activities
MQRM	Medical Quality Review Meeting
[redacted]	[redacted]
PN	Preferred Name
PT	Preferred Term
SD	Standard Deviation
SEM	Standard Error of the Mean
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Term	Definition / description
SDG	Standardised Drug Grouping
SOC	System Organ Class
SSc	Systemic Sclerosis
TSAP	Trial Statistical Analysis Plan
ULN	Upper Limit of Normal
[redacted]	[redacted]
WHO-DD	World Health Organization Drug Dictionary

3. INTRODUCTION

As per ICH E9 (1), 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.

In this document, the parent trial refers to SENSCIS® or 1199.340 trial. All analyses will be done in patients coming from both SENSCIS and 1199.340 trials. In addition, a selected set of analyses will be repeated in patients coming from SENSCIS only.

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

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

The following further categorical endpoints were added:

5. ENDPOINT(S)

5.1 PRIMARY ENDPOINT(S)

The primary focus is on safety endpoints. Please refer to CTP Section 2.1.2.

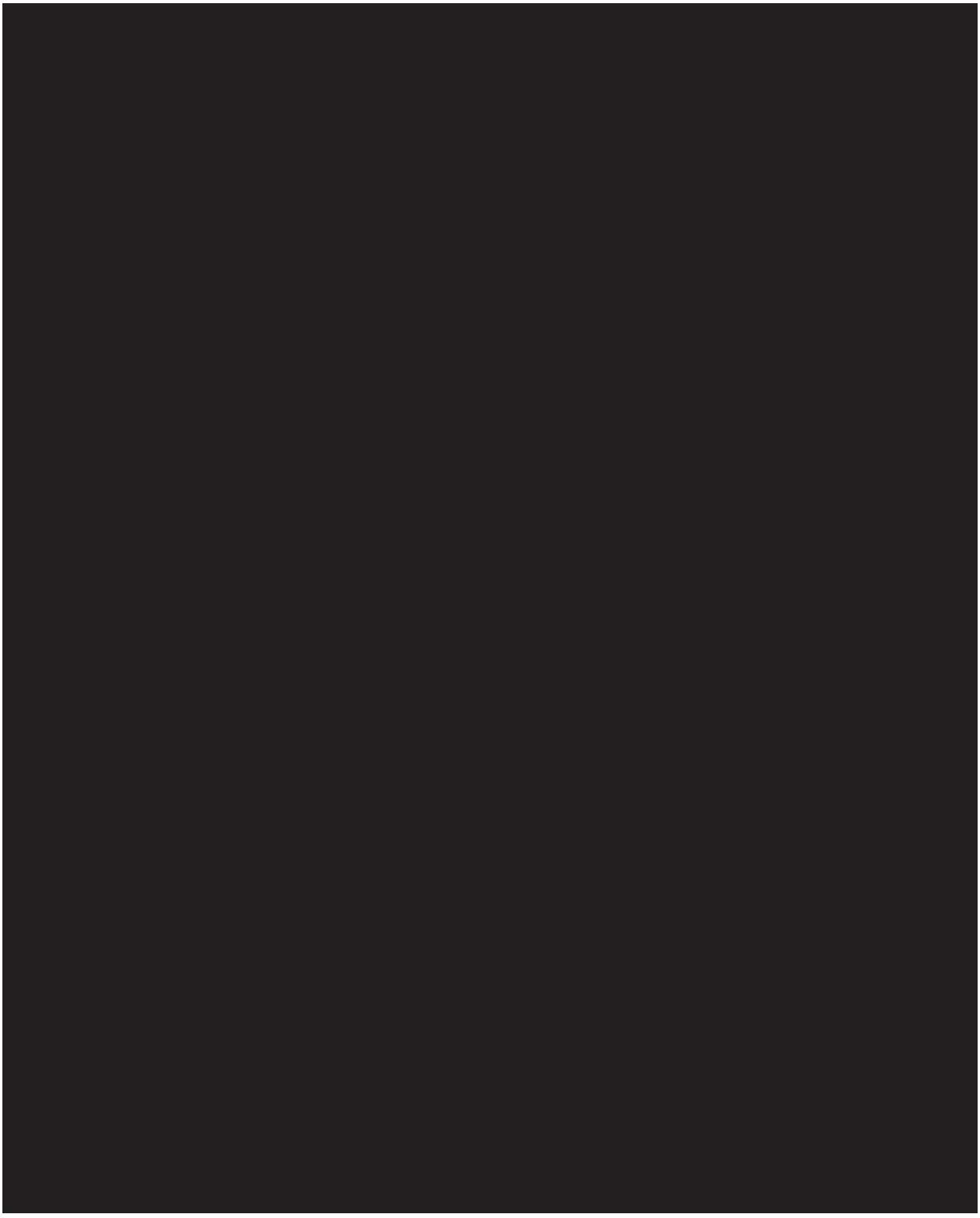
5.2 SECONDARY ENDPOINT(S)

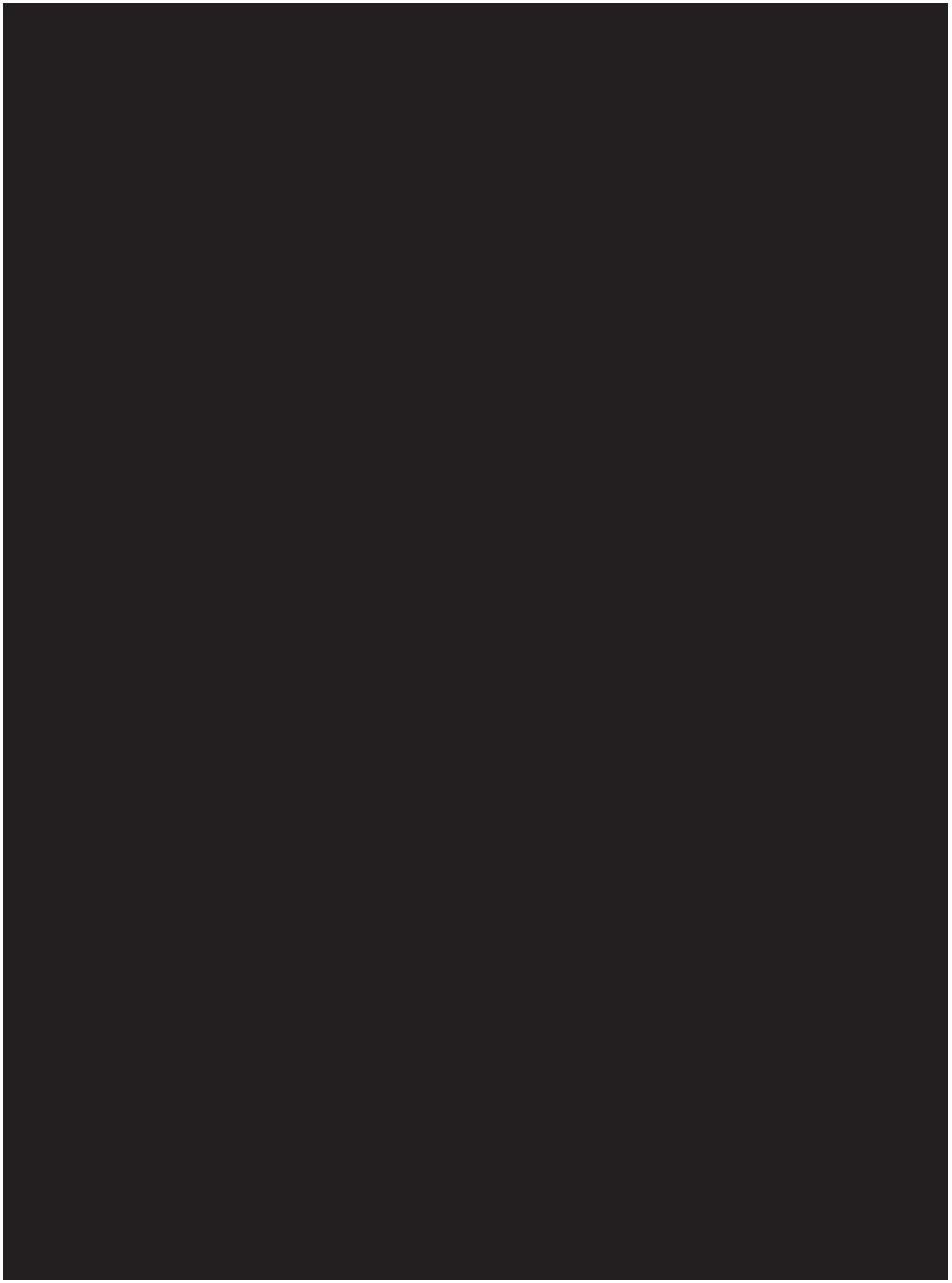
5.2.1 Key secondary endpoint(s)

