# Trial Statistical Analysis Plan

**c02035901-05**

| | |
|---|---|
| **BI Trial No.:** | 1199.33 |
| **Title:** | An open-label extension trial of the long term safety of oral BIBF 1120 in patients with Idiopathic Pulmonary Fibrosis (IPF)<br><br>(Including Protocol Amendment 3 [c01765254-09] and local Protocol Amendments in China [c09814738-01] Czech Republic [c09951371-01] Russia [c09951303-01]) and Turkey [c14915336-01]. |
| **Investigational Product(s):** | Nintedanib, BIBF 1120 |
| **Responsible trial statistician(s):** | [redacted]<br><br>Phone : [redacted]<br>Fax : [redacted] |
| **Date of statistical analysis plan:** | 25 JUL 2017 REVISED |
| **Version:** | REVISED |

# 1. TABLE OF CONTENTS

# LIST OF TABLES

# 2. LIST OF ABBREVIATIONS

Include a list of all abbreviations used in the TSAP

| Term | Definition / description |
|---|---|
| AE | Adverse event |
| ALT | Alanine Aminotransferase |
| AST | Aspartate Aminotransferase |
| BI | Boehringer-Ingelheim |
| BMI | Body Mass index |
| BRPM | Blinded report planning meeting |
| BSA | Body Surface Area |
| CRF | Case Report Form |
| CI | Confidence Interval |
| CT | Concomitant Treatments |
| CTP | Clinical Trial Protocol |
| CTR | Clinical Trial Report |
| DM&SM | Boehringer Ingelheim Data Management and Statistics Manual |
| E | Efficacy |
| ECG | Electrocardiogram |
| EMA | European Medicines Agency |
| EOT | End of treatment visit |
| ERS | European Respiratory Society |
| FVC | Forced Vital Capacity |
| HR | Heart rate |
| HRCT | High Resolution Computerized Tomography |
| ICH | International Conference on Harmonisation |
| IPF | Idiopathic Pulmonary Fibrosis |
| IPV | Important Protocol Violation |
| IXRS | Interactive phone/web Response System |
| MQRM | Medical Quality Review Meeting |
| N | Number of patients |
| NA | Not Applicable |

| Term | Definition / description |
|---|---|
| OC | Observed Case |
| PN | Preferred Name |
| PT | Preferred term |
| PV | Protocol violation |
| S | Safety |
| SD | Standard deviation |
| SDG | Standardised Drug Groupings |
| SEM | Standard Error of the Mean |
| SOC | System Organ Class |
| SSC | Special Search Category |
| TS | Treated Set |
| TSAP | Trial statistical analysis plan |
| ULN | Upper Limit of Normal |

# 3. INTRODUCTION

As per ICH E9 (5), 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 Trial Statistical Analysis Plan (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, randomization.

In the following, the term ‘parent trial’ refers to 1199.32 or 1199.34 trial. All the following analyses mentioned in this TSAP concern 1199.33 data.

Interim outputs will be produced in the scope of the submission of Nintedanib in IPF. These are detailed in Section 9.2.

SAS® Version 9.2 (or later) will be used for all analyses.

# 4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

Although not planned in the CTP, the time to liver enzyme elevation will be analysed in this study.

As per CTP amendment 2, regular interim analyses every 48 weeks have been cancelled, but some interim analyses may be done upon request from Health Authorities or for publication purposes.

# 5. ENDPOINTS

## 5.1 PRIMARY ENDPOINTS

The primary focus is on safety endpoints. Please refer to CTP Section 5.1.1.

## 5.2 SECONDARY ENDPOINTS

### 5.2.1 Key secondary endpoints

Not applicable.

