TRIAL STATISTICAL ANALYSIS PLAN

c30127921-03

BI Trial No.:	1199-0248 (INBUILD®-ON)
Title:	An open-label extension trial of the long-term safety of nintedanib in patients with Progressive Fibrosing Interstitial Lung Disease (PF-ILD)
Investigational Product:	Nintedanib
Responsible trial statistician:	[redacted] Phone: [redacted]
Date of statistical analysis plan:	18 MAY 2022 REVISED
Version:	3

1. TABLE OF CONTENTS

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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALK	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
auto	Autoimmune ILDs
BI	Boehringer Ingelheim
BIcMQ	Boehringer Ingelheim customised MedDRA Query
bid	bis in die (twice a day)
bpm	Beats per Minute
CDG	Customised Drug Groupings
CRF	Case Report Form
CSD	Company Standard Displays
CTCAE	Common Terminology Criteria for Adverse Events
CT	Computed Tomography
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DBL	Data Base Lock
DMARD	Disease-Modifying Anti-Rheumatic Drugs
ECG	Electrocardiogramm
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EoT	End-of-Text
FEV1	Forced Expiratory Volume in 1 second
[redacted]	[redacted]
GGT	Gamma-Glutamyl-Transferase
GLI	Global Lungs Initiative
HRCT	High-Resolution Computer Tomography
HP	Hypersensitivity pneumonitis

Term	Definition / description
IC	Informed Consent
ICH	International Conference on Harmonisation
ILD	Interstitial Lung Disease
IMP	Investigational Medicinal Product
INR	International Normalised Ratio
iNSIP	Idiopathic nonspecific interstitial pneumonia
iPD	Important Protocol Deviation
IRT	Interactive Response Technology
LLN	Lower Limit of Normal
LLT	Lowest Level Term
Max	Maximum
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MQR	Medical and Quality Review
PD	Protocol Deviation
PF-ILD	Progressive Fibrosing Interstitial Lung Disease
PN	Preferred Name
pred	Predicted
PT	Preferred Term
qd	quaque die (once a day)
SAE	Serious Adverse Event
SAS	Statistical Analyses Software as developed by SAS Institute
SCS	Screened Set
SD	Standard Deviation
SDG	Standardised Drug Grouping
[redacted]	[redacted]
SGOT	Aspartate Aminotransferase
SGPT	Alanine Aminotransferase
SOC	System Organ Class
TS	Treated Set
TS150S	Treated Set – 150 mg bid starting dose

Term	Definition / description
TSAP	Trial Statistical Analysis Plan
uIIP	Unclassifiable idiopathic interstitial pneumonia
UIP	Usual Interstitial Pneumonia
ULN	Upper Limit of Normal
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.

INBUILD®-ON is the open-label extension of INBUILD® trial 1199.0247 which is also called parent trial throughout this document. Therefore, this TSAP also assumes familiarity with the TSAP of INBUILD® trial 1199.0247.

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

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

Kaplan-Meier analyses and descriptive statistics were added for the following:

- [redacted]
- [redacted]
- [redacted]
- Time to first liver enzyme elevation (see Section 5.4.4.1 for details)
- Time to first dose reduction (see Section 5.4.3.1.1 for details)
- Time to first treatment interruption (see Section 5.4.3.1.1 for details)
- Time to premature treatment discontinuation (see Section 5.4.3.1.1 for details)
- Time to first dose reduction or treatment interruption (see Section 5.4.3.1.1 for details)

All times mentioned above are considering the extension trial only.

[redacted]

- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

There are several terms than can be used interchangeably for the Investigational Medicinal Product (IMP) in this trial such as “trial drug”, “trial medication”, “study drug”, “study medication”, or even “nintedanib” as this is an open-label trial.

5. ENDPOINTS

For endpoints or other variables where derived "last contact date" is utilised, e.g. time-to-event analyses, the following will apply:
The derived last contact date when the subject was known to be alive is defined as the latest date recorded in the electronic Case Report Form (eCRF) from the dates listed below (in case a date is planned to be imputed for the analysis, the imputed date will also be used):

- Last visit date,
- Last reported Adverse Event (AE) date (excluding end dates when outcome is fatal or unknown),
- Last reported concomitant therapy date,
- Last laboratory sample date,
- Last reported nintedanib intake date (non-imputed),
- Last reported dose change / interruption date,
- [redacted]
- Last contact date as collected on the end of study eCRF page (if reason for non-completion is not "Death").

5.1 PRIMARY ENDPOINT

The primary endpoint is the incidence of overall adverse events over the course of this extension trial.

5.2 SECONDARY ENDPOINTS

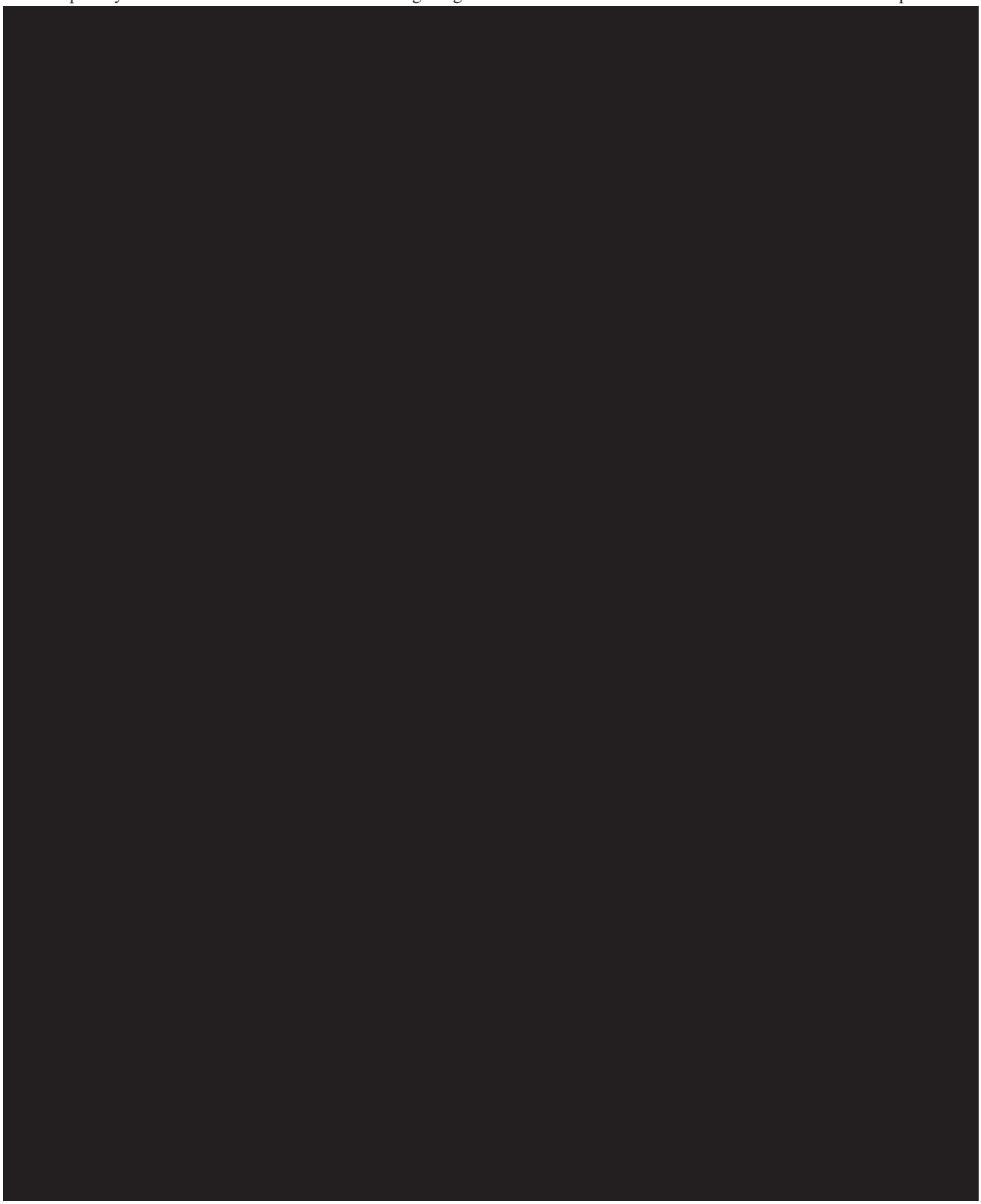
Not applicable.

