TRIAL STATISTICAL ANALYSIS PLAN

Document No.:	**c40328414-01**
BI Trial No.:	**1199-0434**
Title:	A double blind, randomized, placebo-controlled trial evaluating the efficacy and safety of nintedanib over 52 weeks in Chinese patients with Chronic Fibrosing ILDs with a Progressive Phenotype revised protocol version 5.0 [c34975667-06]
Investigational Product(s):	Ofev®, Nintedanib
Responsible trial statistician(s):	[redacted]
Date of statistical analysis plan:	07 JUN 2024 SIGNED
Version:	1.0

1. TABLE OF CONTENTS

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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BI	Boehringer Ingelheim
CI	Confidence Interval
CTR	Clinical Trial Report
DBL	Database Lock
eCRF	Electronic Case Report Form
FVC	Forced Vital Capacity
HRCT	High-Resolution Computer Tomography
ICH	International Conference on Harmonization
ILD	Interstitial Lung Disease
IPF	Idiopathic Pulmonary Fibrosis
MedDRA	Medical Dictionary for Regulatory Activities
SD	Standard Deviation
UIP	Usual Interstitial Pneumonia
TSAP	Trial Statistical Analysis Plan
ULN	Upper Limit of Normal

3. INTRODUCTION

As per ICH E9 (9.1), 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, randomization.

The objective of the current trial is to generate additional data on the efficacy of 150 mg bid nintedanib in Chinese patients with Chronic Fibrosing ILDs with a Progressive Phenotype compared to placebo over 52 weeks. The primary endpoint is defined in the same way as in the INBUILD trial (1199-0247). The efficacy of reduction in lung function decline will be measured by the annual rate of decline in FVC for nintedanib compared to placebo over 52 weeks.

Unless otherwise noted, SAS® Version 9.4 and R Version 4.0.1 (or higher) will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

4.1 CLARIFICATION

- Comparing with the INBUILD trial (1199-0247), the duration of treatment of this study is only 52 weeks. The primary endpoint will include data collected up to last treatment visit, instead of day 373.
- The main analysis for primary efficacy endpoint of this study will be based on the treated set (according to randomized treatment), using all available data from baseline (excluded) up to week 52 visit. For patients who prematurely discontinued study treatment, data collected at follow-up visit and visits after treatment discontinuation will be included in the analysis.

[redacted]

- Due to the possible occurrence of mis-stratifications during the randomization process, the HRCT pattern as reported in the eCRF will be used in all analyses.
- Three patients were randomized by mistake, whose HRCT pattern was recorded incorrectly in the Interactive Response Technology (IRT) system. Two patients were randomized under “other HRCT fibrotic patterns” and the other one was randomized under “HRCT with UIP-like fibrotic pattern only”. They will be counted in the subpopulation of patients as collected in the eCRF in all analyses within the CTR.

[redacted]

5. ENDPOINTS(S)

5.1 PRIMARY ENDPOINT(S)

The primary efficacy endpoint is the annual rate of decline in Forced Vital Capacity (FVC) over 52 weeks expressed in mL. The analysis will be based on FVC values obtained at all post-baseline visits over 52 weeks. Handling of missing data is described in Section 6.6.

5.2 SECONDARY ENDPOINT(S)

Not applicable since there is no secondary endpoint.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

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

- Screening: From informed consent to randomization
- Treatment period: From first trial drug intake to last trial drug intake
- Residual effect period / Safety follow-up: From the last trial drug intake plus 1 day to last trial drug intake plus 7 days
- Off-treatment period: From start date of trial drug interruption to re-start of trial drug

All analyses will be based on the planned treatment groups (Nintedanib 150 mg bid vs. Placebo) as randomized by IRT. The subjects will be analyzed according to the stratum to which they actually belong to, regardless of any stratification error at randomization.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Potentially important protocol deviations (iPDs) will be handled according to BI standards (9.5). The number and proportion of patients with iPDs will be presented for completeness purposes and to demonstrate the adherence to the CTP. Handling of iPDs in analysis is included in the DV domain specifications and stored within the TMF.

6.3 INTERCURRENT EVENTS

Intercurrent events and handling strategies with respect to the primary efficacy endpoint are described in Table 6.3:1.

For the main analysis, intercurrent events such as premature treatment discontinuation and restricted medication use will be handled by applying treatment policy strategy, i.e., all available data collected up to week 52 visit will be included in the analysis.

Death will be handled by applying while-alive strategy, i.e., data collected while patient is alive will be included in analysis.