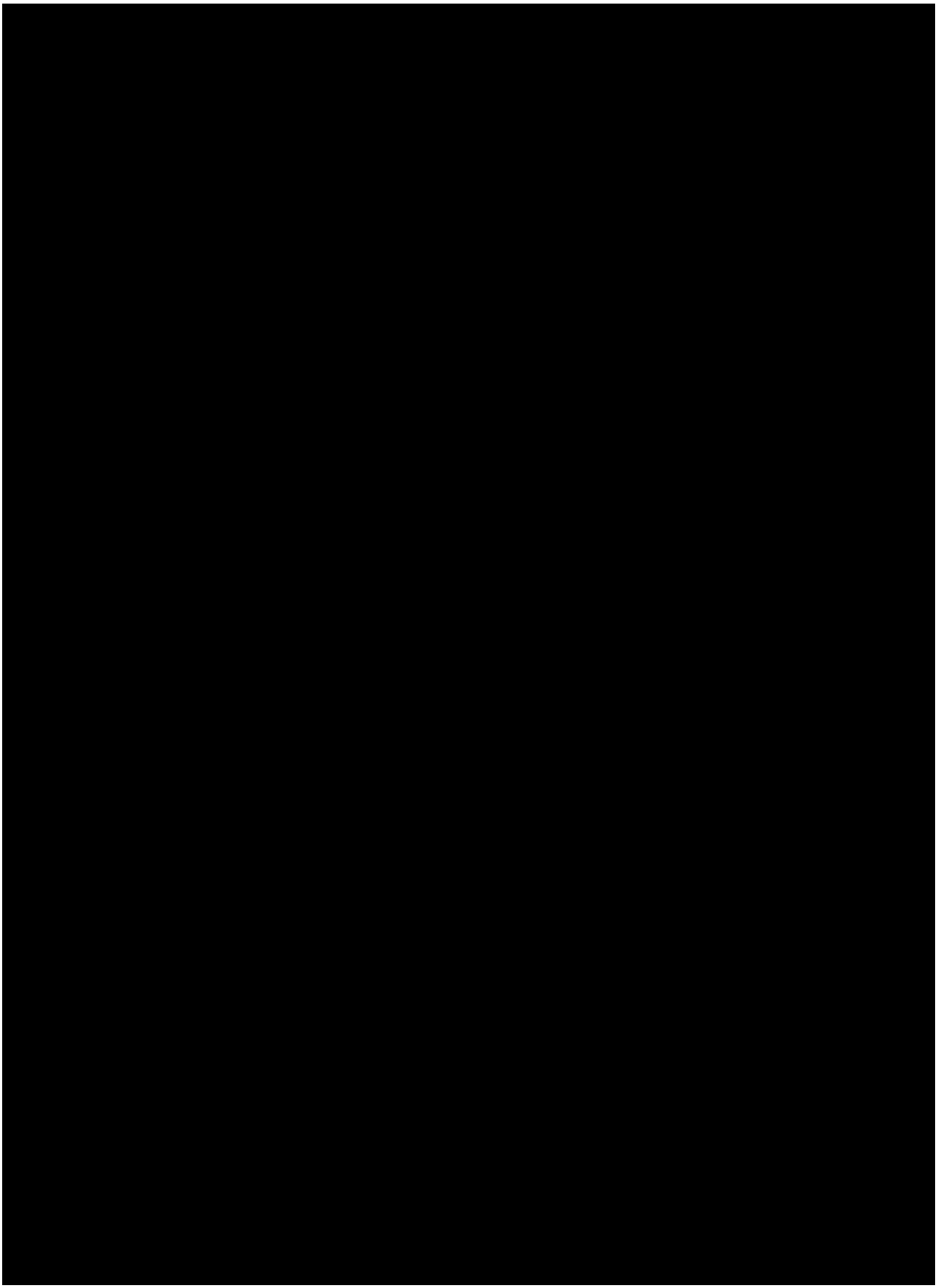
### 5.2.2 Other Secondary endpoints

Not applicable.

[redacted]

[redacted]

[redacted]



# 6. GENERAL ANALYSIS DEFINITIONS

## 6.1 TREATMENT(S)

For treatment specifications, see Section 4 of CTP.

The following periods of interest will be defined: previous trial, between trials, screening, off-treatment, treatment period, post-treatment, follow-up and post-study as follows:

Note: the last day of each of the following periods is excluded.

- Previous trial: from screening in parent trial to the last trial drug intake in parent trial plus 28 days plus one day / or to the date of trial completion in parent trial plus one day / or to date of informed consent in 1199.33, whichever occurs later

- Between-trials: from end of previous trial period (see above) to date of informed consent in 1199.33

- Screening: from date of informed consent in 1199.33 to first trial drug intake in 1199.33

- Treatment period: from first trial drug intake in 1199.33 (or re-start of treatment if interruption) to last trial drug intake (or date of interruption if interruption) plus one day

- Off-treatment: from date of start of interruption to re-start of treatment

- Post-treatment: from the last trial drug intake plus one day to last trial drug intake plus 28 days plus one day

- Follow-up: from last trial drug intake plus 28 days + one day (after post-treatment period) to date of trial completion plus one day. This period is only created if last trial drug intake took place more than 28 days before trial completion.

- Post-study: from the last trial drug intake plus 28 days plus one day to database lock or from the date of trial completion (after follow-up period) plus one day to database lock, whichever occurs later

Most treatment periods are optional (e.g. “Between-trials”, “Screening” and “Follow-up” will not concern all the patients).

For safety analyses (Section 7.8), data from first trial drug intake in 1199.33 up to 28 days after last trial drug intake (included) will be considered as on-treatment period.

## 6.2 IMPORTANT PROTOCOL VIOLATIONS

The following table defines the different categories of important protocol violations (IPV) to be considered. Important efficacy IPVs are those that can potentially influence outcome measures. Important safety IPVs are those that potentially affect the rights or safety of study subjects. All these important protocol violations are listed with appropriate flags indicating their potential impact on the analyses. No patients will be excluded from the analyses based on those IPVs as no per protocol analysis is planned. Important protocol violations will be described only.

Table 6.2: 1 Important protocol violations

| Category/ Code | | Description | Requirements | **Efficacy(E) or Safety (S)** |
|---|---|---|---|---|
| **A** | | **Entrance criteria not met** | | |
| | A1 | Inclusion criteria not met | | |
| | A1.7 | Parent study not completed | Inclusion criteria 2 not met (or parent trial not completed or follow-up visit in parent trial not performed, as per definition of inclusion criteria 2, but according to other CRFs information)<br>Automatic IPV | E |
| | A2 | Exclusion criteria not met | | |
| | A2.1 | Laboratory values indicate additional risk: > 3 X ULN for AST, ALT and >2xULN for Bilirubin | Laboratory values for AST, ALT or Bilirubin out of protocol defined ranges with no elevation recorded at end of parent trial, or exclusion criteria 1 or 2 not met<br>Manual IPV | S |
| | A2.3 | Patient with other disease(s) which are excluded as per exclusion criteria | Exclusion criteria 3-4-5-8 not met<br>Automatic IPV | S |
| | A2.4 | Forbidden previous therapy | Exclusion criteria 7 not met<br>Manual IPV | E |
| | A2.5 | Time period between parent trial and Visit 2 not observed | Exclusion criteria 6 not met / Time period > 12 weeks between last trial drug intake of the parent trial and Visit 2 of this study<br>or<br>Visit 1 did not occur at least one day after the Follow-up Visit of the parent trial<br>Automatic IPV | S |

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

| | | | | |
|---|---|---|---|---|
| **B** | | **Informed consent** | | |
| | B1 | Informed consent not given or given too late | Inclusion criteria 1 not met and / or informed consent date missing<br>OR<br>Informed consent date was after Visit 1 date<br>Manual review of MQRMs listings | S |
| **C** | | **Trial medication and randomisation** | | |
| | C1 | Incorrect trial medication taken | Medication kit assigned at visit 2 not matching treatment dose actually received by patient<br>or<br>Medication kit received at visit 2 does not correspond to the dose to be received according to CTP (150mg bid for patients on 150 bid in parent trial)<br>Automatic IPV | E |
| | C3 | Overall Compliance not between 80% and 120% inclusive | Compliance <80% or >120%<br>Automatic IPV | E |
| | C4 | Drug interruption longer than 46 days ; or 93 days in the case of acute exacerbations or unrelated AEs | Automatic IPV (reviewed in MQRM listings) | E |
| | C6 | Dose Change not in agreement with the protocol procedures (see Section 4.2.1 of CTP) | Manual review of MQRMs listings | S |
| | C7 | Drug not permanently discontinued despite criteria of Section 3.3.4.1 of CTP met | Manual review of MQRMs listings | S |
| **D** | | **Concomitant medication** | | |
| | D1 | Prohibited medication use during the treatment period | • Investigational therapy<br>• Full dose concomitant anticoagulation<br>• Fibrinolysis<br>• Antiplatelet therapy<br>Manual review of MQRMs listings | S |

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

| | | | | |
|---|---|---|---|---|
| E | | **Missing data** | | |
| | E4 | 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 Visit 9 of the parent trial and visit 1 is > 6 weeks.<br><br>Automatic IPV | S |
| **F** | | **Incorrect timing** | | |
| | **F1** | No adequate follow-up after liver enzyme elevation (see Table 10.1.1 of CTP) | Manual review of MQRMs listings | S |

Automatic PVs are those detected via an automated programming process using SAS.
Manual PVs are those identified during the MQRM meeting through patient listings and/or Manuel PV log.