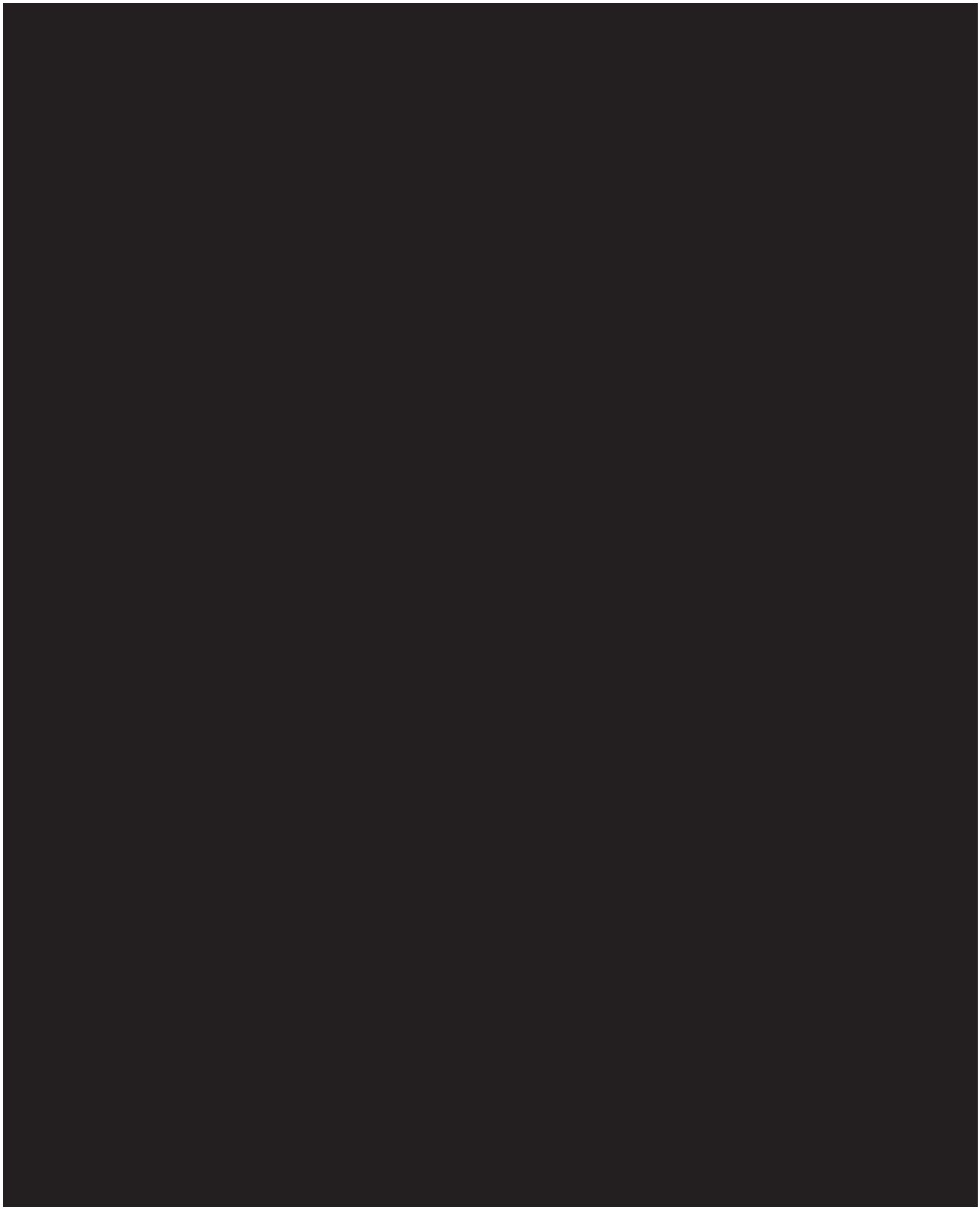
5.2.1 Key secondary endpoints

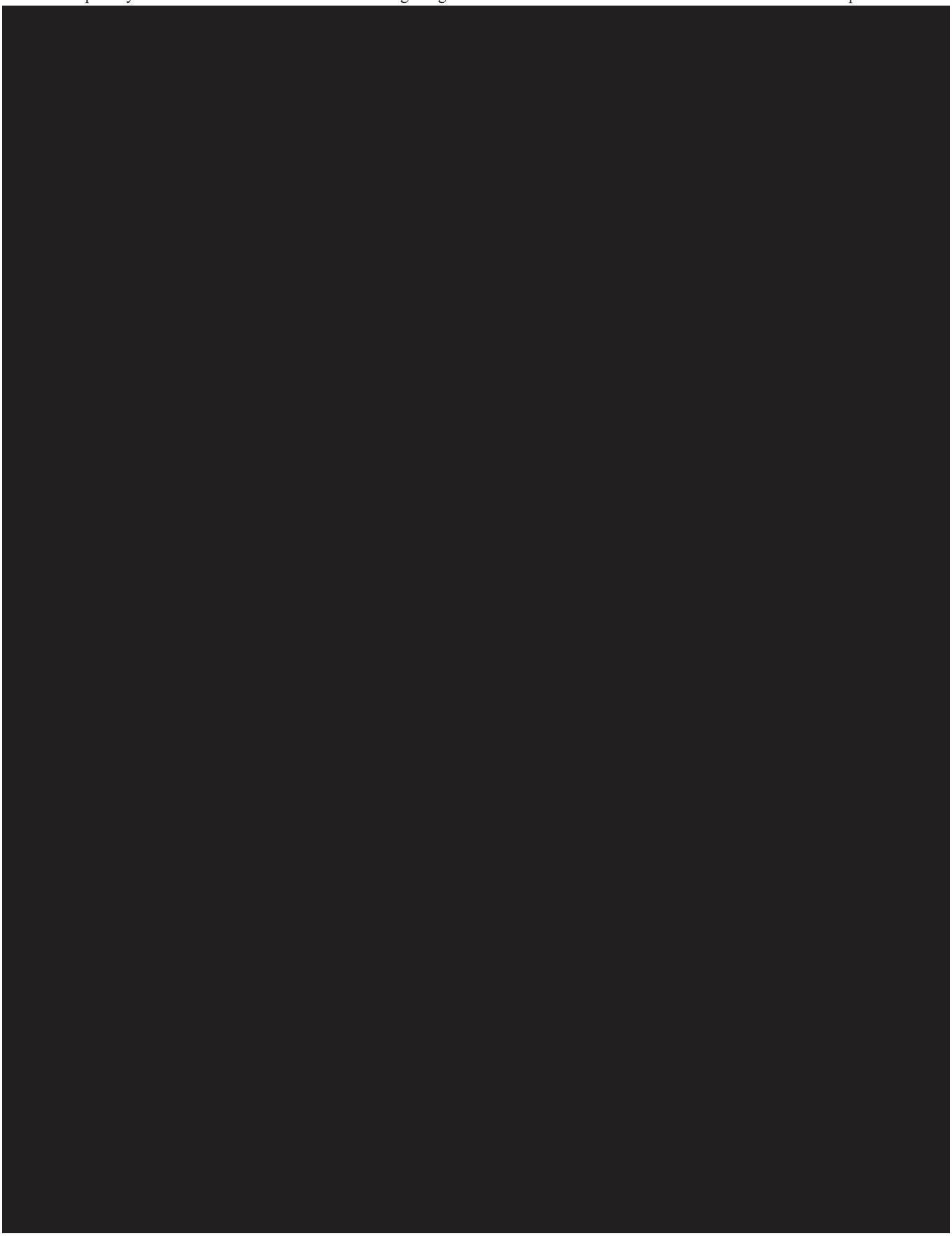
Not applicable.

5.2.2 Secondary endpoints

Not applicable.







5.4 OTHER VARIABLES

5.4.1 Demographics and baseline characteristics

5.4.1.1 Demographic data

- Gender (Male; Female)

- Ethnicity (Hispanic/Latino; Not Hispanic/Latino)
  Note: For this study collection of ethnicity was not allowed at sites in France as per French law.

- Race: single race respondents, multiple race respondents (all combinations ticked), and all race categories regardless of how many race categories were ticked
  Note: For this study collection of race was not allowed at sites in France as per French law.

- Age [years] at time of informed consent (IC) in extension trial (transferred by IRT) as continuous variable and in categories:
  <30 years; >=30 to <45 years; >=45 to <60 years; >=60 to <75 years; >=75 years

- Age [years] at time of IC in parent trial (transferred by IRT) as continuous variable and in categories:
  <30 years; >=30 to <45 years; >=45 to <60 years; >=60 to <75 years; >=75 years

- Weight [kg] (at inclusion in extension trial, i.e. Visit 1) as continuous variable and in categories: <30 kg; >=30 to <60 kg; >=60 to <90 kg; >=90 kg

- Height [cm] (at inclusion in extension trial, i.e. Visit 1) as continuous variable

- Body mass index [kg/m²] (at inclusion in extension trial, i.e. Visit 1), calculated as

$$\frac{Weight\ [kg]}{Height\ [m] * Height\ [m]}$$

  as a continuous variable and in categories:
  < 18.5 kg/m²; >=18.5 to <25 kg/m²; >=25 to <30 kg/m²; >=30 kg/m²

- Smoking status (Never; Current; Former)

- Pack years (for subjects with smoking status "*Current*" or "*Former*") as continuous variable and in categories: <20 pack years; >=20 to <40 pack years; >= 40 pack years

- Duration of exposure to trial drug in parent trial will be calculated based on first and last trial drug intake <u>in parent trial</u> in days as

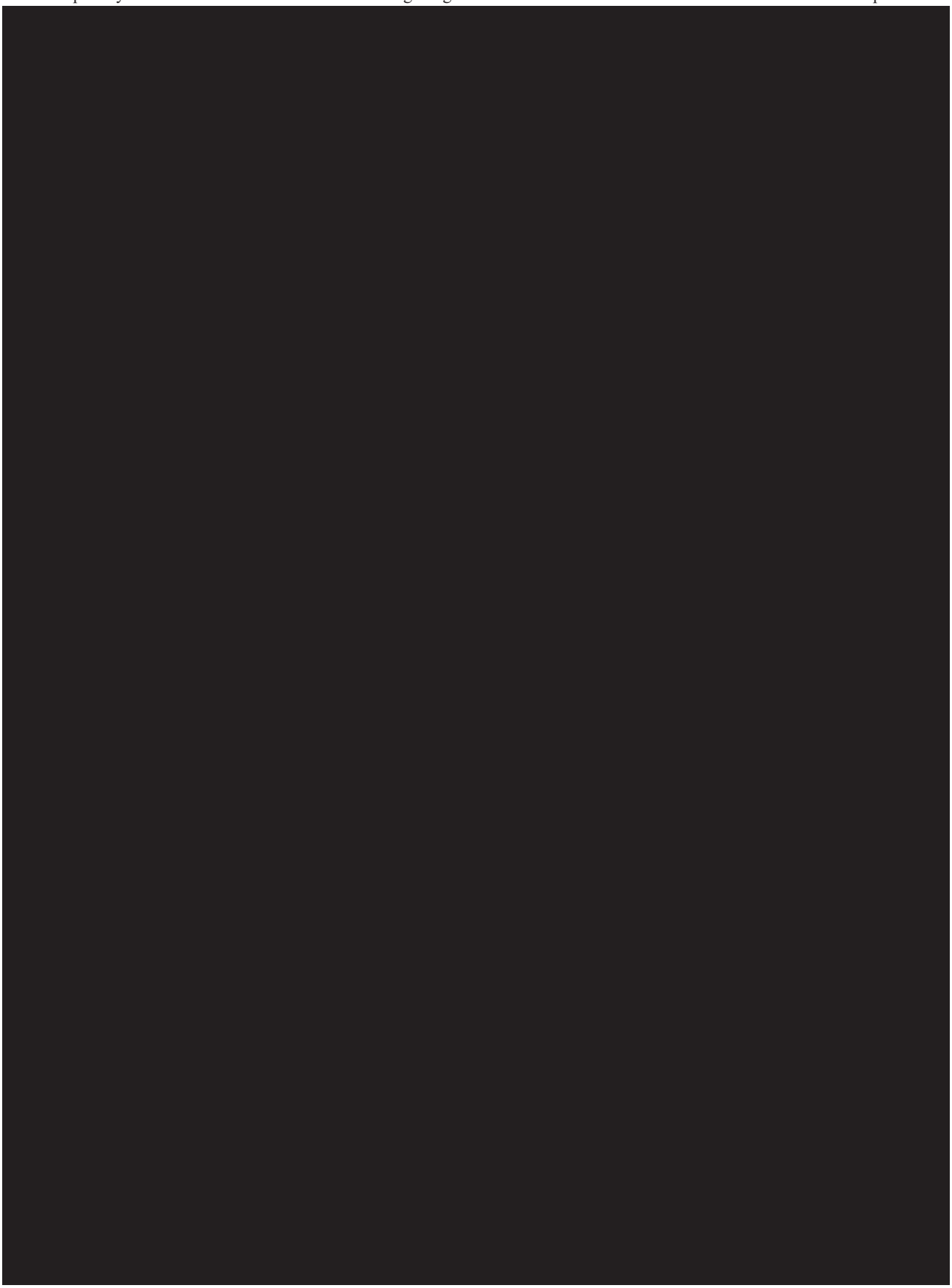
$$Date\ of\ last\ trial\ drug\ intake - Date\ of\ first\ trial\ drug\ intake + 0.5\ days,$$

  assuming that only one capsule was taken on day of last trial drug intake. In case of first trial drug intake was at 2:30 p.m. or later another half day will be subtracted. Duration in months will then be calculated as

$$\frac{Duration\ of\ exposure\ to\ trial\ drug\ in\ parent\ trial\ [days]}{30.5}$$

  Duration of exposure to trial drug in parent trial will be summarised as continuous variable [months] and in categories:

  - <=12 months (365 days);
  - >12 to <=18 months (547 days);
  - >18 to <=24 months (730 days);
  - >24 to <=30 months (912 days);
  - >30 months



5.4.1.3 Baseline characteristics for lung function

- FVC [mL] (at inclusion in extension trial, i.e. Visit 1)
- FVC [% pred] (at inclusion in extension trial, i.e. Visit 1)
- FEV1/FVC (at inclusion in extension trial, i.e. Visit 1)

5.4.2 Compliance

Only compliance in the extension trial will be considered.