The use of Pirfenidone and Nintedanib (non-IMP prescribed by investigator) are prohibited during the trial and considered as important protocol violations. In the supplementary analysis, prohibited medication and restricted medication will be handled by applying while-on-treatment strategy, i.e., data collected after the initiation of prohibited or restricted medication will not be included in the analysis.

Further details of intercurrent event handling strategies will be described in Section 7.

Table 6.3: 1 Intercurrent events and handling strategies

Intercurrent event	**Main analysis strategy**	**Supplementary strategy**
Treatment discontinuation	Treatment policy	While-on-treatment
Initiation of restricted medication	Treatment policy	While-on-treatment
Initiation of prohibited medication	Treatment policy	While-on-treatment
Death	While-alive	While-alive

6.4 SUBJECT SETS ANALYSED

Patient sets analyzed are defined as:

- Screened set (SCS):
  This subject set includes all subjects who signed informed consent.
- Randomized set (RS):
  This subject set includes all randomized subjects, whether treated or not.
- Treated set (TS):
  This subject set includes all subjects who were dispensed study medication and were documented to have taken at least one dose of investigational treatment.

Table 6.4: 1 Subject sets analyzed

	Subject set		
Class of analysis	Screened set	Randomized set	Treated set
Primary endpoint			X
Further endpoint			X
Safety and treatment exposure			X
Demographic & baseline characteristics			X
Disposition		X	
Reason for non-randomization	X		

6.5 SUBGROUPS

Subgroup analysis is not planned.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

In general, missing data will not be imputed. Exceptions and further details will be described in Section 7.

For continuous efficacy endpoints, missing data will be handled by the Random Slope and Intercept (RSI) model and Mixed Models for Repeated Measures (MMRM), assuming a missing at random mechanism.

For binary endpoints, missing data will be considered as worst-case outcome in the main analysis, e.g., no response.

[redacted]

Missing or incomplete AE and CM dates are imputed according to BI standards (9.2).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

As a general rule, the last assessment / measurement observed prior to the start of trial medication will be assigned to baseline. Note that for some trial procedures (e.g., body weight, vital signs, laboratory tests), this may be the value measured on the same day as trial medication started. In these cases, it will be assumed that the measurements were taken prior to the intake of any study medication (if the measurement time was not captured). If no further data available, this can also be the last screening assessment.

Visit windowing will be performed as described in Table 6.7: 1, Table 6.7: 2 and Table 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 statistical tables. However, in listings, all visits performed will be displayed (even if outside time-window), along with the re-calculated visit.

[redacted]

If after windowing of visits at baseline, the last value prior to first drug intake will be taken into account. If after windowing of post-baseline visits, two or more visits fall in the same interval, then the measurement closest to the planned visit will be taken into account. In case two measurements are equidistant from the planned visit, then the last one will be used in analysis.

7. PLANNED ANALYSIS

The labelling and display format of statistical parameters will follow BI standards (9.3). For End-Of-Text tables, the set of summary statistics are: N / Mean / SD / Min / Median / Max. In case extreme data outside of the expected range are observed, quartiles and percentiles will be presented additionally.

Tabulations of frequencies for categorical data will include all categories depicted in the eCRF 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). The category missing will be displayed only if there are actually missing values.

Unless otherwise noted, all analyses will be conducted on the treated set (TS).

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Descriptive statistics will be provided for disposition, demographics, baseline disease characteristics, presented by treatment groups and overall total.

Disposition table will include the number of patients randomized and treated. The number and percentage of patients who completed and prematurely discontinued study treatment will be summarized by treatment groups, the reasons for treatment discontinuation will be shown. Similarly, the number and percentage of patients who completed and prematurely discontinued observation period will also be summarized by treatment groups, the reason for study discontinuation will be shown. Where percentages are shown, the denominator will be the number of patients treated in each treatment group.

In addition, the reason for non-randomization will be summarized based on the screened set.

Demographics such as Age, Sex, Race, Ethnicity, Weight (kg), Height (cm) and BMI will be summarized by treatment groups.

Trial indication characteristics including original underlying ILD diagnoses and baseline disease extent as collected in eCRF will be summarized by treatment group. In addition, the underlying ILD diagnosis grouping will be summarized by treatment group, the grouping will be determined by medical review and documented prior to DBL.

[redacted]

7.2 CONCOMITANT DISEASES AND MEDICATION

Concomitant diseases and concomitant medications will be descriptively summarized by treatment groups and overall total.

Concomitant diseases will be coded according to the most recent version of MedDRA. Concomitant medications will be coded according to the most recent version of the World Health Organization – Drug Dictionary (WHO-DD).

A medication will be considered concomitant to treatment if it:

- is ongoing at the start of trial medication intake.

- starts within the treatment period (see Section 6.1 for a definition of study phases).