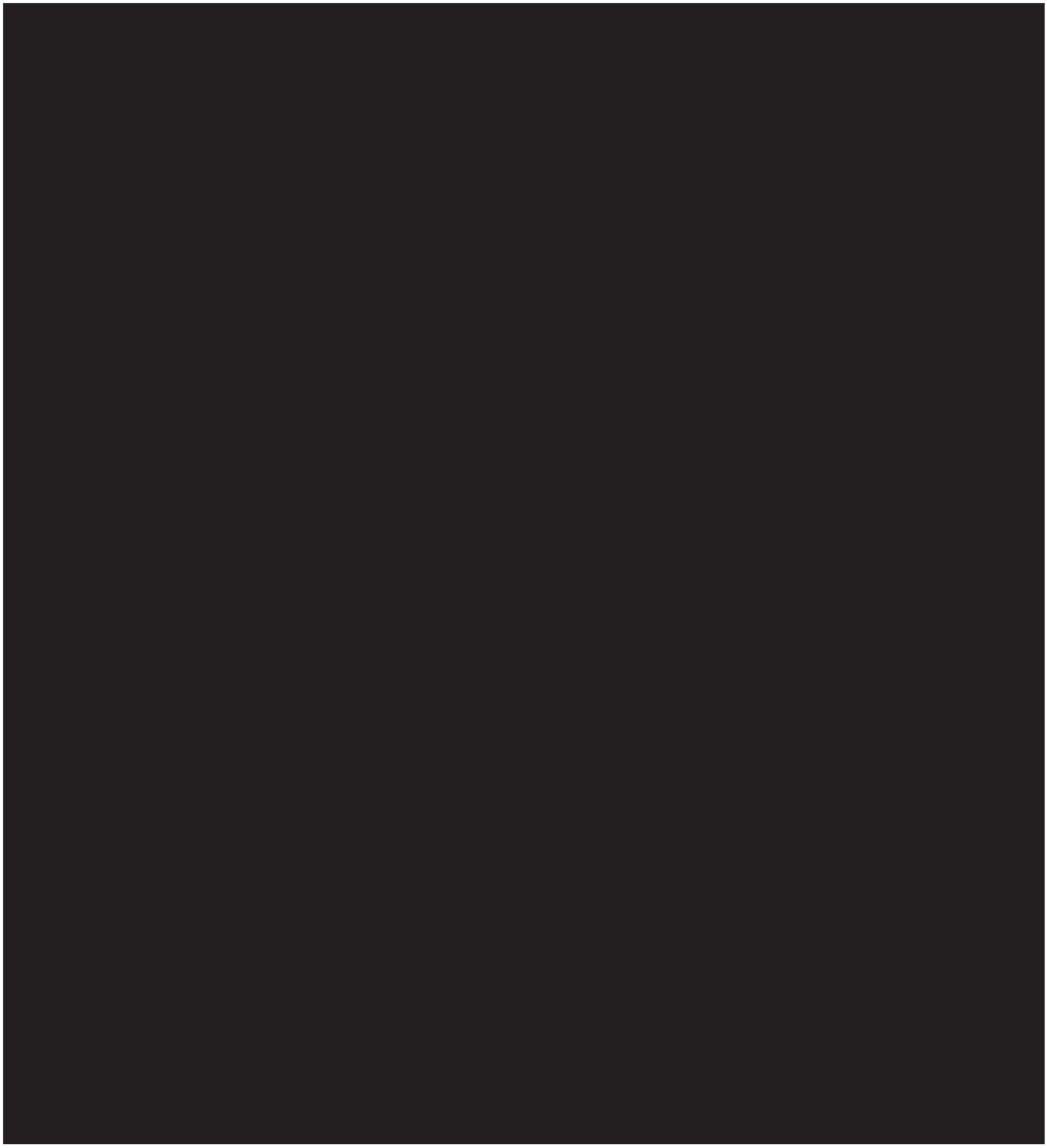
Not applicable.

5.2.2 Secondary endpoint(s)

Not applicable.







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 (as collected in parent trial): single race respondents, multiple race respondents (all combinations ticked), and all race categories regardless of how many race categories were ticked
- Ethnicity (as collected in parent trial)
- Age [years] will be calculated as: year of informed consent in extension trial 1199.225 - year of birth
- Age in classes [years] (<30; >=30 to <45; >=45 to <60; >=60 to <75; >=75)
- Age at randomisation in parent trial [years] (as derived in the parent trial CRF as year of informed consent in parent trial - year of birth)
- Age at randomisation in parent trial in classes [years] (<30; >=30 to <45; >=45 to <60; >=60 to <75; >=75)
- Weight [kg] (at inclusion in extension trial 1199.225) as continuous variable and in classes (<30; ≥30 to <60; ≥60 to <90; ≥90)
- Height [cm] (at inclusion in extension trial 1199.225)
- Body mass index [kg/m2], at inclusion in extension trial 1199.225: Weight [kg] / Height [m] * Height [m], as a continuous variable and in classes (< 18.5; >=18.5 to <25; >=25 to <30, >=30)

5.4.1.2 Other baseline characteristics

The following baseline efficacy variables and SSc characteristics will be summarised for the parent trial:

- FVC in mL and in % predicted at randomisation
- Modified Rodnan Skin Score (mRSS)
- Digital ulcers count and net burden [fingers]
- SGRQ Total, Symptoms, Activities and Impact scores
- Time since first onset of non-Raynaud symptom [years]
- Time since first onset of Raynaud symptom [years]
- Time since first diagnosis of SSc-ILD [years]
- SSc subtype (diffuse cutaneous SSc, limited cutaneous SSc)
- ATA status (positive, negative)

5.4.2 Compliance

Compliance (%) at each visit is collected in the eCRF and will not be recalculated. An overall compliance will be calculated as a time-weighted average over all visits. Each weight will be based on the number of days between the compliance measurement and the previous one (or the date of first trial drug intake for the first compliance measurement). If compliance is missing for at least one expected visit then overall compliance will be missing.

Likewise, compliance will be calculated at 1 year (up to 52 weeks [Visit 7]), at 2 years (up to 100 weeks [Visit 10]), and at each year (based on data collected every 48 weeks).

Overall and annual compliance will be summarised and categorised into classes: <50%, >=50% to <80%, >=80% to <= 120%, > 120%.

5.4.3 Exposure

Exposure will be calculated during 1199.225 extension trial. The date of first trial drug intake is recorded at visit 2.

- Duration of exposure [months] = (Date of last trial drug intake– date of first trial drug intake in extension trial 1199.225 +1 day) /30.5. Treatment interruptions will not be subtracted from this duration of exposure.
- Duration of exposure in categories: <= 3 months (91 days); > 3 months (91 days) to <= 6 months (182 days); > 6 months to <= 12 months (365 days); > 12 months to <= 18 months (547 days); > 18 months to <= 24 months (730 days); > 24 months to <=36 months (1095 days); > 36 months to <=48 months (1460 days); > 48 months to <=60 months (1825 days); > 60 months to <=72 months (2190 days); >72 months

- Duration while 150 mg bid actually taken [months]: Sum of each continuous duration of exposure to 150 m bid [days] /30.5. This duration of exposure will be adjusted for treatment interruptions, dose reductions and dose increases.