5.4.2.1 Over the whole trial

Compliance [%] will be calculated as:

$$\frac{Number\ of\ capsules\ actually\ taken}{Number\ of\ capsules\ which\ should\ have\ been\ taken} \times 100\%$$

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

$$(\ Duration\ of\ exposure\ over\ the\ whole\ trial) \times 2,$$

using duration of exposure as defined in Section 5.4.3.1 below. 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, i.e. duration of interruptions due to AE will be subtracted from the duration of the treatment period for compliance calculation.

Compliance [%] will be summarised as continuous variable and in categories:
<50%; >=50 to <80%; >=80 to <=120%; >120%.

If the amount of capsules taken is not reported for at least one expected visit or no final compliance assessment on or after the day of last trial drug intake is available the compliance will not be calculated.

5.4.2.2 Over 48 weeks and over 96 weeks

The number of capsules which should have been taken over 48 weeks and over 96 weeks respectively will be calculated as:

$$(Date\ of\ last\ nintedanib\ intake^{[1]} - Date\ of\ first\ nintedanib\ intake + 1) \times 2$$

[1] Or Week 48/Week 96 compliance assessment, if earlier.

In case of last nintedanib intake happened until Week 48/Week 96 compliance assessment, half a day will be subtracted assuming that only one capsule was taken on day of last nintedanib intake.

5.4.3 Exposure

Only exposure in the extension trial will be considered.

5.4.3.1 Over the whole trial

Duration of exposure [days] over the whole trial will be calculated as

$$Date\ of\ last\ nintedanib\ intake - Date\ of\ first\ nintedanib\ intake + 0.5\ days,$$

assuming that only one capsule was taken on day of last nintedanib intake. Treatment interruptions will not be subtracted from this duration of exposure.

Duration of exposure [weeks] will be calculated as

$$\frac{Duration\ of\ exposure\ [days]}{7}$$

Duration of exposure [months] will be calculated as

$$\frac{Duration\ of\ exposure\ [days]}{30.5}$$

Duration of exposure will be summarised as continuous variable [months] and in categories:

- <=3 months (91 days);
- >3 to <=6 months (182 days);
- >6 to <=12 months (365 days);
- >12 to <=18 months (547 days);
- >18 to <=24 months (730 days);
- >24 to <=36 months (1095 days);
- >36 months

Further categories might be defined if needed.

Duration of exposure on actual dose (100 or 150 mg bid) [months] will be calculated as

$$\frac{Sum\ of\ each\ continuous\ duration\ of\ exposure\ to\ 100/150\ mg\ bid\ [days]}{30.5}$$

This duration of exposure will be adjusted for treatment interruptions, dose reductions and dose increases and will be summarised as continuous variable and in categories:

- No 100/150 mg
- <=3 months (91 days);
- >3 to <=6 months (182 days);
- >6 to <=12 months (365 days);
- >12 to <=18 months (547 days);
- >18 to <=24 months (730 days);
- >24 to <=36 months (1095 days);
- >36 months

Off-treatment duration [weeks] will be calculated as

$$\frac{Sum\ of\ each\ continuous\ duration\ of\ off-treatment\ periods\ [days]}{7}$$

Total dose [g] will be calculated as

*Duration of exp. on 100 mg [days] * 0.2 g + Duration of exp. on 150 mg [days] * 0.3 g.*

Dose intensity [%] will be calculated as

$$\frac{Total\ dose\ [g]}{0.3\ g \times Duration\ of\ exposure\ [days]} \times 100\%$$

Dose intensity [%] will be summarised as continuous variable and in categories:

- <=30%; >30 to <=50%; >50 to <=90%; >90 to <100%; =100%.
- <=90%, >90%

5.4.3.1.1 Exposure-related time-to-event analyses

Exposure-related time-to-event analyses will be performed for the following items:

- 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]

Time-to-event [days] for exposure-related analyses is derived based on first nintedanib intake in extension trial as

Date of event/censoring – Date of first nintedanib intake + 1 day

For the above mentioned time-to-event analyses subjects with no such event occurred during the extension trial will be censored according to the mechanism for censoring as described in Table 5.4.3.1.1: 1.

[redacted]

These time-to-event analyses will also be summarised in categories:

- <=1 month (31 days)
- >1 to <=3 months (91 days)
- >3 to <=6 months (182 days)
- >6 to <=12 months (365 days)
- >12 to <=18 months (547 days)
- >18 to <=24 months (730 days)
- >24 to <=36 months (1095 days)
- >36 months
- Censored

Further categories might be defined if needed.

5.4.3.2 Over 48 weeks and over 96 weeks

Duration of exposure [days] over 48 weeks and over 96 weeks respectively will be calculated as

Date of last nintedanib intake[1] – Date of first nintedanib intake + 1 day

[1] Or Week 48/Week 96 time point (Day 379/Day 715, i.e. 378/714 days after date of Visit 1), if earlier.

In case of last nintedanib intake happened until Week 48/Week 96 time point, half a day will be subtracted assuming that only one capsule was taken on day of last nintedanib intake. Treatment interruptions will not be subtracted from this duration of exposure.

Other variables relative to exposure, such as for example duration of exposure [months] or duration off-treatment, total dose or dose intensity will be derived as defined in Section 5.4.3.1. However, last category for duration of exposure and duration of exposure on actual dose will be “>12 months” for the analyses over 48 weeks and “>18 months” for the analyses over 96 weeks.

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]
- ALT >=5 fold ULN and/or AST >=5 fold ULN
- ALT >=3 fold ULN and/or AST >=3 fold ULN

[1] 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 subjects 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 [2]
- ALT and/or AST >=3 fold ULN and unexplained INR >1.5 [2]
- ALT and/or AST >=3 fold ULN and unexplained eosinophilia (>5%) [2]
- 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 Table 9.3: 1 for the list of relevant MedDRA preferred terms to support the derivation of a potential hepatic injury)

[2] in the same blood draw sample

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 and AST and/or ALT
- >=1.5 fold ULN; >=2 fold ULN for Bilirubin
- >=1.5xULN; >=2 fold ULN for alkaline phosphatase (ALK)
- >=3xULN for Gamma-Glutamyl-Transferase (GGT)

Note: ULN refers to the Upper Limit of Normal from the central or local laboratory analysing samples from this extension trial.

5.4.4.1 Time-to-event analyses for liver enzyme elevations

Time to first occurrence in extension trial of the above described liver enzyme elevations [days] will be analysed as

Date of event/censoring – Date of first nintedanib intake + 1 day

Subjects with no such event occurred during the trial will be censored according to the mechanism for censoring as described in Table 5.4.4.1: 1.

These times to onset of first event in extension trial will also be summarised in categories:

- <=1 month (31 days)
- >1 to <=3 months (91 days)
- >3 to <=6 months (182 days)
- >6 to <=12 months (365 days)
- >12 to <=18 months (547 days)
- >18 to <=24 months (730 days)
- >24 to <=36 months (1095 days)
- >36 months
- Censored

Further categories might be defined if needed.

5.4.5 Marked changes in vital signs

A marked increase in vital signs 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,

at any visit.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

For treatment specifications, please refer to CTP Section 4.

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.

- Post-IC period (optional[a]): From date of informed consent to first nintedanib intake.
- Treatment period: From first nintedanib intake (or re-start of treatment if interruption) to last nintedanib intake (or 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 last nintedanib intake plus one day to last nintedanib intake plus 28 days plus one day.
- Follow-up period (optional[a]): From last nintedanib intake plus 28 days plus one day (after residual effect period) to last contact date (as collected on the end of study eCRF page) plus one day. This period is only created if last nintedanib intake took place more than 28 days before last contact date (as collected on the end of study eCRF page).
- Post-study period (optional[a]): From last nintedanib intake plus 28 days plus one day or from last contact date (as collected on the end of study eCRF page) plus one day, whichever occurs later.

[a] This period is optional insofar as it does not necessarily exist for all subjects.
[b] In addition, a residual effect period of 7 days will be used for safety analyses to more closely reflect the period of time after the last nintedanib intake.

For subjects who did not receive any dose of nintedanib in extension trial, Post-IC period is the only period defined.

For subjects who died during the trial, periods with above defined start date after date of death do not exist and last existing period is defined until date of death plus one day only.