Concomitant medication use will be summarized with frequency and percentage of subjects by ATC3 class and preferred name, grouped by randomized treatment.

On-treatment restricted medication and prohibited medication will be summarized by treatment groups, definitions of restricted and prohibited medications are depicted in CTP Section 4.2.2., prohibited medication will be documented in the iPD specification.

7.3 TREATMENT COMPLIANCE

The overall compliance (%) will be summarized by treatment groups and overall total. If the number of capsules actually taken is missing for an expected visit, the overall compliance is not calculated.

Compliance will be calculated over 52 weeks as:

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

The number of capsules which should have been taken over the 52-week treatment period will be calculated as:

Number of capsules = (date of last drug intake – date of first drug intake + 1) × 2

In case of dose reduction to 100 mg bid, the calculation of compliance remains the same. The duration of treatment interruptions due to AE will be subtracted from the studied treatment duration when calculating number of capsules should have been taken.

Compliance will be categorised into classes: <50%, ≥50% - <80%, ≥80% - ≤ 120%, > 120%. Compliance category will be summarized by treatment groups and overall total.

7.4 PRIMARY OBJECTIVE ANALYSIS

7.4.1 Main analysis

The primary efficacy endpoint is the annual rate of decline in Forced Vital Capacity (FVC; expressed in mL) over 52 weeks. The main analysis will be based on the TS (according to randomized treatment), using all available data from baseline (excluded) up to week 52 visit. For patients who prematurely discontinued study treatment, data collected at follow-up visit and visits after treatment discontinuation will be included in the analysis. For patients who had multiple FVC measurements on the same day, the last measurement will be used in the analysis. Intercurrent event handling strategies for main analysis are described in Section 6.3.

The main analysis uses a restricted maximum likelihood (REML) based approach with a random slope and intercept model. The analysis will include the fixed, categorical effects of treatment, HRCT pattern at baseline, fixed continuous effects of time and baseline FVC as well as the treatment-by-time and baseline-by-time interactions. Random effects will be included for patient response for both time and intercept. The HRCT pattern at baseline collected in eCRF will be used in the analysis.

The statistical model can be written as follows:

$$y_{ijkm} = (\mathrm{a}_i + \vartheta_m + \beta_0 S_i + \tau_k) + (\mathrm{g}_i + \beta_s S_i + \varphi_k)\mathrm{t}_{ij} + e_{ij}$$

$$(a_i, g_i) \sim N_2\ (\mathbf{0}, \boldsymbol{\Sigma})$$
$$e_{ij} \overset{iid}{\sim} N\ (0, \sigma^2)$$

The components of the model are as follows:

y_{ijkm}	=	FVC for patient i with HRCT pattern m at time j receiving treatment k
a_i	=	random intercept effect for patient i, i=1,2,…
ϑ_m	=	intercept coefficient of HRCT pattern m, m=1,2. (“other HRCT fibrotic patterns” as the class reference)
β_0	=	intercept coefficient of baseline FVC
S_i	=	baseline FVC measurement for patient i
τ_k	=	intercept coefficient of the effect of treatment k, k=1,2
g_i	=	random slope effect for patient i
β_s	=	slope coefficient of baseline FVC
φ_k	=	slope coefficient of the effect of treatment k
t_{ij}	=	time of measurement j for patient i, j= 1,2,… J_i
e_{ij}	=	the random error associated with the time j of patient i. Measurement errors are independent and normally distributed with mean 0 and variance σ^2, and uncorrelated with a_i and g_i.
$\boldsymbol{\Sigma}$	=	a 2x2 unstructured covariance matrix