## 6.3 PATIENT SETS ANALYSED

- Treated Set (TS):
  This patient set includes all patients coming from 1199.32/34 who were dispensed study medication and were documented to have taken at least one dose of investigational treatment.

All analyses will be performed on the Treated Set. Patients will be analysed according to their randomized treatment group in parent studies 1199.32/34 (e.g. Nintedanib 150mg or placebo), and overall (total column). The column of main interest in the tables will be the total column (overall both treatment group in parent studies 1199.32/34) as all patients are treated on Nintedanib during the extension study.

## 6.5 POOLING OF CENTRES

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

## 6.6 HANDLING OF MISSING DATA AND OUTLIERS

All analyses will be evaluated by observed case analysis (OC), i.e. using only available data without imputation.

Missing or incomplete AE dates are imputed according to BI standards (see "Handling of missing and incomplete AE dates"). (1)

For spirometry endpoints, missing data will not be imputed.

For more details about handling of missing data, see Section 7.5 of CTP.

### 6.6.1 Time to event endpoints

Missing data for time-to-event endpoints are managed by censored data analyses. No specific procedures need to be specified to handle them.

If a patient has no event during the studied period then he will be censored on the day corresponding to the end date of the studied period. The studied period for each type of endpoint is detailed in Table 6.6.1: 1.

Table 6.6.1: 1 Censoring rules for time to event endpoints

| Endpoint | Studied period | Censoring rule |
|---|---|---|
| Time to death<br>Time to first IPF acute exacerbation | From first trial drug intake in 1199.33 to last contact date | Patients with no event at the cut-off date will be censored at their last contact date |
| Time to first dose reduction<br>Time to first treatment interruption<br>Time to permanent treatment discontinuation | From first trial drug intake in 1199.33 to last trial drug intake | Patients with no event at the cut-off date will be censored at their last trial drug intake |
| Time to first occurrence of adverse event of particular note<br>Time to first liver enzyme elevation | From first trial drug intake in 1199.33 to last trial drug intake + 28 days | Patients with no event at the cut-off date will be censored at their last trial drug intake + 28 days |

Cut-off date = Date of the interim database lock

### 6.6.2 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.

## 6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

As a general rule, last available assessment before first trial drug intake will be used as baseline in 1199.33. If no assessment is available at visit 2, visit 1 will be used as baseline in 1199.33.

A windowing will be performed for all endpoints as described in Table 6.7: 1, in order to assign data to the relevant study visit based on the actual day of the assessment. Data will be analyzed 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.

Table 6.7: 1 Time windowing rules for spirometry, physical exam, vital signs, pregnancy test

| Time window of actual day [1] | | | Allocated to | | |
|---|---|---|---|---|---|
| Start ($S_n$) day | End (included) ($E_n$) day | Length of the time-window [days] | Visit number (n) | Visit name | Planned day of the visit ($V_n$) |
| 1 | 1 | 1 | 1 or 2 [2] | Baseline | 1 |
| 2 | 22 | 21 | 3 | 2 weeks | 15 |
| 23 | 36 | 14 | 4 | 4 weeks | 29 |
| 37 | 64 | 28 | 5 | 6 weeks | 43 |
| 65 | 127 | 63 | 6 | 12 weeks | 85 |
| 128 | 211 | 84 | 7 | 24 weeks | 169 |
| 212 | 295 | 84 | 8 | 36 weeks | 253 |
| 296 | 393 | 98 | 9 | 48 weeks | 337 |
| 394 | $V_p + (V_{p+1}-V_p)/2 = 505$ | $E_p-S_p+1$ | 10 | 64 weeks | 449 ($V_p$) |
| $V_p + 1 + (V_{p+1}-V_p)/2$ | $V_{p+1} + (V_{p+2}-V_{p+1})/2$ | $E_{p+1}-S_{p+1}+1$ | 11 | 80 weeks | 561 ($V_{p+1}$) |

Table 6.7: 1 Time windowing rules for spirometry, physical exam, vital signs, pregnancy test (cont'd)

| | | | | | |
|---|---|---|---|---|---|
| ... | ... | ... | ... | Every 16 weeks thereafter | Vp+2 |
| ... | ... | ... | ... | ... | $V_{p+...}$ |

[1] First trial drug intake date is taken into account as a reference to calculate time windows [2] Depending on the last assessment before first trial drug intake (included), refer to Section 6.7 for baseline definition

Table 6.7: 2 Time windowing rules for laboratory measurements

| Time window of actual day [1] | | | Allocated to | | |
|---|---|---|---|---|---|
| Start ($S_n$) day | End (included) ($E_n$) day | Length of the time-window [days] | Visit number | Visit name | Planned day of the visit ($V_n$) |
| 1 | 1 | 1 | 1 or 2 [2] | Baseline | 1 |
| 2 | 22 | 21 | 3 | 2 weeks | 15 |
| 23 | 36 | 14 | 4 | 4 weeks | 29 |
| 37 | 64 | 28 | 5 | 6 weeks | 43 |
| 65 | 106 | 42 | 6 | 12 weeks | 85 |
| 107 | 148 | 42 | 6a | 18 weeks | 127 |
| 149 | 190 | 42 | 7 | 24 weeks | 169 |
| 191 | 232 | 42 | 7a | 30 weeks | 211 |
| 233 | 274 | 42 | 8 | 36 weeks | 253 |
| 275 | 316 | 42 | 8a | 42 weeks | 295 |
| 317 | 365 | 49 | 9 | 48 weeks | 337 |