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

No per protocol set analysis will be performed for this study; however, the following list in Table 6.2: 1 below defines the different categories of potentially important protocol deviations (iPD), and it shows whether subjects will potentially be excluded from evaluations performed in this trial. Potentially iPDs will be handled according to BI standards (3). The proportion of subjects 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		**Eligibility Criteria**		
	A1	Potential risk related to fetotoxicity a) Women who are pregnant, nursing, or who plan to become pregnant while in the trial b) Women who are of childbearing potential not willing or able to use highly effective methods of birth control per ICH M3	a) (exclusion criterion 6 met) b) (inclusion criterion 3 not met) and subject entered the trial *Automatic iPD* *Additional note:* *In the CTR Table it should show which criteria are violated; however, deviations of multiple sub-categories will only count once towards the overall category.*	None
	A2	Subjects with other underlying diseases or conditions that may put the subject at risk when participating in the trial	Exclusion criterion 1 met and subject entered the trial *Automatic iPD*	None
B		**Informed Consent**		
	B1	Informed consent not given	Inclusion criterion 2 not met *Automatic iPD*	All
	B2	Informed consent given too late	eCRF date of informed consent is after date of Visit 1 *Automatic iPD* *Additional note:* *Signature of the wrong IC version, and later signature of the correct one will also be part of this iPD category. This can however only be determined via a manual process.*	None

Table 6.2: 1 Important protocol deviations (continued)

Category/Code		Description	Requirements	Excluded from
C		**Trial Medication and Randomization**		
	C1	Trial medication not interrupted a) when ALT or AST >= 5 fold ULN b) or dose reduced when ALT or AST >= 3fold to < 5 fold ULN	Based on eCRF dose interruption and lab values between first drug intake and EOT *Manual iPD based on MQR outputs* *Additional note:* *In the CTR Table it should show which criteria are violated; however, deviations of multiple sub-categories will only count once towards the overall category.*	None
	C2	Trial medication not permanently discontinued after signs of liver enzyme elevations were observed that a) are indicative of hepatic injury as defined in Section 5.2.5.1.4 and 4.2.1.2 of the CTP b) correspond to ALT or AST >= 3 fold ULN despite dose reduction or treatment interruption for 2 weeks or more	All subjects where signs of liver enzyme elevations are not dealt with according to the requirements of the CTP. *Manual iPD based on MQR outputs* *Additional note:* *In the CTR Table it should show which criteria are violated; however, deviations of multiple sub-categories will only count once towards the overall category.*	None
	C3	Compliance > 120%	In case calculated overall compliance is missing: If the answer to the question "Did the patient take trial medication as instructed?" of the eCRF is "No" at at least one of the visits where the compliance cannot be calculated, then an iPD will be flagged. Otherwise no iPD although calculated overall compliance is missing. *Manual iPD with review of MQR listings*	None
	C4	Incorrect trial medication taken a) 150 mg capsules used instead of 100 mg capsules b) 100 mg capsules used instead of 150 mg capsules c) qd instead of bid	To be discussed on a case by case basis to determine if iPD *Manual iPD with review of MQR listings* *Additional note:* *In the CTR Table it should show which criteria are violated; however, deviations of multiple sub-categories will only count once towards the overall category.*	None

Table 6.2: 1 Important protocol deviations (continued)

Category/Code		Description	Requirements	Excluded from
	C5	Trial medication interrupted more than 4 weeks for drug-related liver enzyme or bilirubin related AE with duration of more than 4 weeks	To be discussed on a case by case basis to determine if iPD *Manual iPD with review of MQR listings*	None
	C6	More than 16 weeks between ALT, AST or BILI lab tests without trial medication interruption	To be discussed on a case by case basis to determine if iPD *Manual iPD with review of MQR listings*	None
D		**Concomitant Medication**		
	D1	Subjects who received any other investigational drug during the entire duration of their study participation	Any occurrence of such concomitant therapy is to be flagged as iPD. *Manual iPD with review of MQR outputs* *Additional note:* *In the CTR Table it should show which medication was taken; however, deviations regarding multiple medications will only count once towards the overall category.*	None

Automatic PDs are those detected via an automated programming process using SAS®.

6.3 SUBJECT SETS ANALYSED

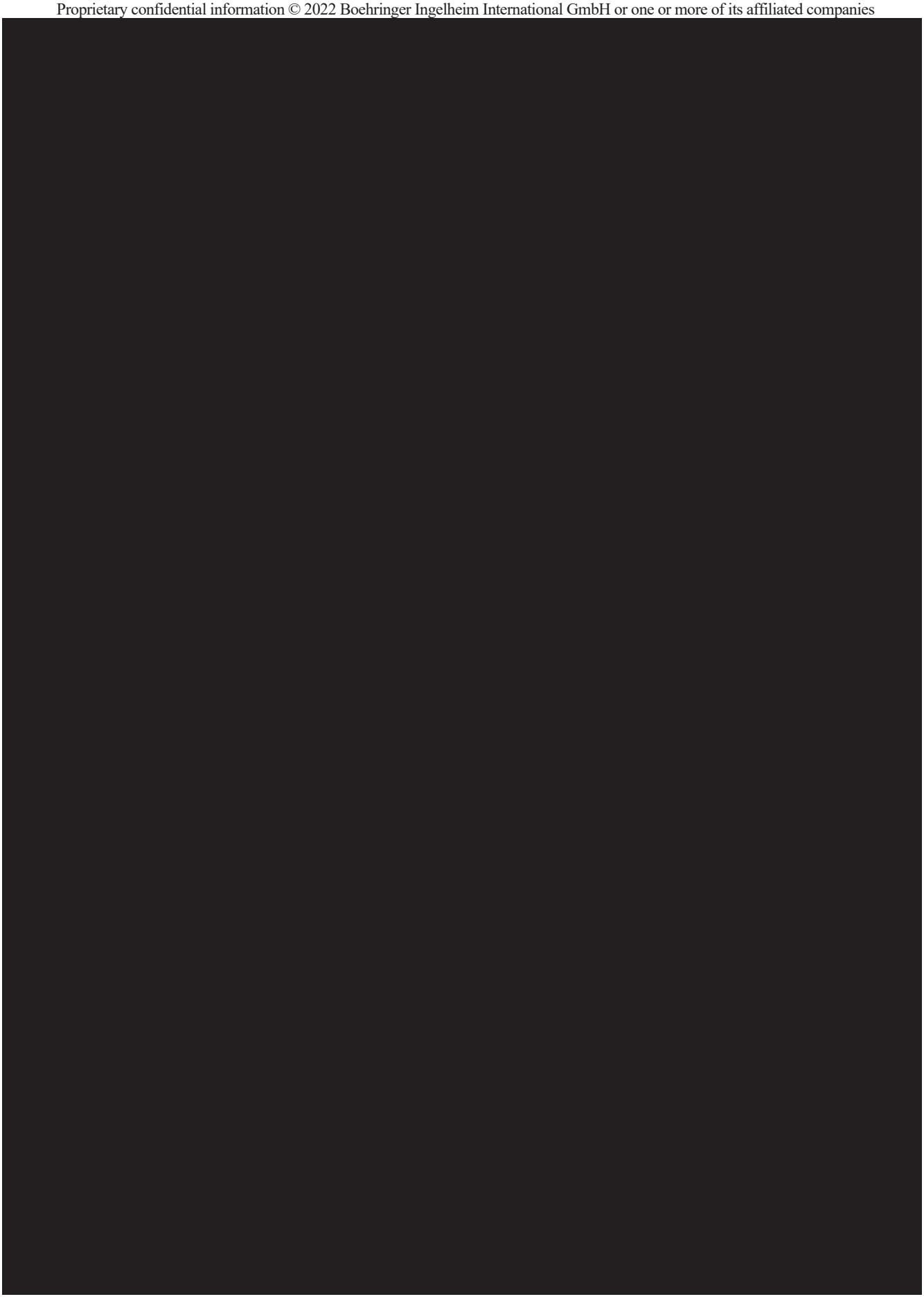
- Screened Set (SCS):
  This subject set includes all subjects having signed informed consent.

- Treated Set (TS):
  This subject set includes all subjects who were dispensed trial medication (nintedanib) and were documented to have taken at least one dose of open-label trial medication (nintedanib).

- Treated Set – 150 mg bid starting dose (TS150S)
  This subject set includes all subjects who were dispensed trial medication (nintedanib) and were documented to have taken nintedanib 150 mg bid as starting dose of open-label trial medication.

All evaluations will be based on the treated set (TS), unless otherwise stated.

Subjects will be analysed according to their randomised treatment group in the parent trial (Placebo or Nintedanib) and overall (Total column).



[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

6.6.1 Primary endpoint

Missing or incomplete AE dates will be imputed according to BI standards (see “Handling of missing and incomplete AE dates”) (6).

[redacted]

[redacted]

6.6.3 Other variables

[redacted]

6.6.3.2 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. Imputed end dates must not be after date of death or last contact date as collected on the end of study eCRF page.

6.6.3.3 Exposure

6.6.3.3.1 Permanent trial drug discontinuation

A missing or incomplete date of last nintedanib intake will be imputed that the derived date is the latest possible date which is on or before date of death, and on or before last contact date from end of study eCRF page.

6.6.3.3.2 Treatment interruptions

For the definition of off-treatment periods an incomplete start or end date for a treatment interruption will be imputed the same way as specified for time-to-event analyses in Section 6.6.2.2. . For duration of interruption no imputation will be applied, i.e. interruptions with missing or incomplete start or end date will have duration missing. Overall duration of interruptions per subject will be missing in these cases as well.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

As a general rule, the last assessment/measurement before or on the date of Visit 1 will be used as baseline.

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, i.e. follow-up visit will be displayed in listings (where applicable) whenever it was performed. A follow-up visit is only scheduled for subjects who prematurely discontinued nintedanib due to adverse event.

Table 6.7: 2 Time windowing rules for physical exam and vital signs

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	Baseline	1
2	22	21	2	2 weeks	15
23	43	21	3	4 weeks	29
44	71	28	4	8 weeks	57
72	127	56	5	12 weeks	85
128	211	84	6	24 weeks	169
212	295	84	7	36 weeks	253
296	379	84	8	48 weeks	337
380	463	84	9	60 weeks	421
464	547	84	10	72 weeks	505
548	631	84	11	84 weeks	589
632	715	84	12 *(p)*	96 weeks	673 (V_p)
$V_p + 1$ $+ \frac{V_{p+1} - V_p}{2}$	V_{p+1} $+ \frac{V_{p+2} - V_{p+1}}{2}$	$\frac{V_{p+2} - V_p}{2}$	$p + 1$	…	V_{p+1} $= V_p + 12 \times 7$
…	…	…	…	Every 12 weeks thereafter	…

V_p denotes the planned day of the visit

[1] Date of Visit 1 in extension trial is taken into account as a reference to calculate time windows

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
1	1	1	1	Baseline	1
2	22	21	2	2 weeks	15
23	43	21	3	4 weeks	29
44	71	28	4	8 weeks	57
72	106	35	5	12 weeks	85
107	148	42	5a [2]	18 weeks	127
149	190	42	6	24 weeks	169
191	232	42	6a [2]	30 weeks	211
233	274	42	7	36 weeks	253
275	316	42	7a [2]	42 weeks	295
317	379	63	8	48 weeks	337
380	463	84	9	60 weeks	421
464	547	84	10	72 weeks	505
548	631	84	11	84 weeks	589
632	715	84	12 *(p)*	96 weeks	673 (V_p)
$V_p + 1$ $+ \frac{V_{p+1} - V_p}{2}$	V_{p+1} $+ \frac{V_{p+2} - V_{p+1}}{2}$	$\frac{V_{p+2} - V_p}{2}$	$p + 1$	…	V_{p+1} $= V_p + 12 \times 7$
…	…	…	…	Every 12 weeks thereafter	…

V_p denotes the planned day of the visit

[1] Date of Visit 1 in extension trial is taken into account as a reference to calculate time windows

[2] Intermediate lab tests ('a'-Visits) to be done as needed for additional safety monitoring at the discretion of the investigator and do not necessarily need to be a site visit.