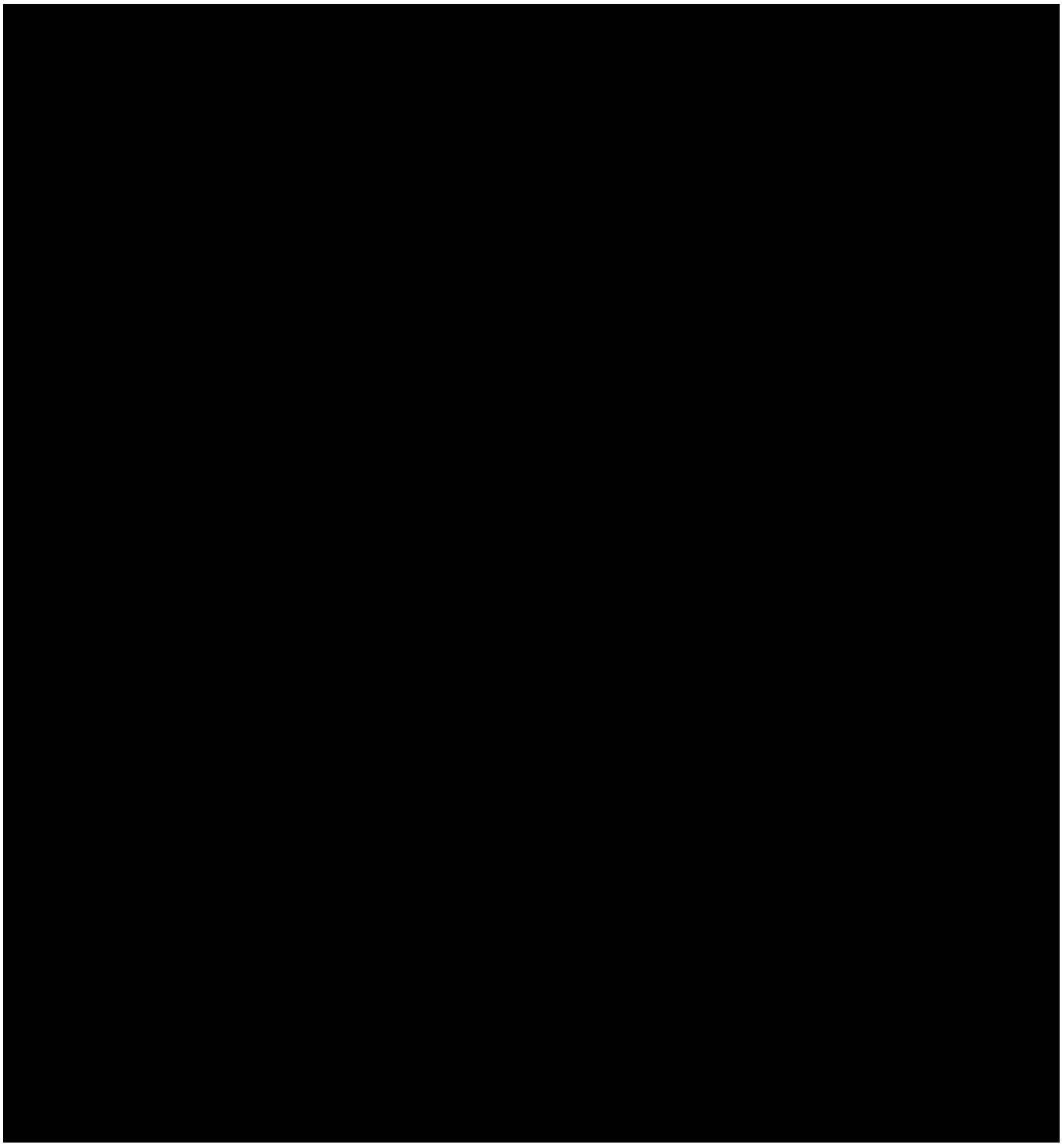
Within patient errors are assumed to follow a random coefficient regression model with random effect for intercept and slope. An unstructured variance-covariance structure will be used to model these random slope and intercept. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors.