- Duration while 100 mg bid actually taken [months]: Sum of each continuous duration of exposure to 100 m bid [days] /30.5. This duration of exposure will be adjusted for treatment interruptions, dose reductions and dose increases.

- Total dose [g]: Duration while 150 mg bid actually taken [days] * 0.3 g + duration while 100 mg bid actually taken [days] * 0.2 g.

- Dose intensity [%]: Total dose [g]*100/{0.3g*(Duration of exposure [days])}

- Dose intensity in categories: <= 30 %, >30% to <=50%, >50% to <=90%, >90% to <100%, >=100%.

5.4.4 Liver enzyme and bilirubin elevations

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

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

[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.

- ALT ≥ 5 fold ULN and/or AST ≥ 5 fold ULN

- ALT ≥ 3 fold ULN and/or AST ≥ 3 fold ULN

- ALT ≥ 1.5 fold ULN and/or AST ≥ 1.5 fold ULN

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

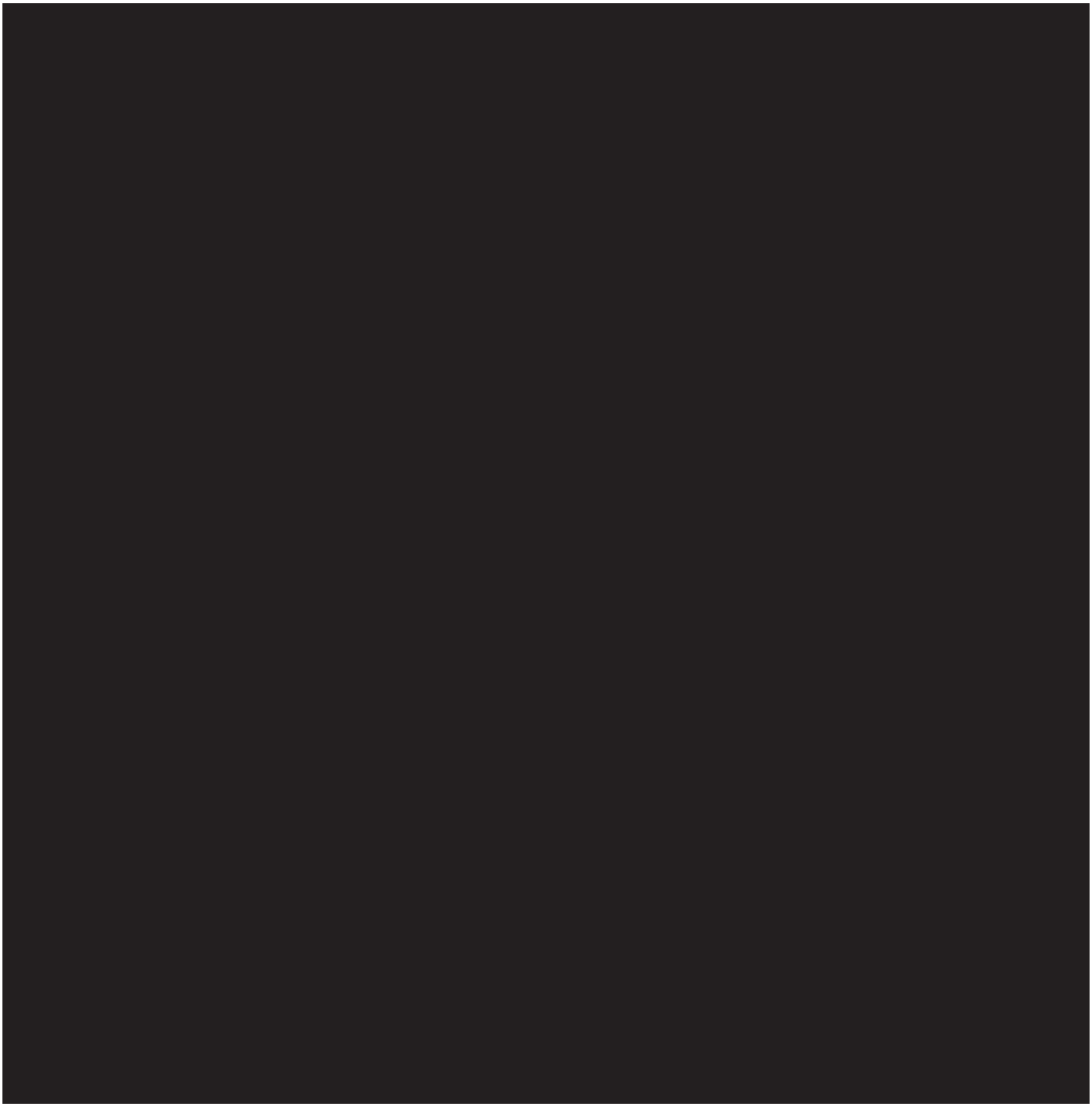
- ALT and/or AST ≥3 fold ULN and unexplained eosinophilia (>5%) in the same sample

- 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 9.2 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:

- ≥1.5 fold ULN; ≥3 fold ULN; ≥5 fold ULN; ≥8 fold ULN for AST and ALT
- ≥1.5*ULN; ≥2 fold ULN for Bilirubin
- ≥1.5*ULN; ≥2 fold ULN for ALK
- ≥ 1xULN; ≥ 3 fold ULN for GGT

Note: ULN refers to the Upper Limit of Normal from the Central Laboratory analyzing samples from this extension trial.



5.4.6 Safety time-to-event analyses

- Time to first dose reduction [days]
- Time to first treatment interruption [days]
- Time to permanent treatment discontinuation [days]
- Time to first dose reduction or treatment interruption [days]
- Time to first liver enzyme elevation (ALT and/or AST >=3xULN).

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

For treatment specifications, see Section 4 of CTP.

The different periods of interest, as per CTP flow chart, are the following:

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

- Previous trial:
    - If date of informed consent in 1199.225 and first trial drug intake in 1199.225 occur after or on last trial drug intake in SENSCIS plus 28 days plus one day or date of trial completion in parent trial (SENSCIS or 1199.340) plus one day, then previous trial period is defined as:

      from informed consent in parent trial to the last trial drug intake in SENSCIS plus 28 days plus one day or to the date of trial completion in parent trial (SENSCIS or 1199.340) plus one day, whichever occurs later

    - If date of informed consent in 1199.225 or first trial drug intake in 1199.225 occur before last trial drug intake in SENSCIS plus 28 days plus one day or date of trial completion in parent trial (SENSCIS or 1199.340), then previous trial period is defined as:

      from informed consent in parent trial to date of informed consent in 1199.225

- Between-trials (optional[a]): from end of previous trial period (see above) to date of informed consent in 1199.225

- Screening (optional[a]): from date of informed consent in 1199.225 to first trial drug intake in 1199.225

- Treatment period: from first trial drug intake in 1199.225 (or re-start of treatment if interruption) to last trial drug intake (or date of interruption if interruption) plus one day

- Off-treatment (optional[a]): from date of start of interruption to re-start of treatment

- Residual effect period: from the last trial drug intake plus one day to last trial drug intake plus 7 days plus one day

- Follow-up (optional[a]): from last trial drug intake plus 7 days plus one day (after residual effect period) to date of last contact as collected in the end of study CRF page plus one day. This period is only created if last trial drug intake took place more than 7 days before the last contact as collected in the end of study CRF page.

- Post-study: from the last trial drug intake plus 7 days plus one day to database lock or from the date of last contact as collected in the end of study CRF page (after follow-up period) plus one day to database lock, whichever occurs later

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

For safety analyses (Section 7.8), data from the treatment period, possible off-treatment periods and residual effect period will be considered as on-treatment.

6.2 IMPORTANT PROTOCOL DEVIATIONS

As there is no Per Protocol Set planned in this trial, none of the iPDs will lead to exclusion from a patient set. However the proportion of patients with iPDs will be presented for completeness purposes and to demonstrate the adherence to the CTP.