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 day of the visit will be taken into account. In case two measurements are equidistant from the planned day of the visit, then the last one will be picked.

7. PLANNED ANALYSIS

Unless otherwise specified, all analyses described in this section will be done on the Treated Set.

The labelling and display format of statistical parameters will follow BI standards (9). For End-Of-Text (EoT) 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 outside the expected range, 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 subjects in the respective subject set whether they have non-missing values or not). The precision for percentages should be one decimal point. The category missing will be displayed only if there are actually missing values.

Unless otherwise specified, all analyses will be provided by randomised treatment group in the parent trial (Placebo or Nintedanib) and overall (Total column).

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

A table in the CTR will present the number of subjects screened, entered and treated.

The completion status of subjects will be summarised by frequency counts with regards to planned treatment period as well as planned (trial) observation period together with corresponding reasons for non-completion. For potential interim analyses the number of subjects who are still ongoing in the trial will be presented in addition.

A similar summary will be provided regarding the first 48 weeks or the first 96 weeks only, i.e. until Week 48/Week 96 time point (Day 379/Day 715, i.e. 378/714 days after date of Visit 1).

Descriptive statistics as well as frequency counts will be provided for all demographic and baseline characteristics depicted in Section 5.4.1.

7.2 CONCOMITANT DISEASES AND MEDICATION

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

7.2.1 Baseline conditions and cardiovascular medical history

Baseline conditions will be coded using the current Medical Dictionary for Regulatory Activities (MedDRA) version in use at BI at the time of (interim) database lock. They will be summarised by MedDRA system organ class (SOC) and preferred term (PT). The CTR table will show the counts of subjects with a baseline condition in each SOC (SOC sorted by standard European Medicines Agency (EMA) order) and then the conditions (preferred terms) under that SOC in descending order of overall prevalence (Total column).

The relevant cardiovascular medical history will be summarised, with particular focus on myocardial infarction, transient ischemic attacks, stroke, cardiac arrhythmia and heart failure.

7.2.2 Concomitant therapies

Concomitant therapies will be coded using the current World Health Organization Drug Dictionary (WHO-DD) version in use at BI at the time of (interim) database lock.

Concomitant therapies will be assigned to the following categories:

- Previous therapies: All therapies with a stop date before date of Visit 1 in extension trial.
- Baseline therapies: All therapies with a start date before date of first nintedanib intake in extension trial and a stop date after or on the day of Visit 1 in extension trial (or ongoing after completion of extension trial).
- On-treatment concomitant therapies: All therapies with a start date after or on the day of first nintedanib intake in extension trial and before or on the day of last nintedanib intake in extension trial.
- Post-study drug discontinuation therapies: All therapies with a start date after last nintedanib intake in extension trial and before or on the last contact as collected on the end of study eCRF page.

Concomitant therapies will be described over the entire duration of the extension trial. Similar summaries will be provided regarding the first 48 weeks or the first 96 weeks only, i.e. until Week 48/Week 96 time point (Day 379/Day 715, i.e. 378/714 days after date of Visit 1).

Table 7.2.2: 1 and Table 7.2.2: 2 summarise the concomitant therapy outputs which will be provided for analyses over the whole trial, over 48 weeks and over 96 weeks respectively, for each category of concomitant therapy created.

Summaries by Anatomical Therapeutic Chemical (ATC) classification and preferred name (PN) will use the ATC3 levels, and will be sorted by alphabetical ATC class and by decreasing order of overall prevalence (Total column) of PN within ATC class.

Summaries by Customised Drug Grouping (CDG) and PN will be sorted by alphabetical CDG name and by decreasing order of overall prevalence (Total column) of PN within CDG. CDGs are built using WHO-DD Standardised Drug Groupings (SDG), Sub-SDGs and ATC4 levels. CDGs are listed in Section 9.2.

Table 7.2.2: 1 Concomitant therapy outputs over the whole trial

	By ATC and PN	**By CDG and PN**
Baseline therapies	X	X
On-treatment concomitant therapies	X	X
All baseline and on-treatment concomitant therapies	X	X
All baseline and on-treatment concomitant therapies with an incidence greater than 2% (in at least one treatment arm)	X	Not required
Post-study drug discontinuation therapies	Not required	Not required

Table 7.2.2: 2 Concomitant therapy outputs over 48 weeks and over 96 weeks

	By ATC and PN	**By CDG and PN**
Baseline therapies	Not required	Not required
On-treatment concomitant therapies	X	X
All baseline and on-treatment concomitant therapies	X	X
All baseline and on-treatment concomitant therapies with a an incidence greater than 2% (in at least one treatment arm)	X	Not required
Post-study drug discontinuation therapies	Not required	Not required

7.3 TREATMENT COMPLIANCE

Only descriptive statistics are planned for this section of the report. The evaluations will be done over the whole trial. A similar summary will be provided regarding the first 48 weeks or the first 96 weeks only.

7.4 PRIMARY ENDPOINT

The primary objective of the trial is to assess the safety of Nintedanib, so please refer to Section 7.8.1.4 for detailed analyses.

7.5 SECONDARY ENDPOINTS

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

7.7 EXTENT OF EXPOSURE

Exposure will be summarised over the whole trial. Similar summaries will be provided regarding the first 48 weeks or the first 96 weeks only.

A summary table showing the duration on treatment in extension trial in months (both, mean and frequency in categories, see Section 5.4.3) will be presented together with duration of exposure in patient-years, total dose (mean) and dose intensity (both, mean and frequency in categories, see Section 5.4.3).

Besides, a summary table showing the duration on actual treatment dose in months (both, mean and frequency in categories, see Section 5.4.3) and off-treatment duration in weeks (mean) will be performed. This will take into account the actual dose following dose reductions or increases. Furthermore, the proportion of subjects on each dose actually taken as first dose in 1199-0248 will be presented.

A summary of dose reductions will be performed including number of subjects with at least one dose reduction, number of dose reductions (total and per subject) and reasons for dose reduction, as well as time to first dose reduction in extension trial (both, quartiles from Kaplan-Meier curve and frequency in categories, see Section 5.3.3.3). Dose intensity of subjects with at least one dose reduction will be summarised in addition. A similar summary will be performed for treatment interruptions. Additionally, the (total) duration of interruptions per subject will be summarised. For dose increases to 150 mg only number of subjects with at least one increase and total number of increases will be summarised.

Time to first dose reduction will only be calculated for subjects with first dose in extension trial 150 mg (see Section 6.3 for further information on this analysis set).

As for the other exposure-related time-to-event analyses, time to premature treatment discontinuation and time to first dose reduction or treatment interruption will be summarised over the whole trial on the Treated Set according to both, quartiles from Kaplan-Meier curve and frequency in categories (see Section 5.4.3.1.1).

Separate Kaplan-Meier plots will be presented by randomised treatment group in the parent trial (Placebo or Nintedanib) and overall (total group) for all exposure-related time-to-event analyses. No statistical tests will be performed. Kaplan-Meier plots present data over the whole trial. Kaplan Meier estimates and confidence intervals (using Greenwood variance formula) for the cumulated time-to-event rate will be calculated at 48 weeks (378 days after date of first nintedanib intake), at every further 48 weeks (336 days) and over the whole trial.

7.8 SAFETY ANALYSIS

All safety analyses will be performed over the whole trial on the treated set. Similar summaries will be provided regarding the first 48 weeks or the first 96 weeks only.

The analysis of safety data will be based on the concept of treatment emergent AEs or measurements. That means that, for analyses over the whole trial, all AEs/laboratory or vital sign measurements occurring between first nintedanib intake till last nintedanib intake + 28 days will be assigned to the on-treatment period. For analyses over 48 weeks and 96 weeks respectively the on-treatment period is defined from date of first nintedanib intake until date of last nintedanib intake + 28 days, or until Week 48/Week 96 time point (Day 379/ Day 715, i.e. 378/714 days after date of Visit 1), if earlier.

All analyses will be performed according to randomised treatment group in the parent trial and overall.

7.8.1 Adverse Events

Adverse events will be coded using the current Medical Dictionary for Regulatory Activities (MedDRA) version in use at BI at the time of database lock. Unless otherwise specified, the analyses of AEs 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 eCRF will be collapsed into an AE provided that all of the following applies:

- All AE attributes are identical (Low Level term ((LLT), intensity, action taken, therapy required, seriousness, reason for seriousness, relationship, outcome, AESI, CTCAE if applicable)

- 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 (6, 7).

All AEs occurring before first nintedanib intake will be assigned to ‘Post-IC period’ and all AEs occurring after the residual effect period will be assigned to ‘follow-up’ or ‘post-study’ (for listings only). All adverse events occurring between the start and the end of an interruption of nintedanib will be assigned to ‘off-treatment’ period in the listings. For details on the treatment definition, see Section 6.1.

According to ICH E3 (*2*), AEs classified as ‘other significant’ need to be reported and will include those non-serious and AEs 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.

Summary tables will be produced for non-serious adverse events meeting part (i) of the definition. Part (ii) of the definition will be covered by the analysis of laboratory data. Please refer to Section 7.8.2 for further information.

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

Table 7.8.1: 1 Protocol-specified AESI

Protocol-specified AESI	**AE type**
Gastrointestinal perforation	AEs established for other tyrosine kinase inhibitors as possible adverse reactions
Hepatic injury	Other AEs of interest

An overall summary of AEs will be presented, by treatment group in the parent trial and overall.

The frequency of subjects with adverse events, will be summarised by randomised treatment group in parent trial (and overall), primary system organ class (SOC) and preferred term (PT). This will be repeated for subjects with adverse events occurring with an incidence in preferred term greater than 5% (in at least one treatment arm). For analyses over the whole trial, time at risk and exposure-adjusted incidence rates with 95% confidence intervals will be presented in addition. Please refer to Section 7.8.1.1 for further details on the derivation of time at risk and exposure-adjusted incidence rates.

Separate tables will be provided for subjects with

- serious AEs (SAEs)
- severe AEs
- other significant AEs (as defined by point (i) of the ICH E3 definition indicated above)
- AEs leading to dose reduction
- AEs leading to permanent treatment discontinuation
- investigator defined drug-related AEs
- AEs leading to death
- protocol-specified AEs of special interest (AESIs) (as ticked on the AE page of the eCRF)
- investigator defined drug-related SAEs.

The system organ classes (SOC) will be sorted according to the standard sort order specified by EMA, preferred terms will be sorted by decreasing frequency in the total column (within SOC).