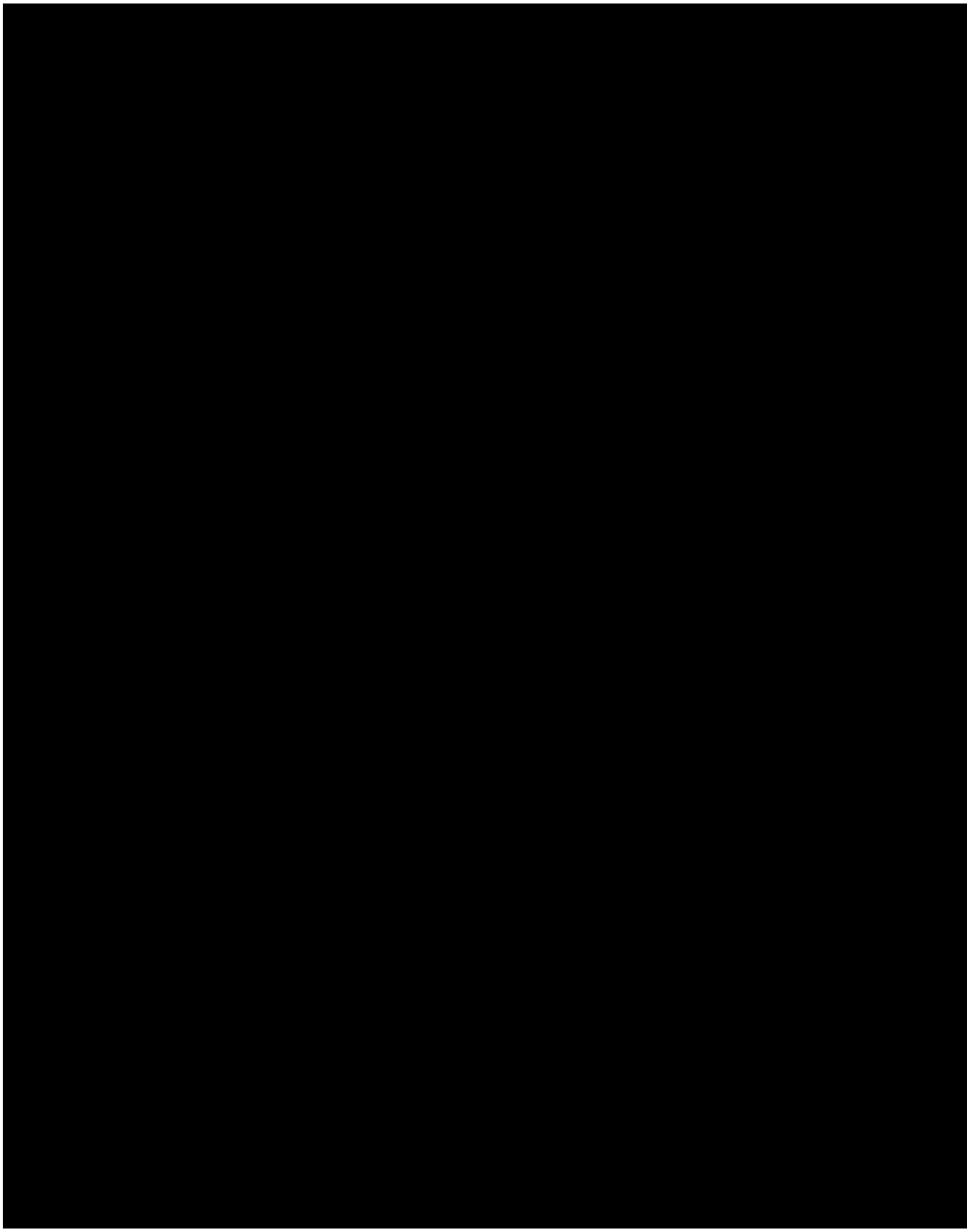
In case of model non-convergence, methods to overcome the issue are described in Section 10.1. The first model to converge will be used as the main analysis on the primary endpoint.

The point estimate of treatment difference between the nintedanib and placebo group as well as two-sided 95% CI will be provided. No formal statistical testing will be performed. The primary treatment comparison of slopes will be assessed through the treatment-by-time interaction coefficient.

SAS code specifications are included in Section 10.2.

[redacted]





[redacted]