Table 6.7: 2 Time windowing rules for laboratory measurements (cont'd)

| | | | | | |
|---|---|---|---|---|---|
| 366 | 421 | 56 | 9a | 56 weeks | 393 |
| 422 | $V_p + (V_{p+1}-V_p)/2 = 477$ | $E_p-S_p +1$ | 10 | 64 weeks | 449 ($V_p$) |
| $V_p + 1+ (V_{p+1}-V_p)/2$ | $V_{p+1} + (V_{p+2}-V_{p+1})/2$ | $E_{p+1}-S_{p+1} +1$ | 10a | 72 weeks | 505 ($V_{p+1}$) |
| ... | ... | ... | ... | Every 16 weeks thereafter | $V_{p+2}$ |
| ... | ... | ... | ... | ... | $V_{p+...}$ |

[1] First trial drug intake date is taken into account as a reference to calculate time windows [2] Depending on the last assessment before first trial drug intake (included), refer to Section 6.7 for baseline definition

For all endpoints, if two post-baseline visits fall in the same time interval after windowing has been applied, the measurement closest to the planned visit will be taken into account. In case two measurements are equidistant from the planned visit, then the last one will be picked.

If after windowing of visits at baseline, two values fall within the same baseline interval, then the last value will be taken into account.

The same rules will be applied for laboratory measurements.

# 7. PLANNED ANALYSIS

For End-Of-Text (EoT) tables, the set of summary statistics is: N / Mean / SD / Min / Median / Max.

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

According to the CTP, there are fewer restrictions in concomitant therapies in 1199.33 as compared to parent trial. No comparison is therefore possible between parent and extension trial, even for placebo-randomized patients in parent trial.

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

A summary of all on-treatment concomitant therapies (including baseline CTs) will be provided by randomised treatment in parent trial , ATC3 codes and Preferred Name (PN) (sorted by alphabetical ATC class and decreasing frequency of preferred names within ATC class).

Post-study drug discontinuation therapies are defined as treatments started between last trial drug intake and the latest between trial completion and last drug intake + 28 days (included). They will be summarized by randomised treatment in parent trial, ATC3 codes and Preferred Name (PN). This aims at flagging concomitant treatments taken by patients after they have stopped the study drug.
Relevant groups of therapies have been defined as Special Search Categories (SSC) or Standardised Drug Groupings (SDG). These are listed in Section 9.3.

The summary of all on-treatment concomitant therapies (baseline CTs and on-treatment CTs) will also be performed by Special Search Category (SSC) or Standardised Drug Groupings (SDG) and Preferred Name (PN) (sorted by alphabetical SSC or SDG and decreasing frequency of preferred names within SSC).

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

## 7.3 TREATMENT COMPLIANCE

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

## 7.4 PRIMARY ENDPOINT(S)

There is no primary endpoint as the primary objective of the trial is to assess the safety of Nintedanib, so please refer to Section 7.8.

## 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.

[redacted]

## 7.7 EXTENT OF EXPOSURE

The data will be analysed on the Treated Set.

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

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.

The proportion of patients on each dose actually taken at visit 2 will be displayed according to:

- randomized treatment group in parent trial (by parent trial and both combined)
- the dose actually taken at the end of parent trial (by parent trial and both combined)
- the dose actually taken at the end of 1199.33 extension trial

A summary of treatment interruption will be performed including number of patients with at least one interruption, number and reason of interruptions, as well as time to first treatment interruption in 1199.33. A similar summary will be performed for dose change.

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

Kaplan-Meier plots of time to permanent treatment discontinuation will be drawn by randomised treatment in parent trial and overall. Similarly, Kaplan-Meier plots will be performed for time to first dose reduction and for time to first treatment interruption by randomised treatment in parent trial and overall. No statistical tests will be performed.

## 7.8 SAFETY ANALYSIS

All safety analyses will be performed on the Treated Set.

### 7.8.1 Adverse events

Unless otherwise specified, the analyses of adverse events will be descriptive in nature and will be based on BI standards (2). All analyses of AEs will be based on the number of patients with AEs and NOT on the number of AEs.

Furthermore, for analysis of AE attributes such as duration, severity, etc. multiple AE occurrence data on the CRF, will be collapsed into AE episodes provided that all of the following applies:

- The same MedDRA lowest level term was reported for the occurrences

- 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)

- Treatment did not change between the onset of the occurrences OR treatment changed between the onset of the occurrences, but no deterioration was observed for the later occurrence

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 1199.33 until 28 days after last drug intake in 1199.33 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 in 1199.33 will be assigned to ‘screening’ and all adverse events occurring after last drug intake + 28 days will be assigned to ‘post-treatment’, ‘post-study’ or ‘follow-up’ (for listings only). Some queries will be edited in case some adverse events are incorrectly reported in 1199.33 instead of parent trial, in order to report these in parent trial instead (before parent trial DBL). Also, all adverse events occurring between the start of an interruption and the end of interruption will be assigned to ‘off-treatment’ period in the listings. For details on the treatment definition, see Section 6.1.

According to ICH E3 (3), AEs classified as ‘other significant’ will include those non-serious and non-significant adverse events with
(i) ‘action taken = discontinuation’ or ‘action taken = reduced’, or
(ii) marked haematological and other lab abnormalities or lead to significant concomitant therapy as identified by the Clinical Monitor/Investigator at a Blinded Report Planning Meeting.

An overall summary of adverse events will be presented.

The frequency of patients with adverse events will be summarised by randomised treatment in parent trial, primary system organ class and preferred term. Separate tables will be provided for patients with other significant adverse events according to ICH E3 (3), for

patients with serious adverse events, for patients with adverse events occurring with an incidence in preferred term greater than 5% (in at least one treatment arm), for patients with protocol specified significant adverse events (as ticked in the AE page of the CRF), for patients with related adverse events, for patients with adverse events leading to dose reduction and for patients with adverse events leading to treatment discontinuation.