7.8.1.1 Exposure adjusted analysis of adverse events

Exposure adjusted analysis of AEs will be presented for analyses over the whole trial. 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

$$\frac{\sum time\ at\ risk\ [days] accross\ all\ contributing\ subjects}{365.25}$$

with for each subjects the time at risk [days] defined as follows:

- *Date of first onset of the AE – date of first nintedanib intake in extension trial +1 day* for subjects with the specific AE

- *End of time at risk – date of first nintedanib intake in extension trial + 1 day*

  for subjects without the specific AE.

The end of time at risk is the minimum of either "date of last nintedanib intake + 28 days", date of last contact date as collected on the end of study eCRF page, date of death or date of the (interim) database lock.

The AE incidence rate [1/100 patient-years (pt-yrs)] will be calculated as

$$\frac{Number\ of\ subjects\ with\ specific\ AE}{Total\ specific\ AE\ time\ at\ risk\ [years]} \times 100$$

The 95% confidence intervals for incidence rates are derived using the method described by Rothman and Greenland (2008) (12).

7.8.1.2 Additional analysis of adverse event groupings by system

Further adverse event groupings by safety topic have been defined outside the trial protocol, which will be continuously updated at project level (11). These safety topics are deemed of particular importance, and these definitions can be based on selection of coded terms based on MedDRA. The latest approved version of the project level overview archived prior to (interim) DBL will be used in the CTR.

The frequency of subjects with adverse events within these groupings will be summarised by system, safety topic, subcategory (if applicable) and preferred term. These displays will focus on subjects with any adverse event, subjects with serious adverse events and subjects with investigator defined drug-related adverse events. For analyses over the whole trial, time at risk and exposure-adjusted incidence rates with 95% confidence intervals will be presented in addition. Please refer to Section 7.8.1.1 for further details on the derivation of time at risk and exposure-adjusted incidence rates.

Systems will be presented in alphabetical order. Safety topics, subcategories (if applicable) and preferred term will be sorted by decreasing frequency in the total column (within system, safety topic or subcategory).

7.8.1.3 Adverse events with additional information collection

Diarrhoea, bleeding and ILD 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 same applies to ILD.

The frequency of subjects with AEs with additional information collection will be summarised by randomised treatment group in the parent trial (and overall), primary SOC and

PT separately for diarrhoea, bleeding and ILD. The additional information collected will also be summarised at the AE level (occurrence level) rather than at the subject level separately for diarrhoea, bleeding and ILD.

For the time to first onset of diarrhoea, bleeding or ILD, respectively, in extension trial Kaplan-Meier plots by treatment will be created. The same censoring rules and categories as for time to first liver enzyme elevation in extension trial will be used. See Section 5.4.4.1 for details.

7.8.1.4 Analysis of the primary endpoint

Only descriptive analyses will be performed. The same methods (i.e. number and frequency of subjects with adverse events, time at risk and exposure-adjusted incidence rates with 95% CI) as described in Section 7.8.1 and Section 7.8.1.1 will be used. The primary endpoint will be assessed on data collected over the whole trial and regardless of randomised treatment group in the parent trial. .

[redacted]

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 (8). Please refer to CTP Section 7.3.4. Laboratory measurements and their corresponding reference range will be used as they were transmitted from the central laboratory or entered in the eCRF for local laboratory data, except for measurements not reported in the standard unit. Such measurements and corresponding reference ranges will be transposed into the standard unit for the analysis. For INR measurements, no reference range is transmitted by the central laboratory, because the central laboratory does not have information on concomitant medication taken by the subjects, and the reference range for INR depends on whether a subject is taking anticoagulants. The reference ranges for INR will therefore by imputed with 0.8 for the lower limit of normal (LLN) and with 1.2 for the ULN, which correspond to the reference range defined by the central laboratory for subjects not taking anticoagulants and which is more conservative than the range for subjects taking anticoagulants (LLN=2, ULN=3).

7.8.2.2 Liver enzyme and bilirubin elevations

A thorough description of liver enzymes and bilirubin elevations, as defined in Section 5.4.4, will be given over the whole trial by randomised treatment group in the parent trial and overall, including:

- Summary table of liver enzyme elevation
- Summary table of individual maximum liver enzyme and bilirubin elevations
- Time to first onset in extension trial and number of subjects with liver enzyme elevation. The time to onset of first liver enzyme and bilirubin elevation [days] will be summarised according to both, quartiles from Kaplan-Meier curve and frequency in categories (see Section 5.4.4.1).
- Kaplan-Meier plot of time to first liver enzyme elevation in extension trial. No statistical test will be performed. Separate plots will be presented by randomised treatment group in the parent trial and overall.
- Single time course profiles of liver enzymes for subjects having liver enzyme elevations (ALT and/or AST >= 3 fold ULN)
- Graphical displays of potential Hy's law cases

7.8.3 Vital signs

Summary statistics will be presented for observed values and change from baseline by visit over extension trial (please refer to Table 6.7: 2 for time windowing definition). The frequency of subjects with marked changes in vital signs at any visit during the extension trial will also be summarised by randomised treatment group in the parent trial and overall according to the definitions in Section 5.4.5 of this document. Furthermore, minimum relative change from baseline in weight will be summarised (both, mean and frequency in categories, see Section 5.4.5). Categorised relative change in weight over the extension trial will also be described according to Body mass index at inclusion in extension trial in categories (<18.5 kg/m², >=18.5 to <25 kg/m², >=25 to <30kg/m², >=30 kg/m²).

7.8.4 ECG

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

7.8.5 Others

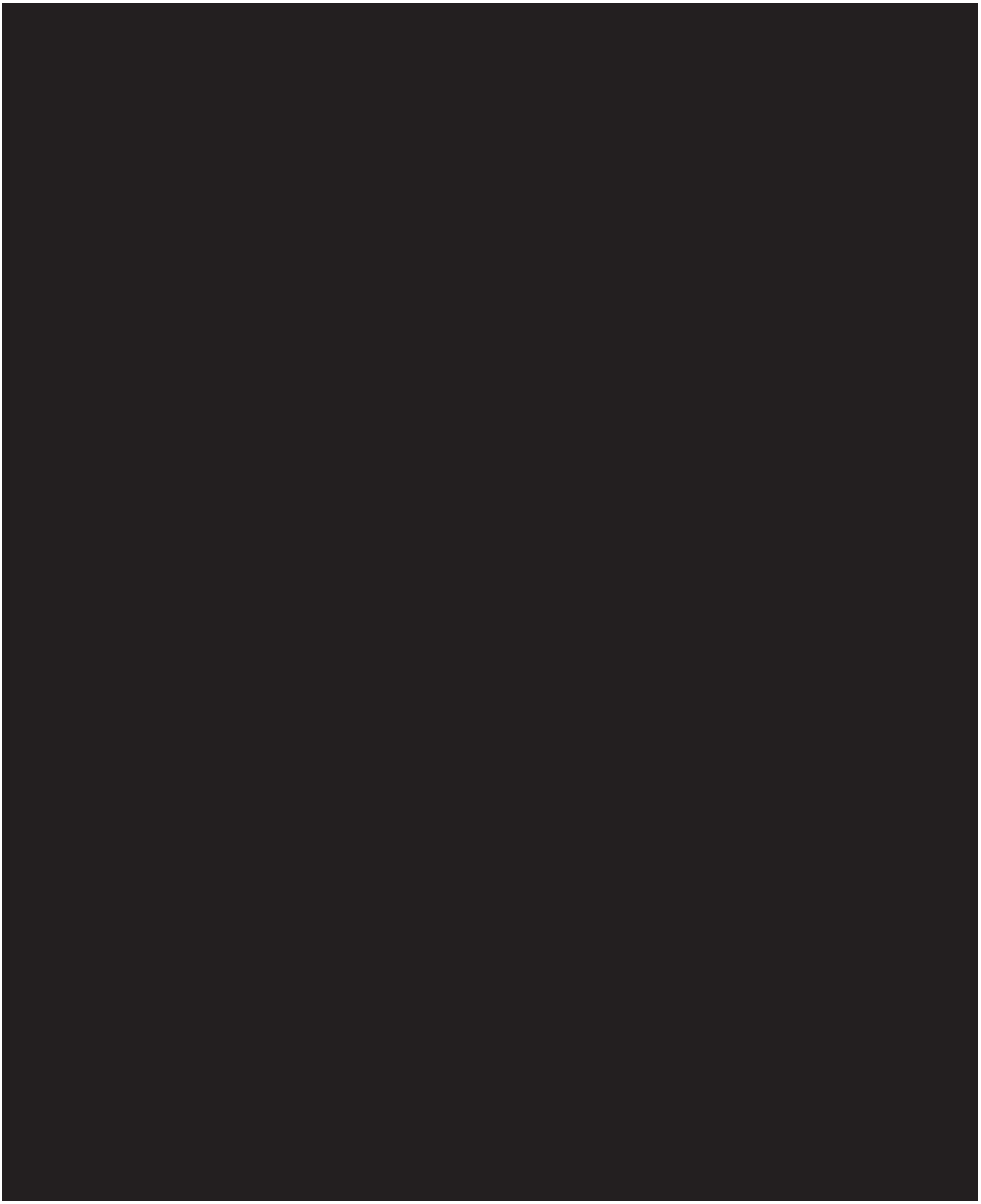
Not applicable.