7.4.3 Supplementary analysis

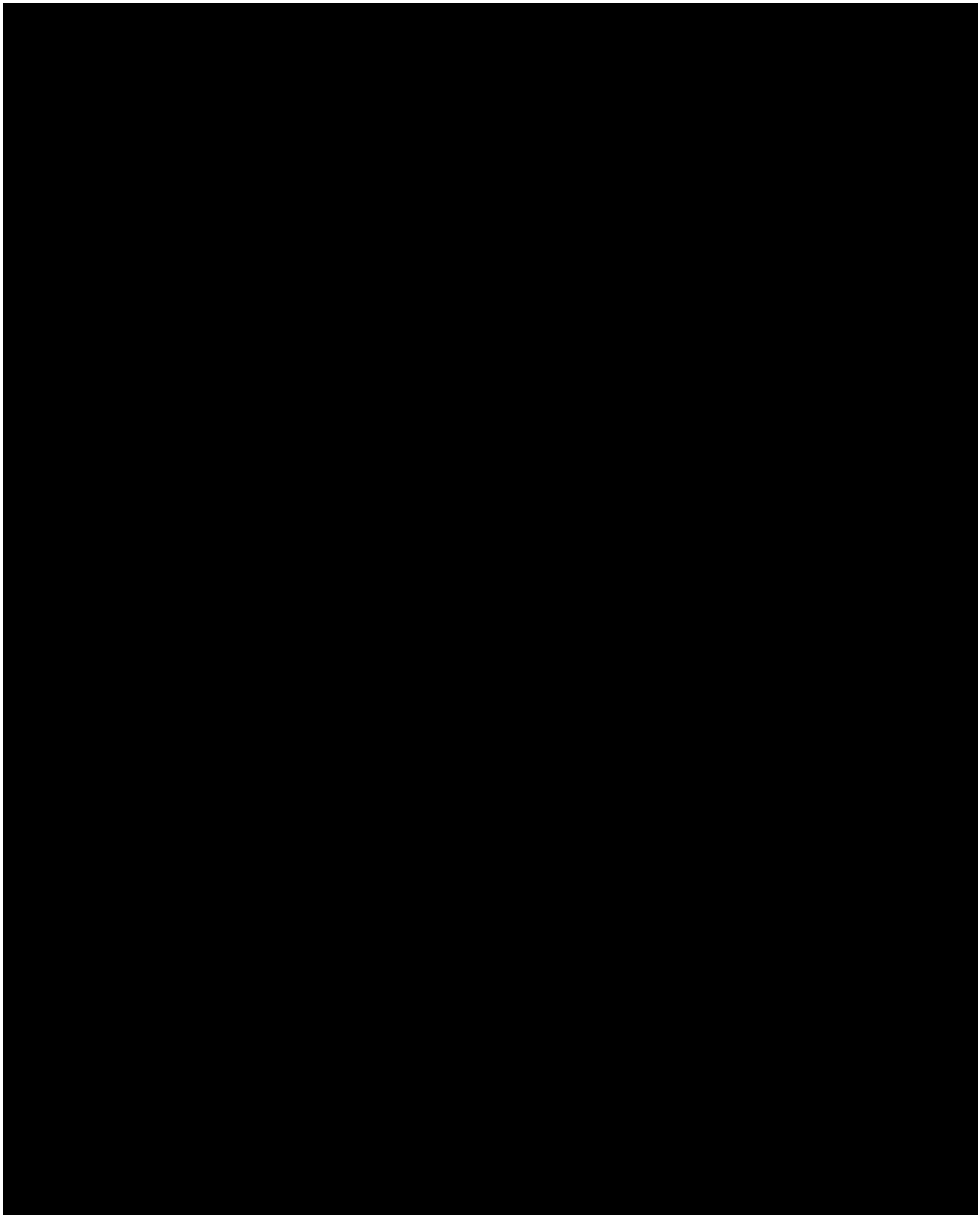
A supplementary analysis including only on-treatment measurements of FVC (ml) will be analyzed. This analysis reflects the expected biologic effect of nintedanib 150 mg bid in the treatment of patients with PF-ILD.

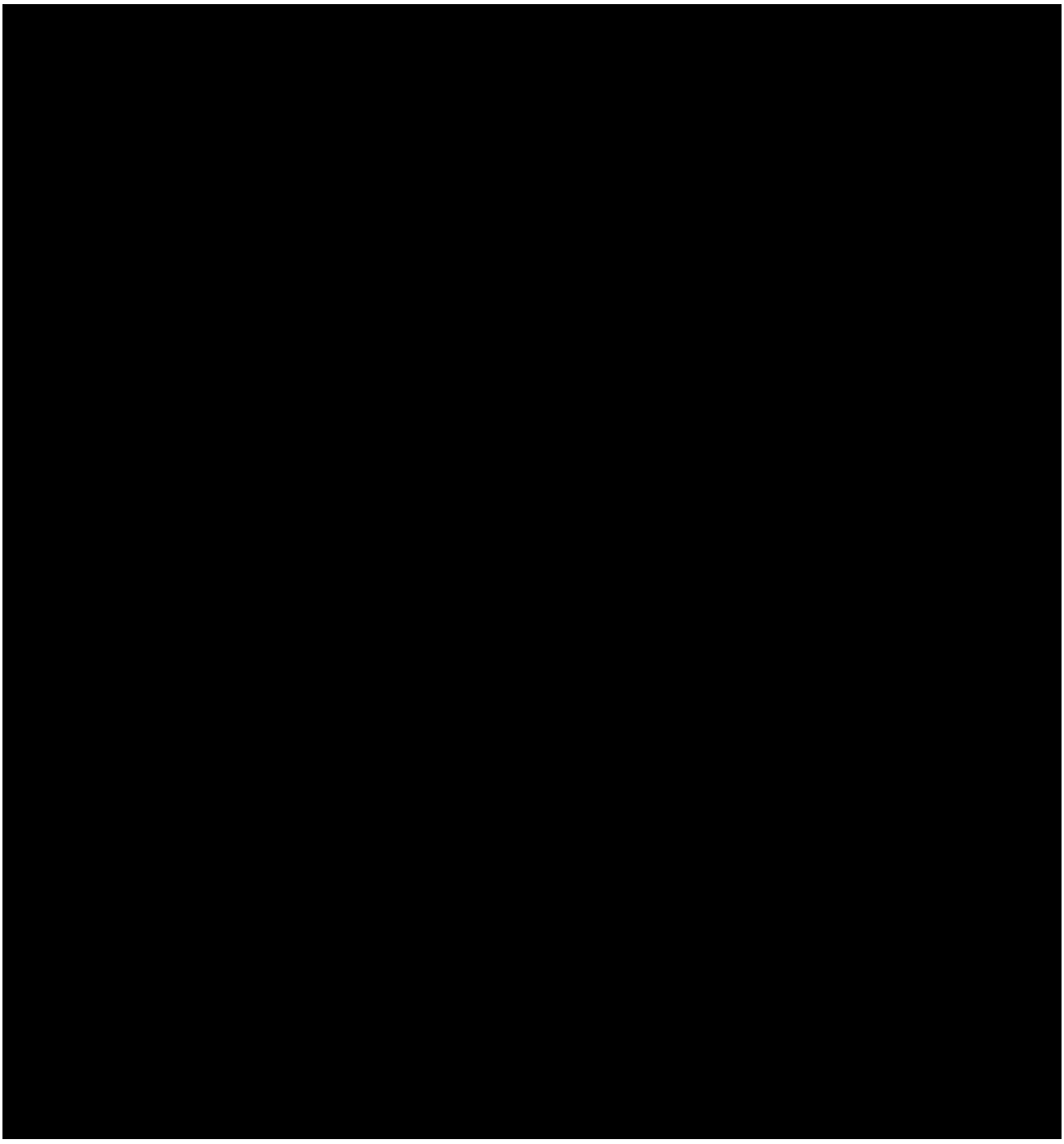
FVC collected from the first drug administration up to the last drug intake plus one day will be included in analysis. The same RSI model used in the main analysis will be applied (see Section 7.4.1). Point estimate and two-sided 95% CI of the treatment effect will be presented. Tables presenting the results of the supplementary analysis will be created in addition to graphical representations.