Table 6.2: 1 Important protocol deviations

Category/Code		**Description**	**Requirements**	**Excluded from**
A		**Entrance Criteria Not Met**		
	A1	**Inclusion criteria not met**		
	A1.7	Parent study not completed	Inclusion criteria 1 not met (or trial drug prematurely discontinued according to CRFs data) *Automatic IPD*	None
	A2	**Exclusion criteria met**		
	A2.1	Patient has laboratory values that indicate additional risk: a) >3xULN for AST/ALT b) >2xULN for Bilirubin c) Creatinine clearance < 30 mL /min (Cockcroft-Gault formula)	Laboratory values out of range or missing at entry in the trial (visit 1 or visit 2) according to the database *Automatic IPD*	None
	A2.2	Patient with other disease(s) which are excluded as per exclusion criteria	At least one of exclusion criteria 4, 5, 6, 7, 10, 12 met *Automatic IPD for exclusion criteria 4, 6, 7, 10, 12 and manual for exclusion criterion 5*	None
	A2.3	Forbidden previous therapy	Exclusion criteria 5, 9 *Manual IPD based on exclusion criteria and / or to be identified at the site level on the manual PD log*	None

Table 6.2: 1 Important protocol deviations (cont'd)

Category/Code		Description	Requirements	Excluded from
	A2.4	Potential risk related to fetotoxicity	Inclusion criteria 3 not met or exclusion criteria 13 met *Automatic IPD*	None
	A2.5	Time period between parent trial and Visit 2 not observed	Exclusion criteria 8 met AND (time period > 12 weeks, i.e. ≥13 weeks between last trial drug intake of 1199.214 and Visit 2 of this study according to CRFs data or time period > 1 week, i.e. ≥2 weeks between last trial drug intake of 1199.340 and Visit 2 of this study) *Automatic IPD*	None
	A2.6	Any condition that makes them an unreliable trial subject or unlikely to complete the trial	Exclusion criteria 11 met *Automatic IPD*	None
	A2.7	Previous enrolment in this trial	Exclusion criteria 14 met *Automatic IPD*	None
B		**Informed Consent**		
	B1	Informed consent not given	Inclusion criteria 2 not met *Automatic IPD*	None
	B2	Informed consent given too late	CRF date of informed consent is after date of Visit 1. Signature of the wrong Informed Consent version, and later signature of the correct one will also be part of this IPD category *Manual IPD*	None
	B3	Informed consent not given or withdrawn for biobanking but biobanking done	According to database and CRF page informed consent for biobanking *Automatic IPD*	None
C		**Trial medication and randomisation**		
	C1	Incorrect trial medication taken	Wrong medication number. Medication kit assigned at visit 2 does not match treatment dose actually received by patient *Automatic IPD*	None
	C2	Trial medication not interrupted (or interruption done too late) when ALT or AST ≥ 5 fold ULN	Based on liver enzyme elevation and interruptions reported during the trial *Manual IPD*	None

Table 6.2: 1 Important protocol deviations (cont'd)

Category/Code		Description	Requirements	Excluded from
	C3	Trial medication not permanently discontinued after signs of liver enzyme elevations were observed that a) are indicative of hepatic injury as defined in Section 5.4.4 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 are not dealt with according to the requirements of the CTP and no confirmed alternative cause found (as confirmed by BI medicine) for the potential drug-induced livery injury (DILI) event. *Manual IPD based on review of MQRM listings*	None
D		**Concomitant Medication**		
	D1	Patient received prohibited concomitant therapies (see Section 4.2.2.1 of the CTP)	Investigational therapies are not allowed *Review of MQRM listings and / or to be identified at the site level on the manual PD log.*	None
E		**Missing data**		
	E1	Patient without any physical assessment for more than 6 months although under study medication	Prior to the start of COVID-19 disruption, no vital signs >6 months. After the start of COVID-19 disruption, no vital signs or local labs >6 months. *Manual IPD*	None
	E2	Flow chart not observed for the planning of visit 1 and 2	Visit 1 and Visit 2 occurred on the same date whereas the period between last available laboratory test within SENSCIS™ or 1199-0340 and Visit 2 of the extension trial (1199.225) is > 6 weeks (i.e. ≥7 weeks) *Automatic IPD*	None

6.3 SUBJECT SETS ANALYSED

All analyses will be performed on the Treated Set, as defined in Section 7.3 of the CTP, including patients coming from SENSCIS and 1199.340.

Patients will be analysed according to their randomised treatment group in the parent trial (placebo or nintedanib) and overall (Total column). Patients from 1199.340 will be combined with placebo patients from SENSCIS in the outputs, due to their short exposure to nintedanib during 1199.340. Patients in the placebo column are those who initiated nintedanib in the extension study, whilst patients in the nintedanib column are those who continued nintedanib.

The column of main interest in the tables will be the total column (includes both treatment groups) as all patients are treated with nintedanib during the extension study.

In addition, a selected set of analyses will be repeated in patients coming from SENSCIS only (see Section 9.6 for further details) and in patients with pulmonary hypertension at baseline (see Section 9.7 for further details).

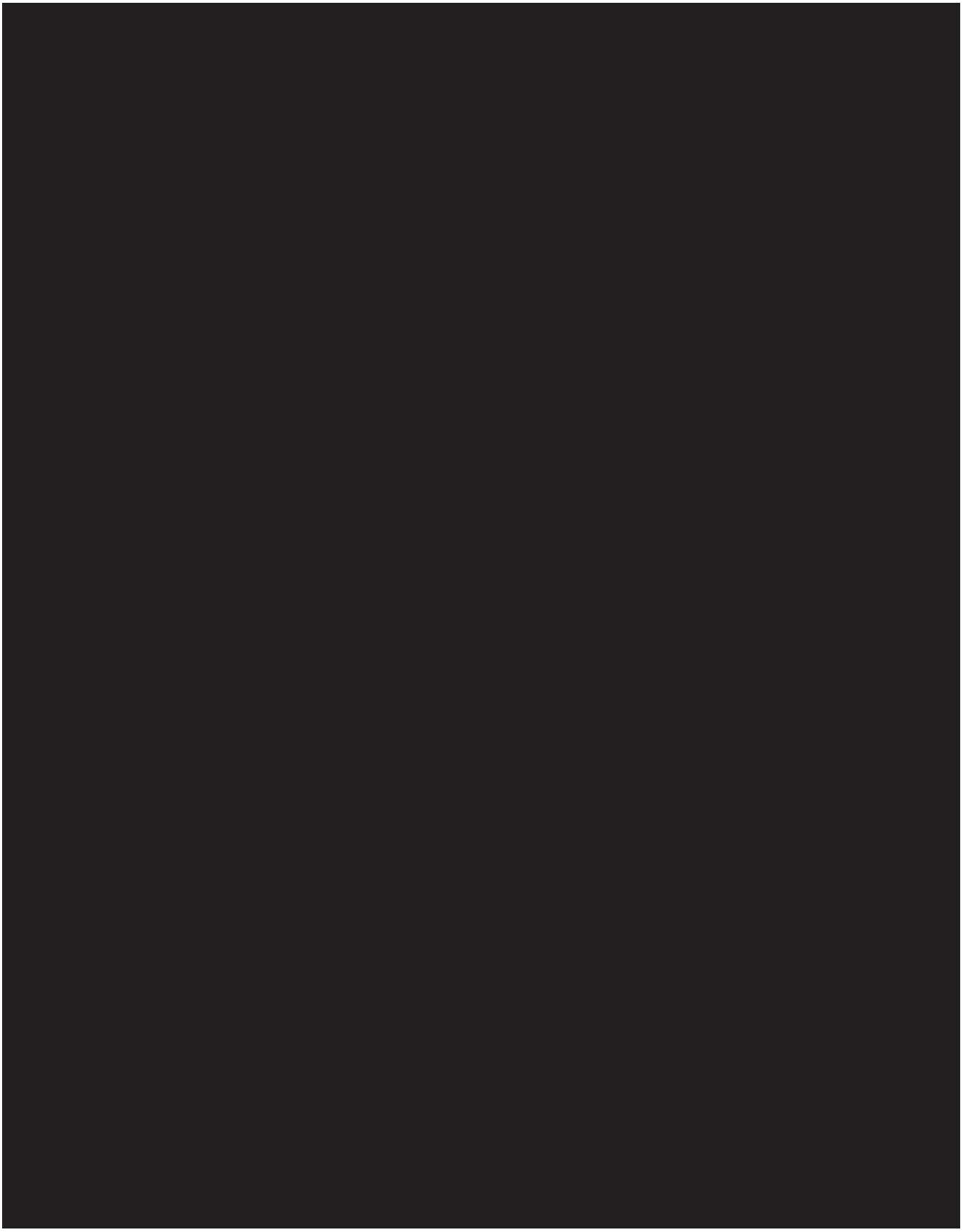
[redacted]

6.5 POOLING OF CENTRES

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

6.6 HANDLING OF MISSING DATA AND OUTLIERS

[redacted]



6.6.2 Other endpoints

6.6.2.1 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.