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

Specific tables will be created in order to describe selected adverse events of particular note, such as diarrhoea events:

- Display of the diarrhoea specific page of the CRF
- Summary of diarrhoea events including time to onset, number and duration of episodes
- Summary of diarrhoea adverse events including seriousness, clinical consequences (dose -reduction, drug discontinuation or drug interruption) and outcome
- Kaplan-Meier plots of time to first diarrhoea event, by randomised treatment in parent trial and overall

Specific summary tables including seriousness, clinical consequences and outcome will also be presented to describe the following adverse events of particular note: nausea, vomiting, dehydration and weight decrease adverse events. Depending on the number of patients having such adverse events, summary tables including time to onset, number of episodes and duration together with Kaplan-Meier plots of time to first event, by randomised treatment in parent trial and overall, may also be produced with and without a y-axis cut-off at 70%.

Topics or syndromes that are medically relevant to the clinical development program are specified in Table 7.8.1: 1. The frequency of patients with AEs within these topics or syndromes will be summarised by treatment, topic or syndrome and preferred term. A separate table will be provided for patients with serious AEs (SAEs), by treatment, topic or syndrome and preferred term.

Table 7.8.1:1 Aggregated adverse events by topic or syndrome

| **Organ system** | **Topic or Syndrome** | **Term selection** |
|---|---|---|
| Gastrointestinal disorders | | |
| | Pancreatitis | SMQ Acute pancreatitis |
| | Perforation | SMQ Gastrointestinal perforation (narrow) |
| Hepatobiliary disorders | | |

Table 7.8.1:1 Additional aggregated adverse events by topic or syndrome (cont'd)

| | | |
|---|---|---|
| | Liver enzyme and bilirubin elevations | SMQ Drug related hepatic disorders – comprehensive search (narrow);<br>SMQ Liver related investigations, signs and symptoms (broad);<br>SMQ Cholestasis and jaundice of hepatic origin (narrow);<br>SMQ Hepatitis, non-infectious (narrow). |
| | Hepatic injury | SMQ Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (narrow) |
| Vascular disorders | | |
| | Bleeding | SMQ Haemorrhage terms (excl laboratory terms) (narrow) |
| | Venous thromboembolism | SMQ Embolic and thrombotic events, venous (narrow) |
| | Arterial thromboembolism | SMQ Embolic and thrombotic events, arterial (narrow);<br>SMQ Myocardial infarction (narrow). |
| | Stroke | SMQ Ischaemic central nervous system vascular conditions (narrow);<br>SMQ Haemorrhagic central nervous system vascular conditions (narrow). |
| Cardiac disorders | | |
| | Cardiac failure | SMQ Cardiac failure (narrow) |
| | QT prolongation | SMQ Torsade de pointes/QT prolongation (narrow) |
| | MACE | |
| Renal disorders | | |
| | Renal failure | SMQ Acute renal failure (narrow) |

### 7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (4).

Specific tables will be presented 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 episodes
- Kaplan-Meier plot of time to first liver enzyme elevation (if sufficient number of events). No statistical test will be performed.
- Summary table of individual maximum liver enzyme and bilirubin elevations
- Plot of timecourse profile of liver enzyme for patients having liver enzyme and bilirubin elevation

### 7.8.3 Vital signs

Only descriptive statistics are planned for this section of the report, including calculation of the change from baseline.

### 7.8.4 ECG

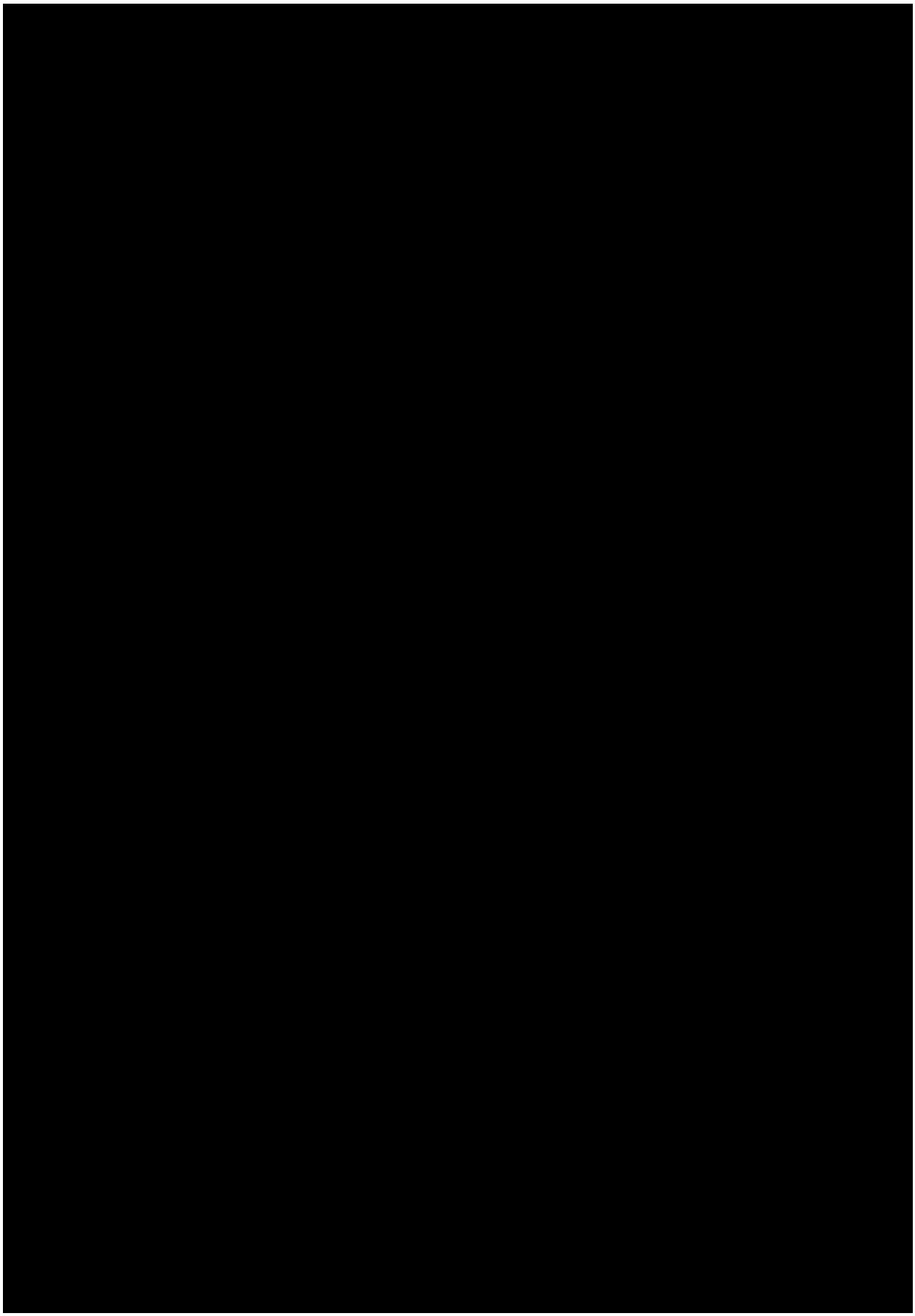
Not applicable (ECG findings are reported as adverse events).