7.5 SECONDARY OBJECTIVE ANALYSIS

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

[redacted]





7.7 EXTENT OF EXPOSURE

Exposure summary will be presented over 52 weeks. The duration on treatment and dose intensity will be computed overall, as well as on the individual dose strengths.

In case last drug administration date is incomplete, assume all prescribed medication at the last clinical visit have been taken. Impute the last drug administration date based on the last clinical visit date and number of capsules dispensed, it could be the end of study date if the imputed last drug administration date occurs after the end of study date.

A summary of treatment interruptions will be created including number of patients with at least one interruption, number and reason of interruptions. A similar summary will be performed for dose changes. Reasons for dose reduction or interruption will be presented.

Duration of exposure [months] = (date of last drug administration – date of first drug administration +1 day) / 30.5

Duration of exposure in categories: ≤3 months (91 days); >3 months (91 days) to ≤ 6 months (182 days); > 6 months (182 days) to ≤12 months (365 days)

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

Duration on actual dose (100 or 150 mg bid) (sum of durations on-treatment for each dose effectively taken): in weeks and in categories (≤ 8 weeks, > 8 weeks)

Total dose [g]: Duration of exposure [days] * actual dose [g]

Dose intensity [%]: amount of drug actually administered over the study (dose 100mg and 150mg) divided by the amount of drug that would have been administered had dose 150mg bid been administered over all the study (from date of first administration to date of last administration, whether or not trial drug was prematurely discontinued). Dose intensity will be summarized in percent and in categories (≤ 30 %, >30% - ≤50%, >50% - ≤90%, >90% - <100%, 100%).

7.8 SAFETY ANALYSIS

All safety analyses will be performed by randomized treatment groups based on the treated set.

7.8.1 Adverse events

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 further details on handling of missing or incomplete AE dates and summarization of AE data, please refer to (9.2, 9.4).

The analysis of AEs will be based on the concept of treatment emergent adverse events (TEAEs). That means that all AEs occurring between first drug intake till 7 days after last drug intake will be assigned to the randomized treatment. All AEs occurring before first drug intake will be assigned to ‘screening’ and all AEs occurring after last drug intake + 7 days will be assigned to ‘follow-up’ (for listings only). For details on the treatment definition, see Section 6.1.

According to ICH E3 (9.7), in addition to deaths and serious adverse events, ‘other significant’ AEs need to be listed in the clinical trial report. These will be any non-serious adverse event that led to an action taken with study drug (e.g., discontinuation or dose reduced). An overall summary of adverse events will be presented.

The frequency of subjects with AEs will be summarized by treatment, primary system organ class and PT (mention MedDRA levels to be displayed in the tables). Separate tables will be provided for subjects with SAEs, other significant AEs, AEs leading to permanent dose reduction, AEs leading to treatment discontinuation, AEs of at least moderate severity, drug-

related AEs, drug-related SAEs, adverse events leading to death and adverse events of special interest (AESI). In addition, selected safety topics / user-defined AE categories (UDAECs) will be summarized by treatment group, these selected AE topics will be determined by medical review and documented prior to DBL.