6.6.2.2 Safety endpoints

Missing or incomplete AE dates will be imputed according to BI standards (see “Handling of missing and incomplete AE dates”) (2).

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 Visit 1 assessment if no available value at Visit 2).

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. No time-windowing will be performed for the follow-up visit (all follow-up visits will be displayed in the tables / listings whenever they were performed).

Table 6.7: 1 Time windowing rules for [redacted] physical exam, vital signs and laboratory measurements (haematology, coagulation, biochemistry – CK, glucose non-fasting, LDH, uric acid, HCG)

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
1	1	1	1 or 2[2]	Baseline	1
2	57	56	3	4 weeks	29
58	127	70	4	12 weeks	85
128	211	84	5	24 weeks	169
212	309	98	6	36 weeks	253
310	421	112	7	52 weeks	365
422	533	112	8	68 weeks	477
534	645	112	9 *(p)*	Every 16 weeks thereafter	589 *(V_p)*
$V_p + 1 + (V_{p+1}-V_p)/2$	$V_{p+1} + (V_{p+2} - V_{p+1})/2$	$(V_{p+2} - V_p)/2$	p+1	…	V_{p+1}

[redacted]

Vp denotes the planned day of the visit

[1] First trial drug intake date in extension trial 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

Table 6.7: 2 Time windowing rules for [redacted] laboratory measurements (biochemistry - BNP, TSH)

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
1	1	1	2	Baseline	1
2	267	266	5	24 weeks	169
268	421	154	7	52 weeks	365
422	533	112	8 *(p)*	Every 16 weeks thereafter	477 (V_p)
$V_p + 1 + (V_{p+1}-V_p)/2$	$V_{p+1} + (V_{p+2} - V_{p+1})/2$	$(V_{p+2} – V_{p)}/2$	p+1	…	V_{p+1}

Vp denotes the planned day of the visit

[1] First trial drug intake date in extension trial is taken into account as a reference to calculate time windows

Table 6.7: 3 Time windowing rules for laboratory measurements (electrolytes, urinalysis, urine pregnancy test, biochemistry – AST, ALT, GGT, ALK, total protein, total bilirubin, creatinine, GFR)

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
1	1	1	1 or 2[2]	Baseline	1
2	22	21	2a	2 weeks	15
23	43	21	3	4 weeks	29
44	71	28	3a	8 weeks	57
72	106	35	4	12 weeks	85
107	148	42	4a	18 weeks	127

Table 6.7: 3 Time windowing rules for laboratory measurements (electrolytes, urinalysis, urine pregnancy test, biochemistry – AST, ALT, GGT, ALK, total protein, total bilirubin, creatinine, GFR) (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
149	190	42	5	24 weeks	169
191	232	42	5a	30 weeks	211
233	281	49	6	36 weeks	253
282	337	56	6a	44 weeks	309
338	393	56	7 *(p)*	52 weeks	365 (V_p)
$V_p + 1 + (V_{p+1}-V_p)/2$	$V_{p+1} + (V_{p+2} - V_{p+1})/2$	$(V_{p+2} - V_{p)}/2$	p+1	Every 8 weeks	V_{p+1}

Vp denotes the planned day of the visit

[1] First trial drug intake date in extension trial 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

7. PLANNED ANALYSIS

All analyses described in this section will be done on the Treated Set.

The list of analyses planned in patients coming from SENSCIS parent trial only is included in Section 9.6.

For End-Of-Text tables, 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, 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 randomised treatment group in parent trial (and overall), System Organ Class (SOC) and Preferred Term (PT). SOC and PT will be sorted by descending frequency (over the Total column).

7.2.2 Concomitant therapies

Concomitant therapies will be described over several study periods:

- Baseline therapies will be defined as treatments with a start date before first trial drug intake in extension trial and a stop date after or on the day of the first trial drug intake in extension trial (or ongoing after first trial drug intake in extension trial).

- On-treatment concomitant therapies are defined as treatments with a start date after or on the day of first trial drug intake in extension trial and before or on the day of last trial drug intake in extension trial.

- Post-study drug discontinuation therapies are defined as treatments with a start date after last trial drug intake in extension trial and before or on the last contact as collected in the end of study CRF page. This aims at flagging concomitant treatments taken by patients after they have stopped the study drug.

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 Total column 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 Total column within a CDG. CDGs are built using WHO-DD Standardised Drug Groupings (SDG), Sub-SDGs and ATC4 levels. CDGs are listed in Section 9.3.

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

	By ATC and PN	**By CDG and PN**
Baseline therapies	16.1.13.1	15.1
On-treatment concomitant therapies	16.1.13.1	16.1.13.1
All on-treatment concomitant therapies* with a frequency >2% (in the Total column)	16.1.13.1	Not required
All on-treatment concomitant therapies*	16.1.13.1	15.1
Post-study drug discontinuation therapies	Not required	16.1.13.1

* including baseline therapies.

7.3 TREATMENT COMPLIANCE

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

7.4 PRIMARY ENDPOINT(S)

The primary objective of the trial is to assess the safety of Nintedanib, so please refer to Section 7.8 for detailed analyses.

7.5 SECONDARY ENDPOINT(S)

7.5.1 Key secondary endpoint(s)

This section is not applicable as no key secondary endpoint has been specified in the protocol.

7.5.2 (Other) Secondary endpoint(s)

This section is not applicable as no secondary endpoint has been specified in the protocol.

7.7 EXTENT OF EXPOSURE

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

For the above mentioned analyses, data will be presented over 52 weeks, 100 weeks, 148 weeks as well as over the whole trial.

The proportion of patients on each dose actually taken at inclusion in 1199.225 will be displayed according to:

- the dose actually taken at the end of parent trial (by parent trial treatment group and all combined)

- last dose actually taken in 1199.225 extension trial

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

A Kaplan-Meier plot of time to permanent treatment discontinuation will be produced. Similarly, Kaplan-Meier plots will be performed for time to first dose reduction, for time to first treatment interruption and for time to first dose reduction or treatment interruption. Plots will be done by randomised treatment group in parent trial and overall. The 25th, median and 75th percentiles derived from the Kaplan-Meier plots of these time-to-event endpoints will be presented as well. No statistical tests will be performed.

For all the above mentioned time to event endpoints, a summary table of time to first onset and number of patients with an event will be presented. The time to onset of first event [days] will also be summarised by categories : <= 1 month (30 days), > 1 month (30 days) to <= 2 months (61 days), > 2 months (61 days) to <= 3 months (91 days); > 3 months (91 days) to <= 6 months (182 days); > 6 months (182 days) to <= 1 year (365 days); > 1 year (365 days) to <= 2 years (730 days); > 2 years (730 days) to <=3 years (1095 days), > 3 years (1095 days).

7.8 SAFETY ANALYSIS

All safety analyses will be performed on treated patients.