[redacted]

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.	*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, EMA webpage.
3.	*001-MCS-40-413:* "Identify and Manage Important Protocol Deviations (iPD)", current version; KMED.
4.	*001-MCS-50-415_RD-03:* “Clinical Trial Analysis Decision Log (template) Decision Log”, current version, Group “Biostatistics & Data Sciences”, KMED.
5.	*BI-KMED-BDS-HTG-0023:* “Standard Table Shells for Inferential and Descriptive Company Standard Displays (CSD-Catalogue)”, current version; KMED.
6.	*BI-KMED-BDS-HTG-0035:* “Handling of Missing and Incomplete AE Dates”, current version; KMED.
7.	*BI-KMED-BDS-HTG-0066:* “ Analysis and Presentation of Adverse Event Data from Clinical Trials”, current version; KMED.
8.	*BI-KMED-BDS-HTG-0042:* “Handling, Display and Analysis of Laboratory Data”, current version; KMED.
9.	*BI-KMED-BDS-HTG-0045:* “Standards for Reporting of Clinical Trials and Project Summaries”, current version; KMED.
10.	*BI-KMED-BDS-HTG-0046:* “Trial Statistical Analysis Plan (TSAP) Process and Timelines”, current version; KMED.
11.	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.
12.	Rothman KJ, Greenland S, Lash TL. Modern epidemiology. 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2008. [R10-1239]
13.	Philip H. Quanjer, Multi-ethnic reference values for spirometry for the 3–95 year age range: The global lung function 2012 equations. [R15-0845]

9. ADDITIONAL SECTIONS



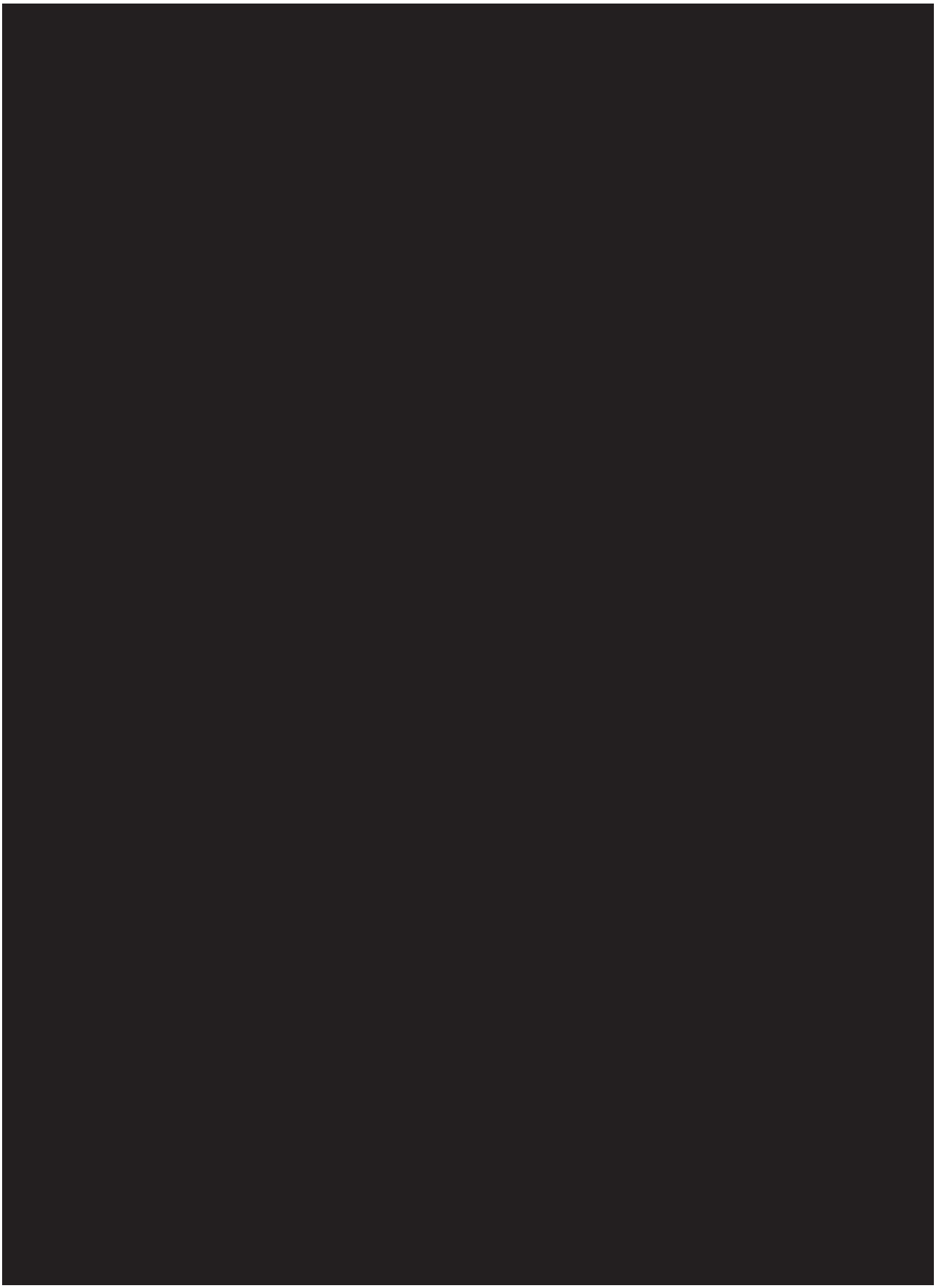
[redacted]

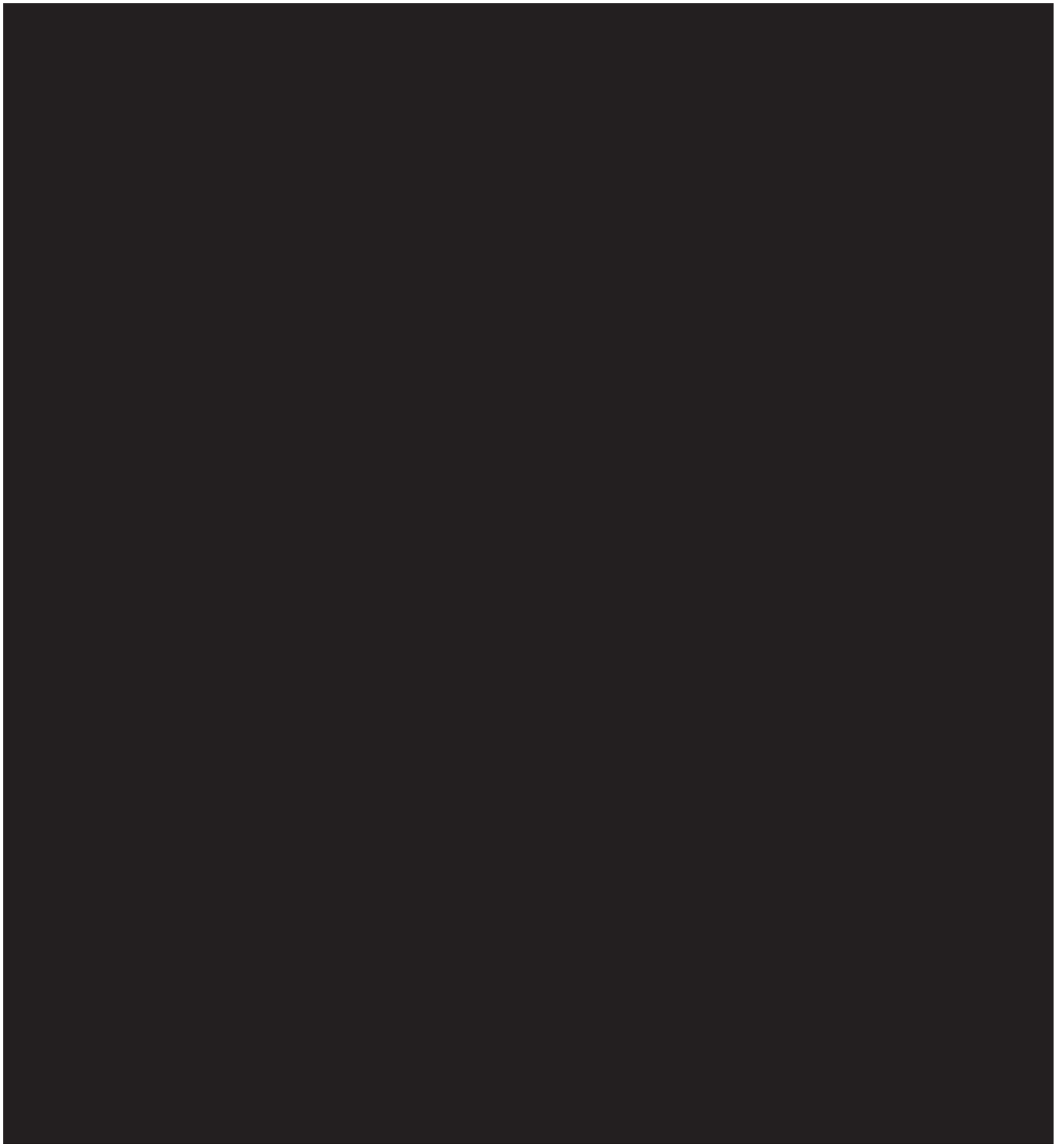
9.3 LIST OF POTENTIAL TERMS FOR HEPATIC INJURY DERIVATION

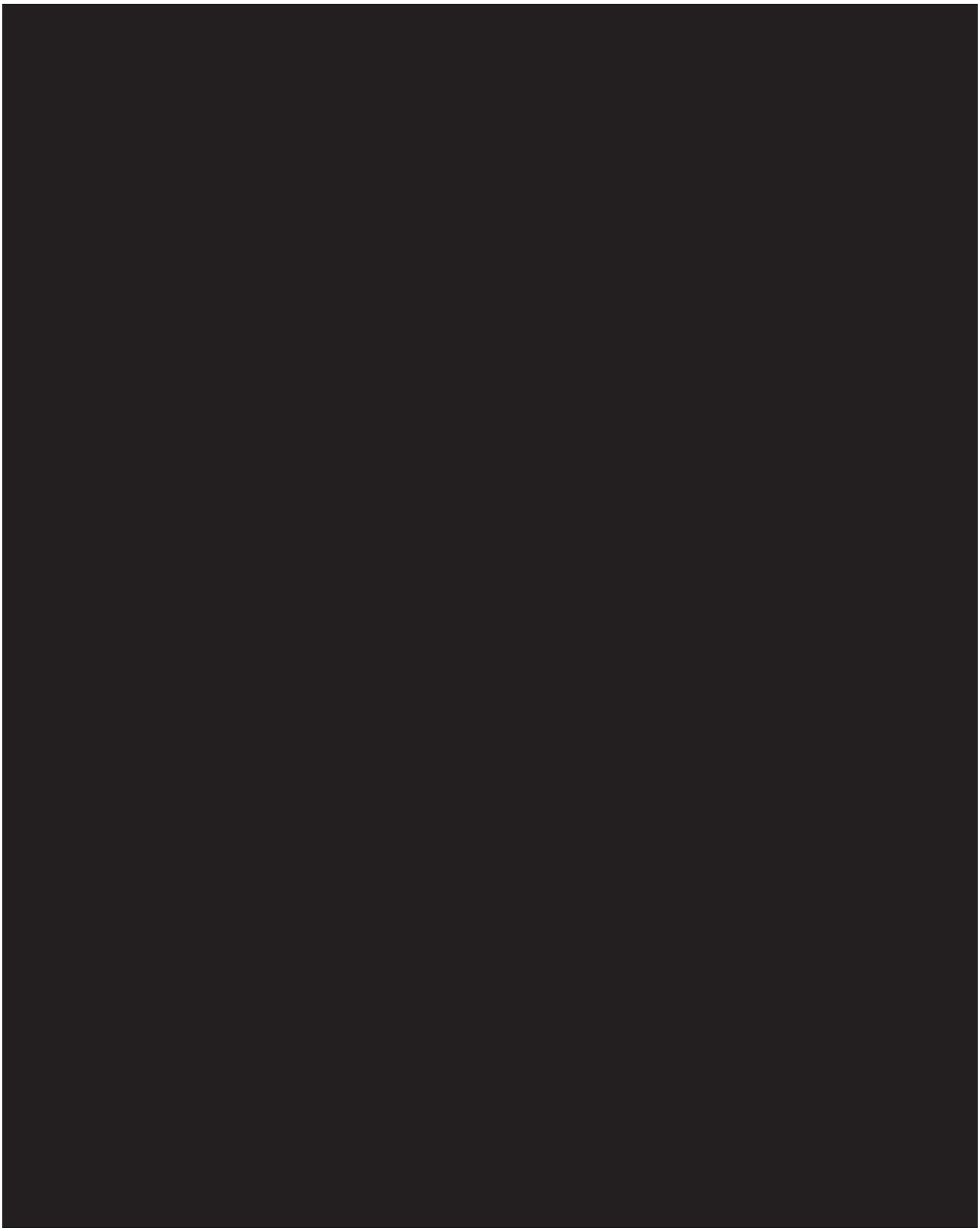
The table below shows the list of potentially relevant MedDRA preferred terms to support the derivation of a potential hepatic injury.