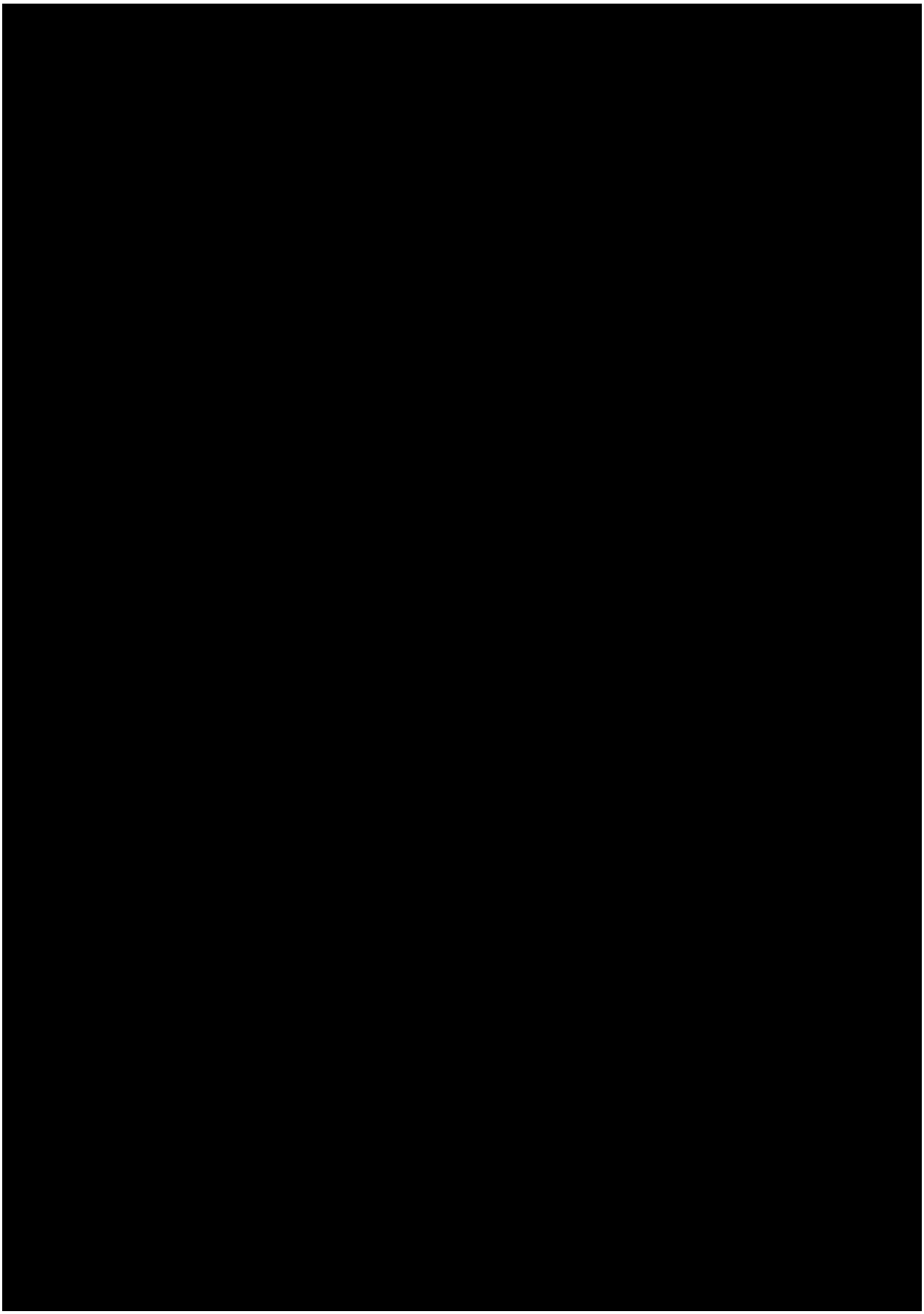
### 7.8.5 Others

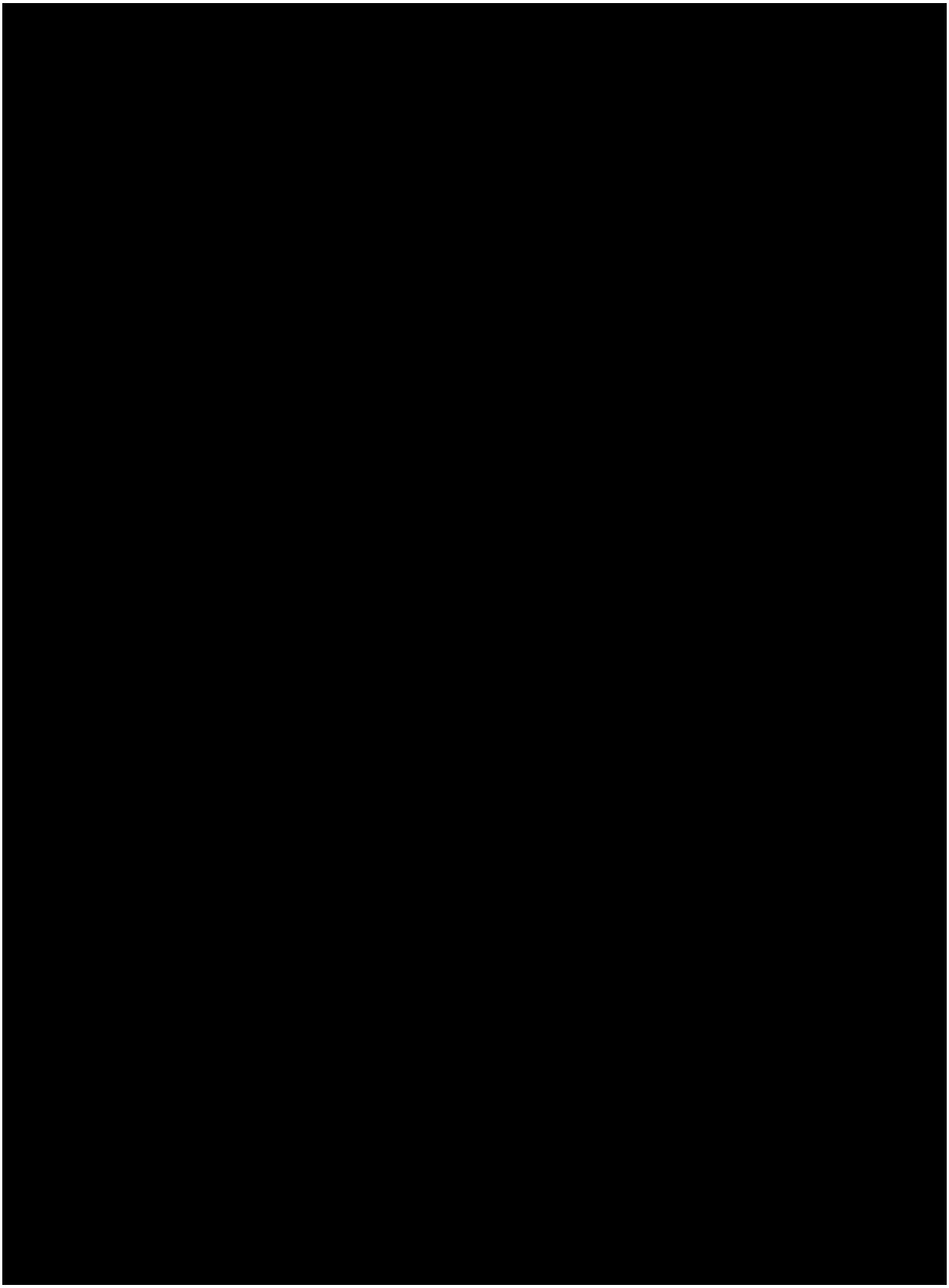
Not applicable.