7.8.1 Adverse events

Unless otherwise specified, the analyses of adverse events will be descriptive in nature. All analyses of AEs will be based on the number of subjects with AEs and NOT on the number of AEs.

For analysis multiple AE occurrence data on the CRF will be collapsed into an AE 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 summarisation of AE data, please refer to (2,3).

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 in extension trial till last drug intake + 7 days will be assigned to the on-treatment period and described according to randomised treatment in parent trial. All adverse events occurring before first drug intake will be assigned to 'previous trial', 'Between-trials' or 'screening'.

All adverse events occurring after the last trial drug intake will be assigned to 'residual effect period' or 'follow-up' or 'post-study' (for listings only). For details on the treatment definition, see Section 6.1.

According to ICH E3 (4), AEs classified as 'other significant' needs to be reported and will include those non-serious and non-significant adverse events with
(i) 'action taken = drug withdrawn' or 'action taken = dose reduced', or
(ii) marked haematological and other lab abnormalities or lead to significant concomitant therapy

An overall summary of adverse events will be presented by randomised treatment in parent trial (and Total).

The frequency of patients with AEs will be summarised by randomised treatment in parent trial (and Total), primary system organ class (SOC) and preferred term (PT). This will be presented using a >5% cut-off in the CTR and repeated without the cut-off in the CTR appendices.

Separate tables will be provided for patients with other significant AEs according to ICH E3 (4), for patients with serious AEs (SAEs), for patients with severe AEs, for patients with AEs leading to dose reduction, for patients with AEs leading to treatment interruption, for patients with AEs leading to discontinuation of trial drug, for patients with investigator defined drug-related AEs, for patients with AEs leading to death and for patients with investigator defined drug-related AEs leading to death. The frequency of patients with serious adverse events occurring with incidence in preferred term > 1% will be presented as well.

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 events that are both serious and investigator defined drug-related.

Data will be presented over 52 weeks, 100 weeks, 148 weeks as well as over the whole trial. The SOCs will be sorted by default alphabetically; PTs will be sorted by frequency in the Total column (within SOC).

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 5.2.11.1. 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 randomised treatment in parent trial (and Total), 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 additional information collected will be summarised at the AE level (occurrence level) rather than at the patient level separately for diarrhoea and bleeding.

Bleeding AEs will also be summarised by system and safety topic, see Section 7.8.1.3 for further details.

For the above mentioned analyses, data will be presented over 52 weeks, 100 weeks, 148 weeks as well as over the whole trial.

7.8.1.3 Additional analysis of adverse event groupings by system

Further adverse event groupings by system and safety topic have been defined outside the trial protocol as medically relevant to the clinical development program and are specified in (8).

The frequency of patients with AEs within these groupings will be summarised by system, randomised treatment group in the parent trial (and overall), safety topic and preferred term. Separate tables will be provided for patients with investigator defined drug-related AEs, serious AEs (SAEs), drug-related serious AEs and bleeding AEs. Data will be presented over 52 weeks, 100 weeks, 148 weeks as well as over the whole trial.

7.8.1.4 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 in the extension trial:

- 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

In the summary of adverse events of particular note including intensity, seriousness, clinical consequences, drug relationship, therapy for event and outcome: for patients with several episodes, the worst intensity, relationship, outcome and clinical consequence during on−treatment period will be displayed. For clinical consequences, the worst category is

considered to be “Drug withdrawn”, then “Dose reduced”, “Dose not changed” and finally “Dose increased”. Worst to best outcome are: “Fatal”, “Recovered/Resolved with sequelae”, “Not Recovered/Not Resolved”, “Recovered/ Resolved”, “Unknown”.

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 randomised treatment in parent trial (and Total).

In addition, for pairs of selected adverse events (from diarrhoea, nausea, vomiting, decreased appetite, dehydration, weight decreased as defined in (8) , the frequency of patients with concurrent AEs will be summarised by treatment where concurrence is defined as an overlap of at least one day.

7.8.1.5 Time at risk analyses

Time at risk analyses of AEs over 1199.225 trial will be presented. Time at risk and incidence rates per 100 patient years will be calculated based on the first onset of an AE in the extension trial.

For a specific AE, the total AE time at risk [years] is defined as the sum of time at risk [days] across all contributing patients / 365.25, with for each patient the time at risk [days] defined as follows:

- Date of first onset of the AE – date of first study medication administration in extension trial +1 day for patients with the specific AE

- End of time at risk – date of first study medication administration in extension trial + 1 day for patients without the specific AE. The end of time at risk is the min (date of last trial drug intake + 7 days, database lock date).

The AE incidence rate [1/100 Patient years (pt-yrs)] = 100 * number of patients with specific AE / total specific AE time at risk [years]

A summary by randomised treatment in parent trial (and Total), primary system organ class (SOC) and preferred term (PT) will be presented.

Separate tables will be provided for patients with other significant AEs according to ICH E3 (4), 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 and for patients with AEs leading to death, for investigator defined drug-related SAEs, for investigator defined drug-related AEs leading to death and pre-specified AESI. The summary of patients with SAEs will also be presented restricted to incidence in preferred term > 1%.

Time at risk analyses of AEs, investigator defined drug-related AEs and SAEs within groupings by system will be also summarised by randomised treatment in parent trial (and Total), safety topic and preferred term.

7.8.2 Laboratory data

7.8.2.1 Standard laboratory analyses

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (5). Please refer to Section 7.3.4 of the CTP for further details.

Summaries of transitions relative to reference ranges and [redacted] will be presented over 52 weeks, 100 weeks, 148 weeks as well as over the whole trial.

7.8.2.2 Liver enzyme and bilirubin elevations

Specific tables and graphs will be presented by randomised treatment in parent trial (and Total) to describe liver enzyme elevations as defined in Section 5.4.4:

- Summary table of liver enzyme elevation including time to first onset and number of patients with liver enzyme elevation. The time to onset of first liver enzyme and bilirubin elevation [days] will be summarised by categories (<=30 days; >30 to <=91 days; >91 to <=182 days; >182 to <=365 days; >365 to <=547 days; >547 to <=730 days, >730 to <=1095 days, >1095 days).

- Kaplan-Meier plot of time to first liver enzyme elevation. No statistical test will be performed.

- Summary table of individual maximum liver enzyme and bilirubin elevations by time period (over 52 weeks, 100 weeks, 148 weeks and over the whole trial).

- Plot of time course profile of liver enzyme for patients having liver enzyme and bilirubin elevation.

Due to a change in the Central Laboratory analyzing samples between SENSCIS and this extension trial, the proportion of patients with liver enzyme and bilirubin elevations according to the cut-offs defined in Section 5.4.4 and using the Upper Limit of Normal from the Central Laboratory from SENSCIS will be described as well in CTR Appendix 16.1.13.1.

7.8.3 Vital signs

Summary statistics will be presented for observed values and change from baseline by visit.