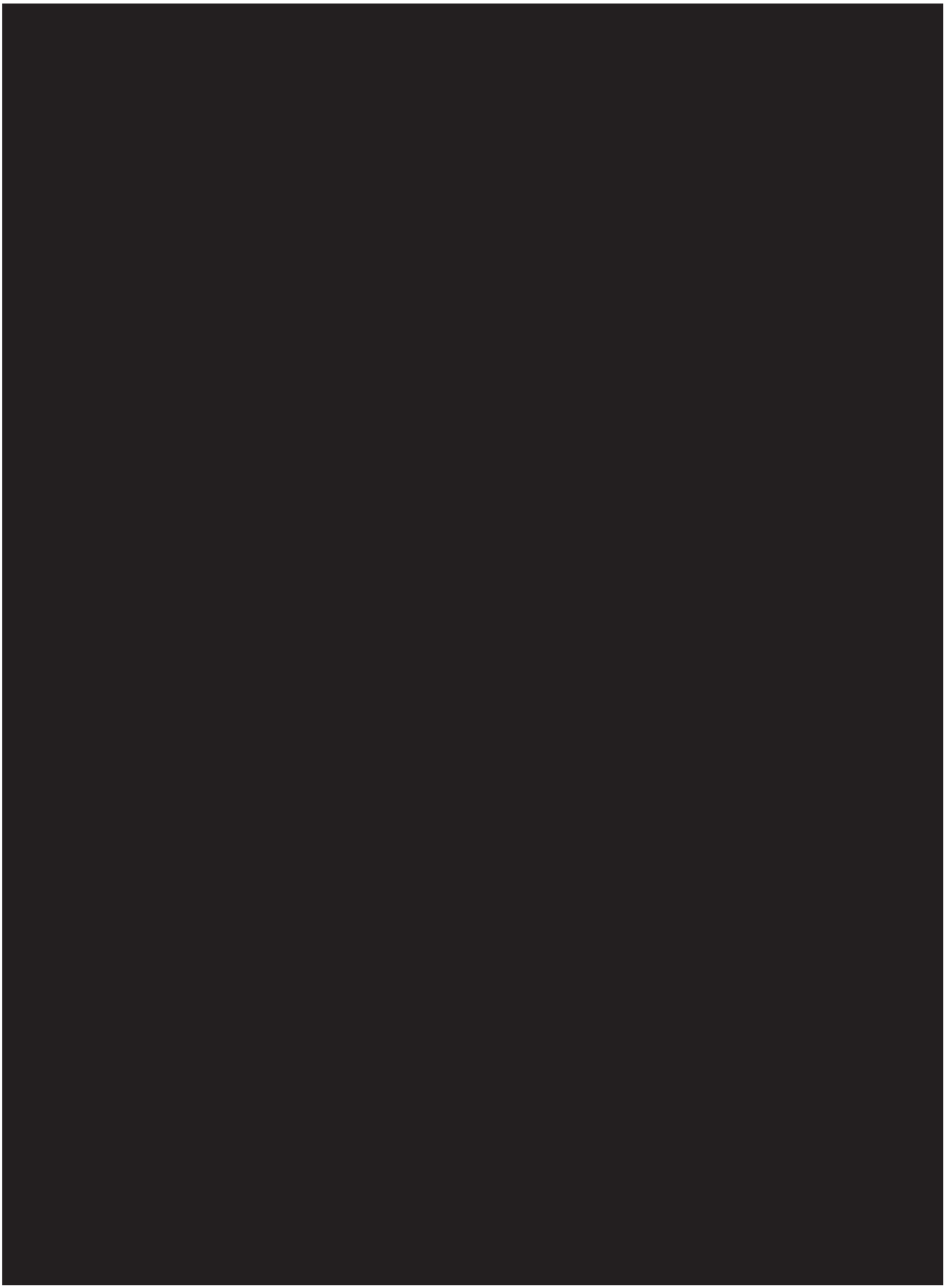
Table 9.3: 1 List of potentially relevant MedDRA preferred terms

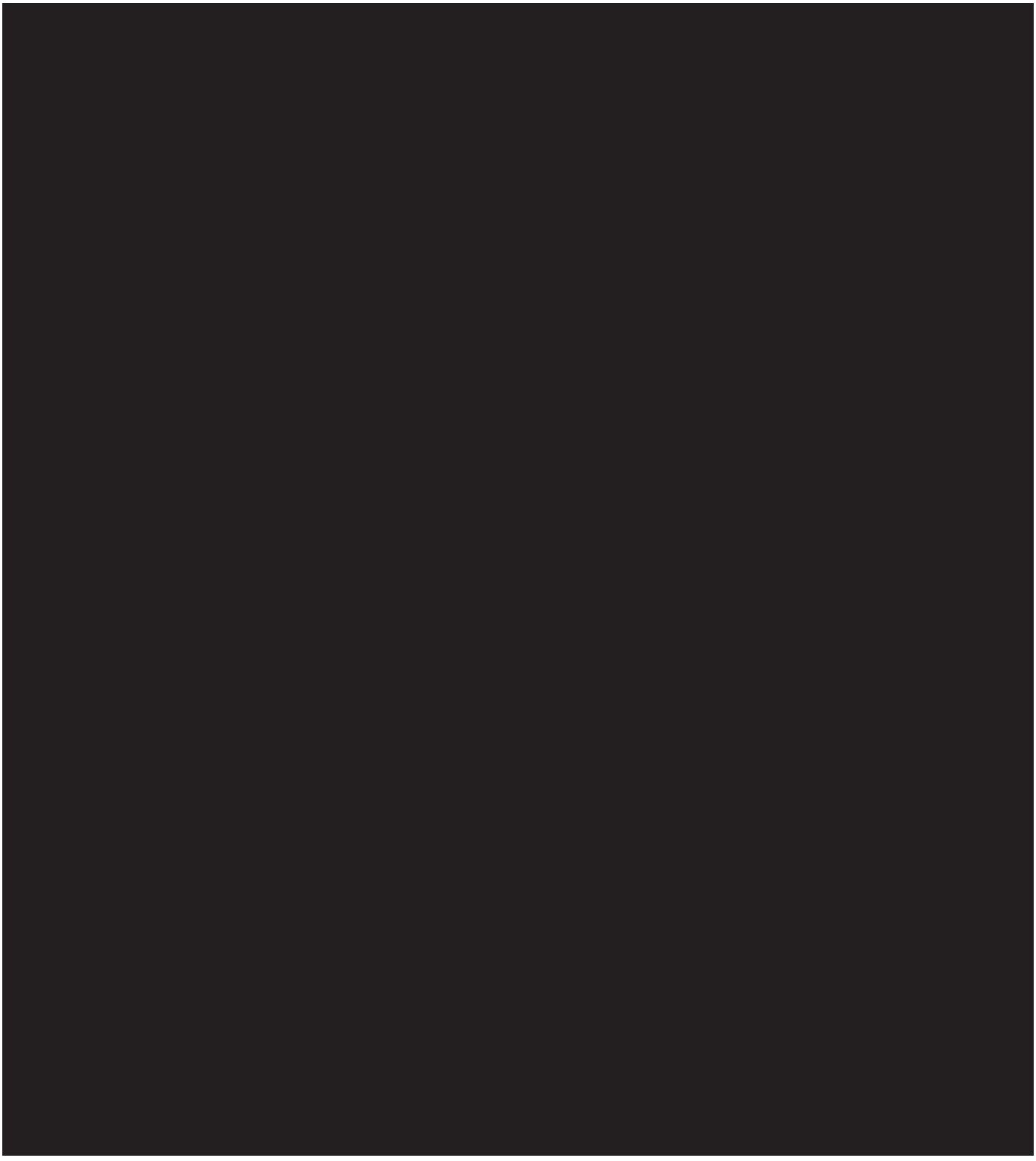
Symptom	Selection via	MedDRA decode	MedDRA code
Vomiting	Preferred Term	Vomiting	10047700
Fatigue	Preferred Term	Fatigue	10016256
Nausea	Preferred Term	Nausea	10028813
Right upper abdominal quadrant pain or tenderness	High Level Term	Gastrointestinal and abdominal pains (excl oral and throat)	10017926
Fever	Preferred Term	Pyrexia	10037660
Rash	BIcMQ	Skin rash potentially related to drug use (BIcMQ) (narrow)	30000087











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	09-DEC-2020	[redacted]	None	This is the version valid at time of interim analysis based on interim data snapshot of 15-OCT-2020 (STATANA scheduled 15-JAN-2021).
2	06-OCT-2021	[redacted]	[redacted]	[redacted]
			5.4.2.2 5.4.3.2	96 weeks analyses specified according to already specified 48 weeks analyses.
			6.2	Important protocol deviations: Further requirements for iPDs A1 and A2 specified: applicable for entered subjects only. Definition of iPD C6 updated: parameters of interest mentioned.
			7.1 7.2.2 7.3 7.7 7.8 7.8.2.2 7.8.3	Wording adapted to keep the specific 48 weeks analyses optional for the final CTR. Option for 96 weeks analyses added accordingly.
			[redacted]	

Table 10: 1 History table (continued)

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
3	11-MAY-2022	[redacted]	4 5.4.3.1.1 7	Wording for "Time to permanent treatment discontinuation" adapted to "Time to premature treatment discontinuation" in order to better reflect what is actually meant. "Permanent" wanted to differentiate from temporary interruptions but is misleading for treatment completers who should not be considered "events" here.
			5	Last spirometry assessment added to list of dates used for derived last contact date when the subject was known to be alive.
			[redacted]	
			7.1 7.2.2 7.3 7.7 7.8	Specific analyses "over 48 weeks" and "over 96 week" respectively are not restricted to the corresponding interim analysis anymore but will also be provided for the final analysis.
			[redacted]	