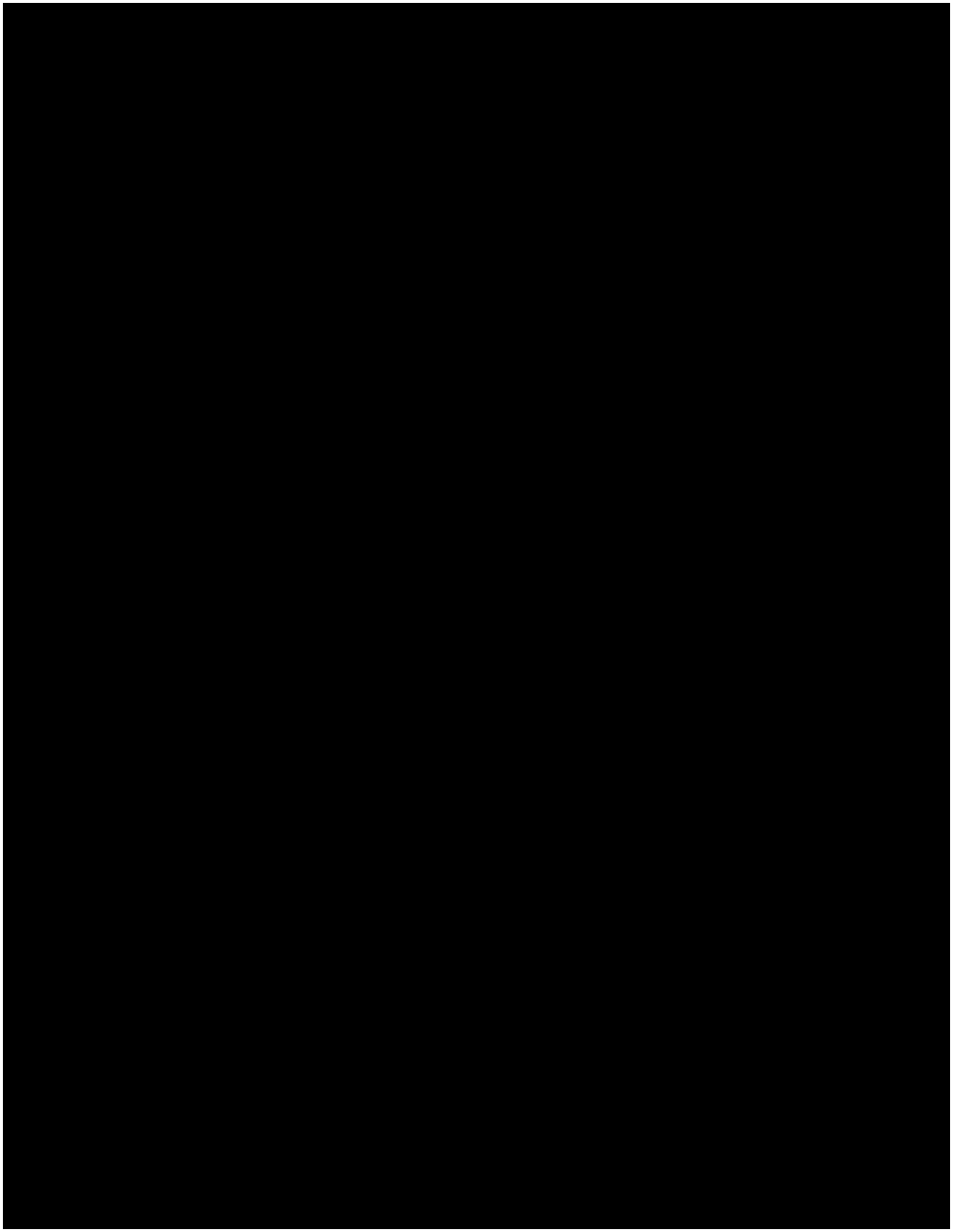
# 8. REFERENCES

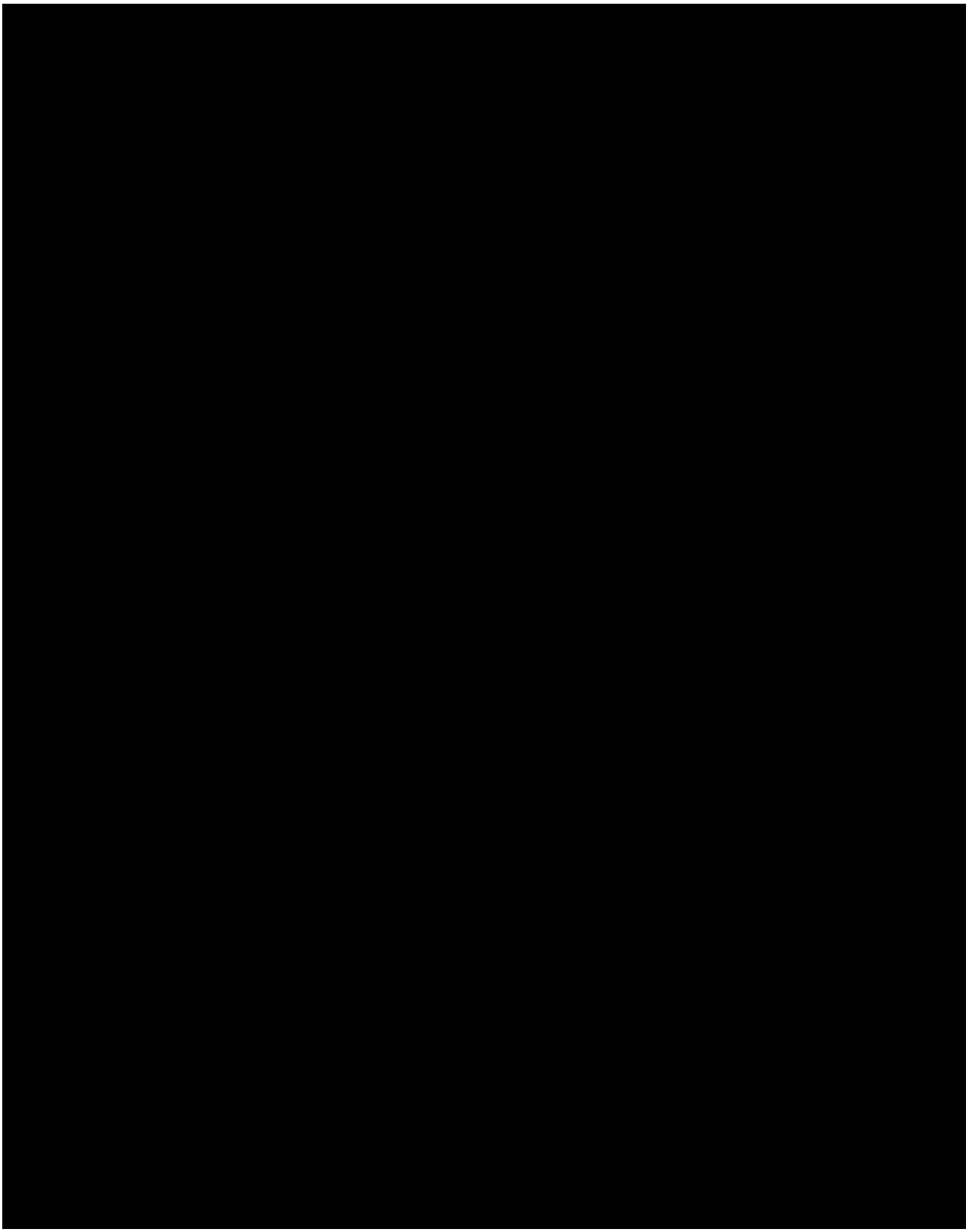

| | |
|---|---|
| 1 | *001-MCG-156_RD-01:* "Handling of missing and incomplete AE dates", current version; IDEA for CON. |
| 2 | *001-MCG-156: "*Analysis and Presentation of Adverse events Data from Clinical Trials", current version; IDEA for CON. |
| 3 | *CPMP/ICH/137/95*: "Structure and Content of Clinical Study Reports", ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version |
| 4 | *001-MCG-157*: "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON. |
| 5 | *CPMP/ICH/361/96*: "Statistical principles for clinical trials", ICH Guideline Topic E9; Note For Guidance on Statistical principles for clinical trials, current version |











# 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 |
|---|---|---|---|---|
| Final | 14-June-13 | [redacted] | None | This is the final TSAP without any modification |
| Revised | 29-September-15 | [redacted] | 4 | As the protocol has been revised, the term "On trial survival" has already been changed into "Time to death" |
| | | | 5.2.2 | In accordance with new SOP, endpoints are now classified as further endpoints and not as secondary endpoints anymore. |
| | | | [redacted] | |
| | | | 6.2 | Precision added for IPV A2.1 |
| | | | 6.6 | A reference to the CTP has been added for the handling of missing data. |
| | | | 7.5.2 | In accordance with new SOP, endpoints are now classified as further endpoints and not as secondary endpoints anymore. |
| | | | [redacted] | |
| | | | 7.7, 7.8.1 | Precision that KM plots will also be performed overall groups and with 70% cut-off for y-axis for AEs of particular note |
| | | | [redacted] | |
| | | | General | Reference section numbers have been updated or removed due to new classification of endpoints and for consistency purposes with revised CTP based on Global amendment 2. |

Table 10: 1 History table (cont'd)

| | | | | |
|---|---|---|---|---|
| Revised | 19-September-16 | [redacted] | 6.3 | The definition of the Treated Set has been updated in order to specify that the Treated Set only includes patients from parent trials 1199.32/34 (and not transitioned patients from study 1199.35). |
| | | | [redacted] | |
| Revised | 25-Jul-17 | [redacted] | 7.2 | The definition of baseline therapies was clarified.<br>A summary of post-study drug discontinuation therapies has been added in order to display the proportion of patients having taken commercial nintedanib after trial drug discontinuation. |
| | | | 7.8 | Some specific AE tables by Topic or syndrome were added, as judged medically relevant for the project. |
| | | | [redacted] | |
| | | | | |