[redacted]

[redacted]

7.8.4 ECG

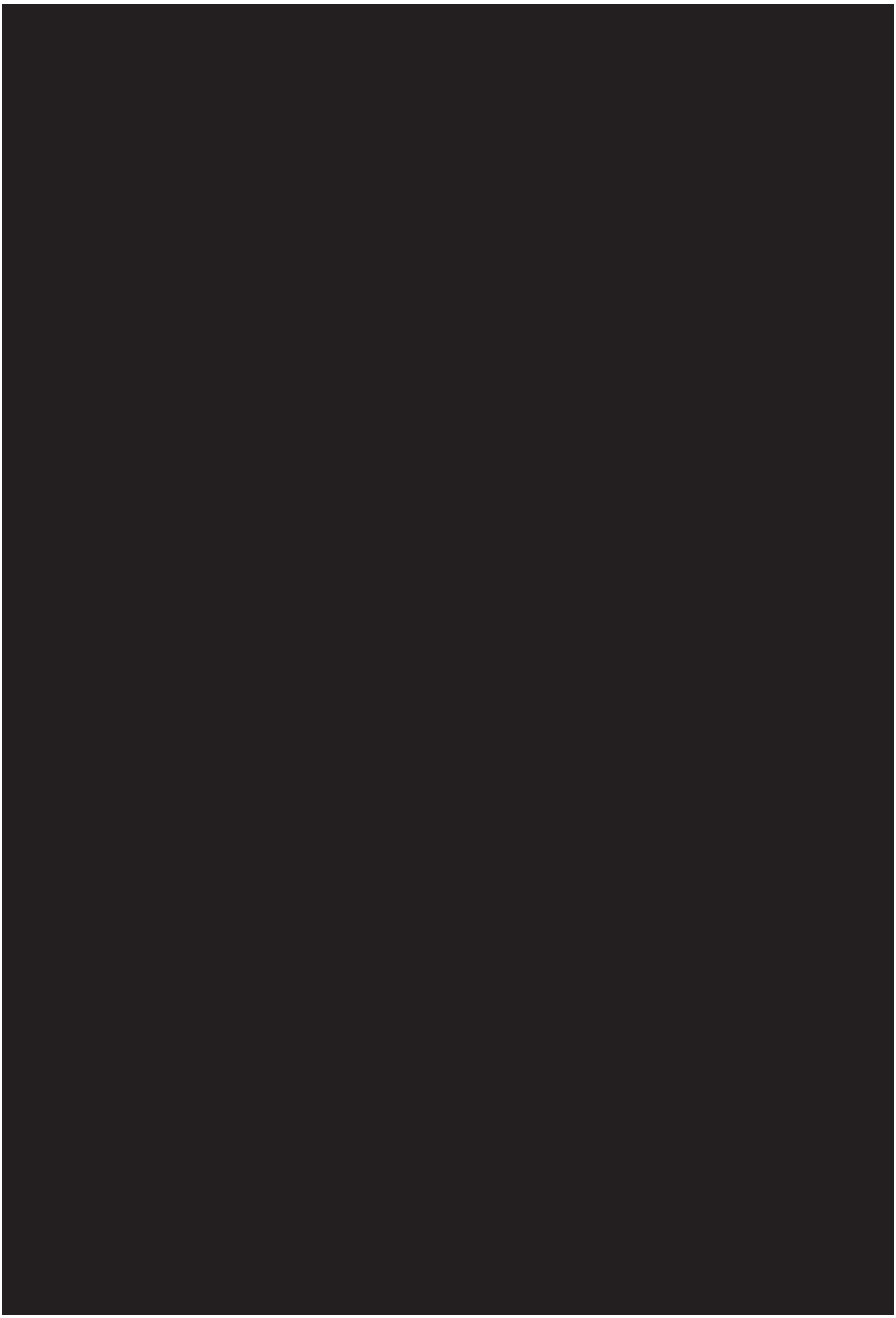
Not applicable (ECG findings are reported as adverse events).

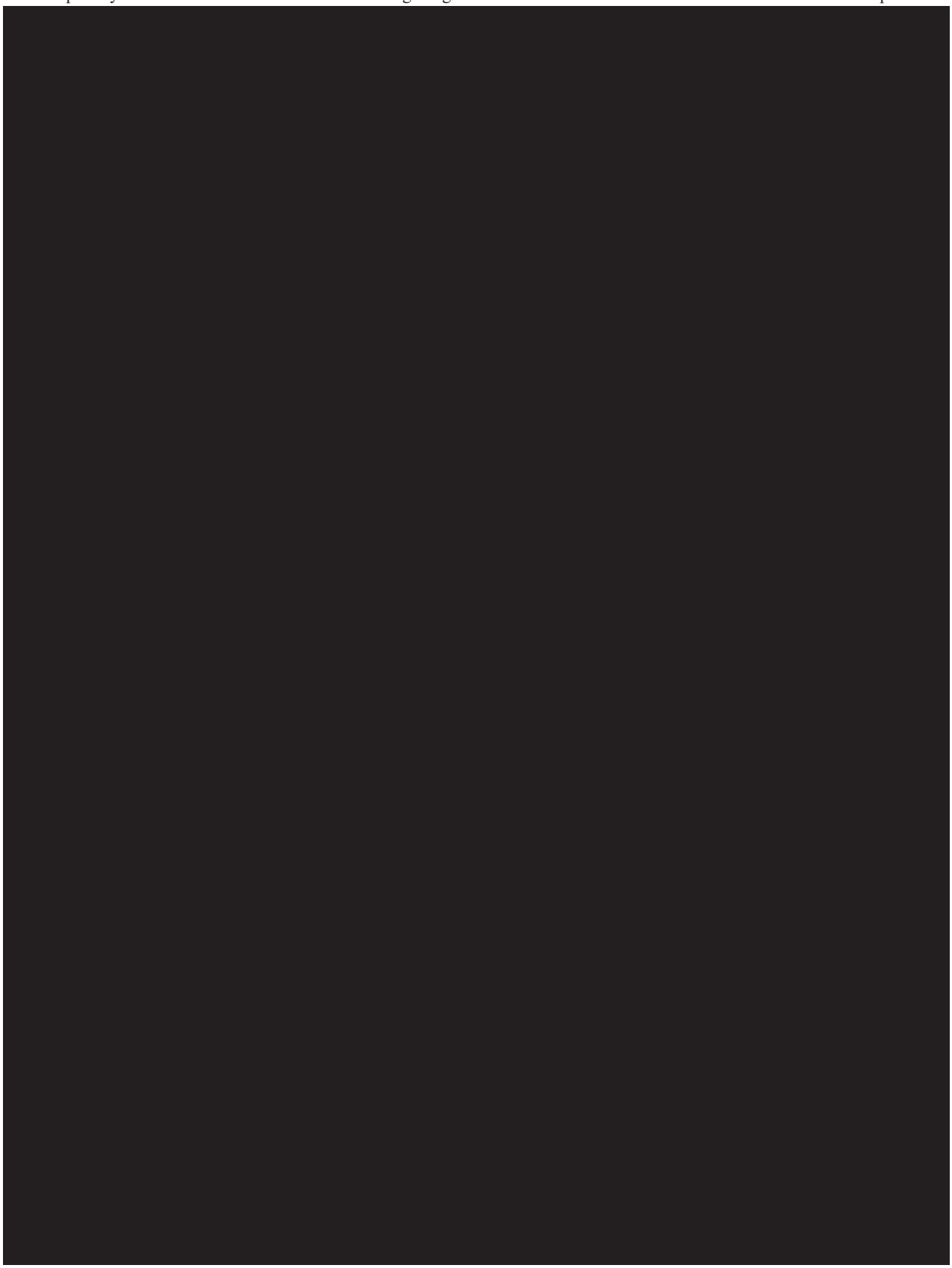
7.8.5 Others

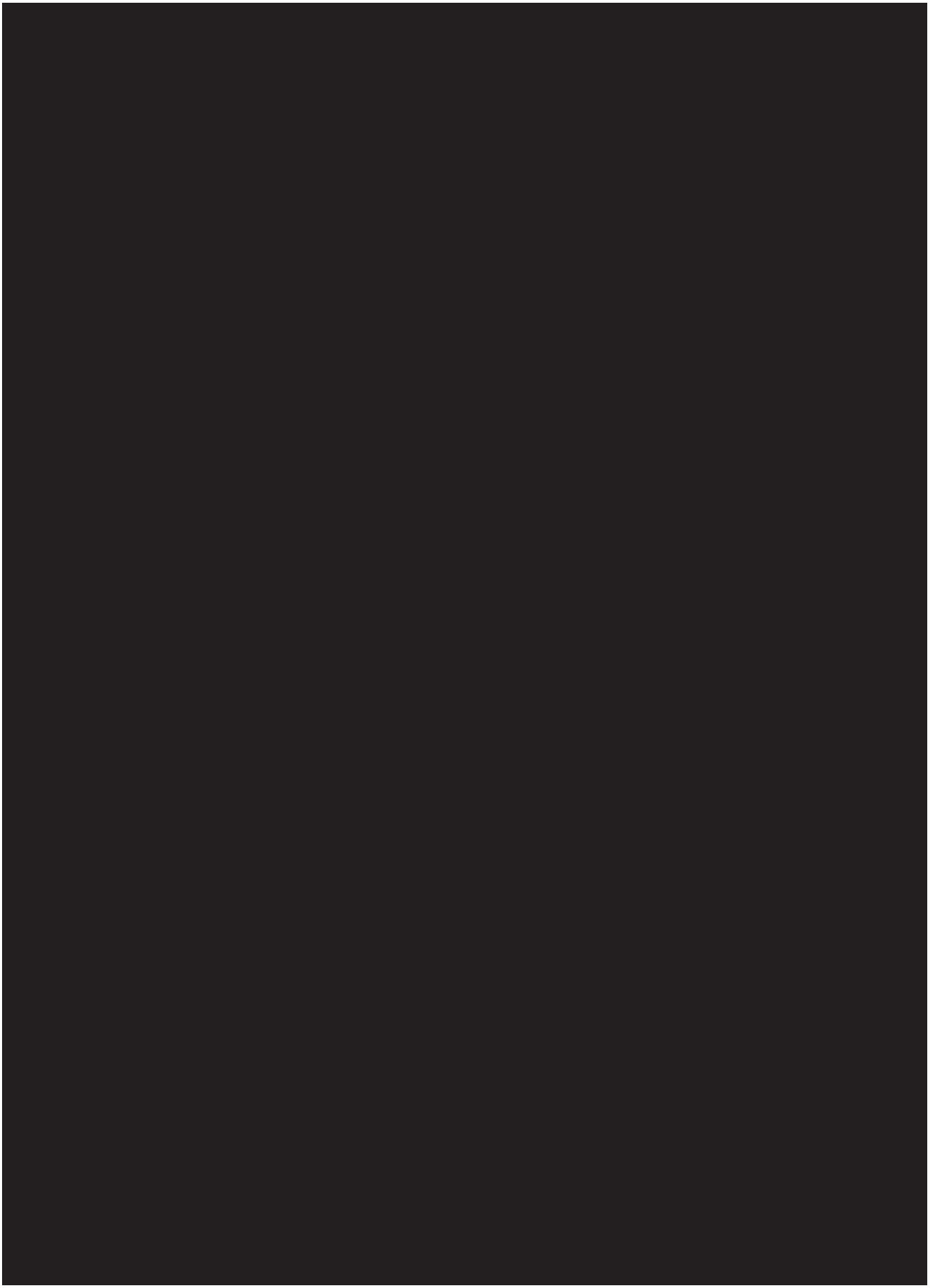
Not applicable.

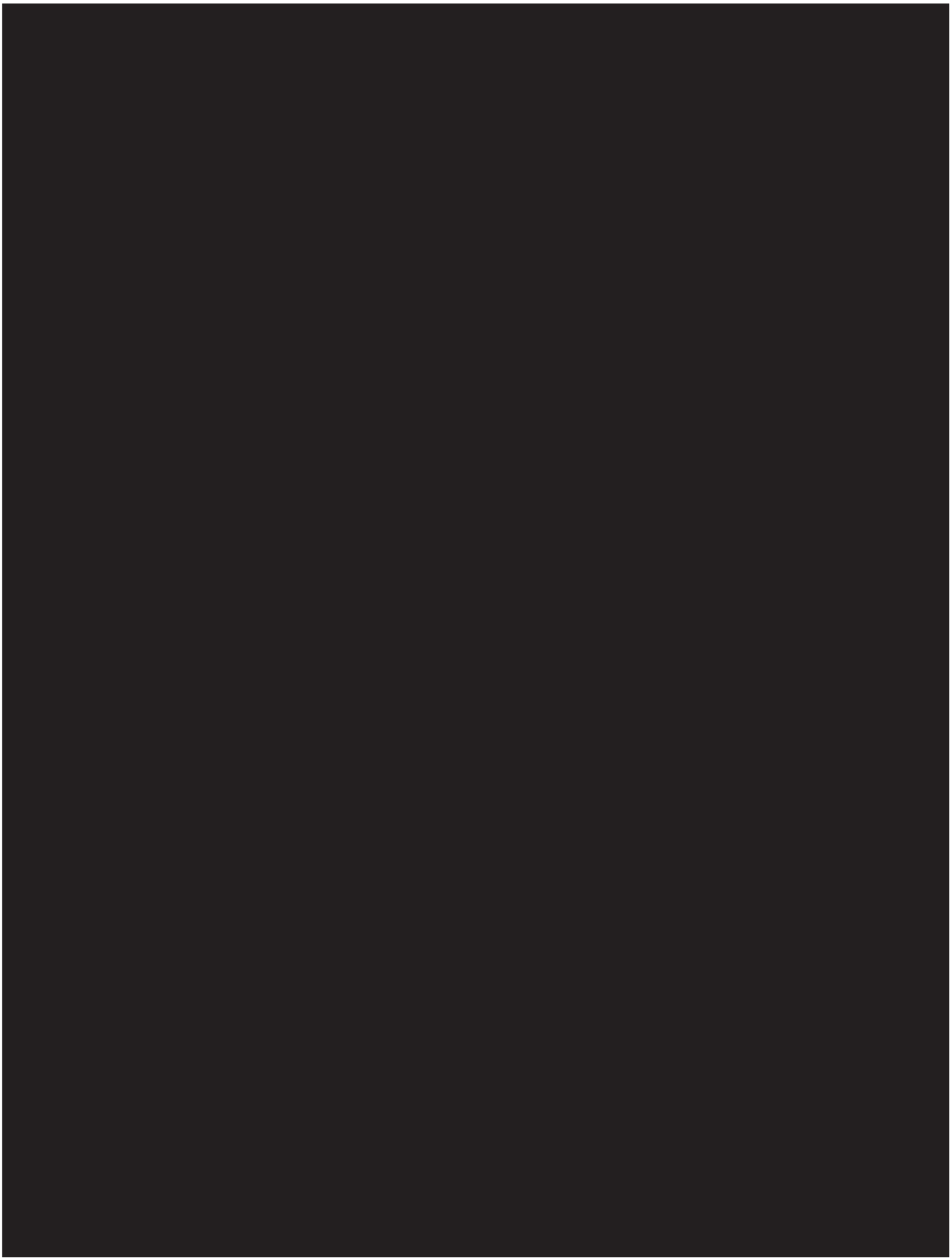
8. REFERENCES

1.	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
2.	*BI-KMED-BDS-HTG-0035:* "Handling of missing and incomplete AE dates", current version; IDEA for CON.
3.	*BI-KMED-BDS-HTG-0041*: "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version; IDEA for CON.
4.	*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
5.	*BI-KMED-BDS-HTG-0042*: "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON.
[redacted]	[redacted]
[redacted]	[redacted]
8.	Specifications for adverse event groupings by safety topic for Nintedanib: Nintedanib / Clinical / Systemic sclerosis/ Project Data Management and Statistics / Section 8 PSAP and Programming / 8-07-other-safety-topic-definition, current version; BIRDS
[redacted]	[redacted]









10. HISTORY TABLE

This is a revised TSAP including the following modifications to the final TSAP.

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1	**31-JAN-2020**	[redacted]	None	This is the final TSAP without any modification
2	**19-FEB-2020**		All	Pre-archive formatting checks implemented
3	**06-APR-2020**		6.7 [redacted]	Time windows for laboratory assessments updated for consistency with protocol [redacted]
4	**09-JAN-2023**		5.4.1 5.4.2 6.2 7.7/7.8.1/7.8.1.2/ 7.8.1.3/7.8.2.1/7.8.2.2 7.8.2.2 [redacted]	[redacted] A2.5 updated to include 1199.340 condition and E1 updated to include local labs after COVID-19 disruption date and therefore now a manual iPD Outputs will be displayed over 52, 100, 148 weeks and over the whole trial Time to elevation categories condensed [redacted]