The system organ classes will be sorted by default alphabetically, PTs will be sorted by frequency (within SOC).

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and based on SI units according to BI standards (9.6). Missing data will not be imputed.

Summary statistics of laboratory tests by functional group over time will be presented by treatment groups.

Potentially clinically significant abnormalities will be identified based on BI standard rules which are based on converted lab values, i.e., using SI units. Frequency tables will summarize the number of patients with potentially clinically significant abnormalities. In addition, lab shift tables will be presented.

Patients having an abnormal lab value at baseline will be presented in a listing separately. A separate listing will present all patients with potentially clinically significant lab values. In addition, a summary table will be prepared for the values outside of the clinically significant reference range including frequency and percentage of patients with abnormal values for relevant laboratory parameter.

A summary table of liver enzymes and bilirubin elevations over 52 weeks will also be provided. Liver enzyme and bilirubin elevations will be reported using the three following definitions:

- ALT and/or AST ≥ 8xULN
- ALT and/or AST ≥ 3xULN AND total bilirubin ≥ 2xULN*
- ALT and/or AST ≥ 3xULN and unexplained INR > 1.5*
- ALT and/or AST ≥ 3xULN and unexplained eosinophilia (>5%)*
- ALT and/or AST ≥ 3xULN and appearance of fatigue, nausea, vomiting, right upper abdominal quadrant pain or tenderness, fever and/or rash

* in the same blood draw sample.

A graphical analysis of the ALT and total bilirubin during the on-treatment period will also be performed according to BI standards (9.6), the so-called eDISH plot. For cases whose total bilirubin, AST/ALT values meet the criteria for Hy's Law (Maximum total bilirubin two or more times the ULN for the parameter, and the maximum ALT and/ or AST value three or more times its ULN) at any individual visit will be presented in a listing, showing the constituent values plus the associated alkaline phosphatase value at that time and the full course of available values for that case obtained during the study.

7.8.3 Vital signs

Summary statistics of vital signs (systolic and diastolic blood pressure, pulse rate and weight) over time will be presented by treatment groups.

The number and percentage of patients with marked changes in vital signs over 52 weeks will also be summarized by treatment.

A marked increase is defined as:

- Systolic Blood Pressure >130 mmHg and increase ≥ 25 mmHg above baseline
- Diastolic Blood Pressure >80 mmHg and increase ≥ 10 mmHg above baseline
- Pulse Rate >100 bpm and increase ≥ 10 bpm above baseline

A marked decrease is defined as:

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

7.8.4 ECG

ECG analysis is not planned.

7.9 OTHER ANALYSIS

Other analysis is not planned.

8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

The treatment information will be released to unblind the trial database after the last patient has completed their End-of-Study/Follow-up visit and all data has been entered and cleaned as defined in the “Data Ready to be Unblinded and/or Final Trial Closure Notification” (RUN) form.

9. REFERENCES

9.1	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note for Guidance on Statistical Principles for Clinical Trials, current version.
9.2	*BI-VQD-01530:* “Handling of Missing and Incomplete AE Dates”, current version, group / owning department “Med Biostatistics & Data Sciences”, DMS for controlled documents.
9.3	*BI-VQD-01538:* “Standards for Reporting of Clinical Trials and Project Summaries”, current version, group / owning department “Med Clinical Development & Operations”, DMS for controlled documents.
9.4	*BI-VQD-01041*: “Analysis and Presentation of AE data from clinical trials”, current version, group / owning department “Med Biostatistics & Data Sciences”, DMS for controlled documents.
9.5	*BI-VQD-12045_40-413:* “Identify and Manage Important Protocol Deviations (iPD)”, current version, group / owning department “Med Clinical Development & Operations”, DMS for controlled documents.
9.6	*BI-VQD-01535*: “Handling, Display and Analysis of Laboratory Data”, current version, group / owning department “Med Biostatistics & Data Sciences”, DMS for controlled documents.
9.7	*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.
[redacted]	
9.9	Rubin, DB. Multiple Imputation for Nonresponse in Surveys. New York: John Wiley & Sons. 1987. [R12-2378]
9.10	Bonella F, Maher T M, Cottin V, et al. Consistent effect of nintedanib on reducing FVC decline across interstitial lung diseases (ILDs)[J]. Eur Respir J, 2020, 56(64): 739.
9.11	Bonella F, Cottin V, Valenzuela C, et al. Meta-analysis of effect of nintedanib on reducing FVC decline across interstitial lung diseases[J]. Advances in Therapy, 2022, 39(7): 3392-3402.
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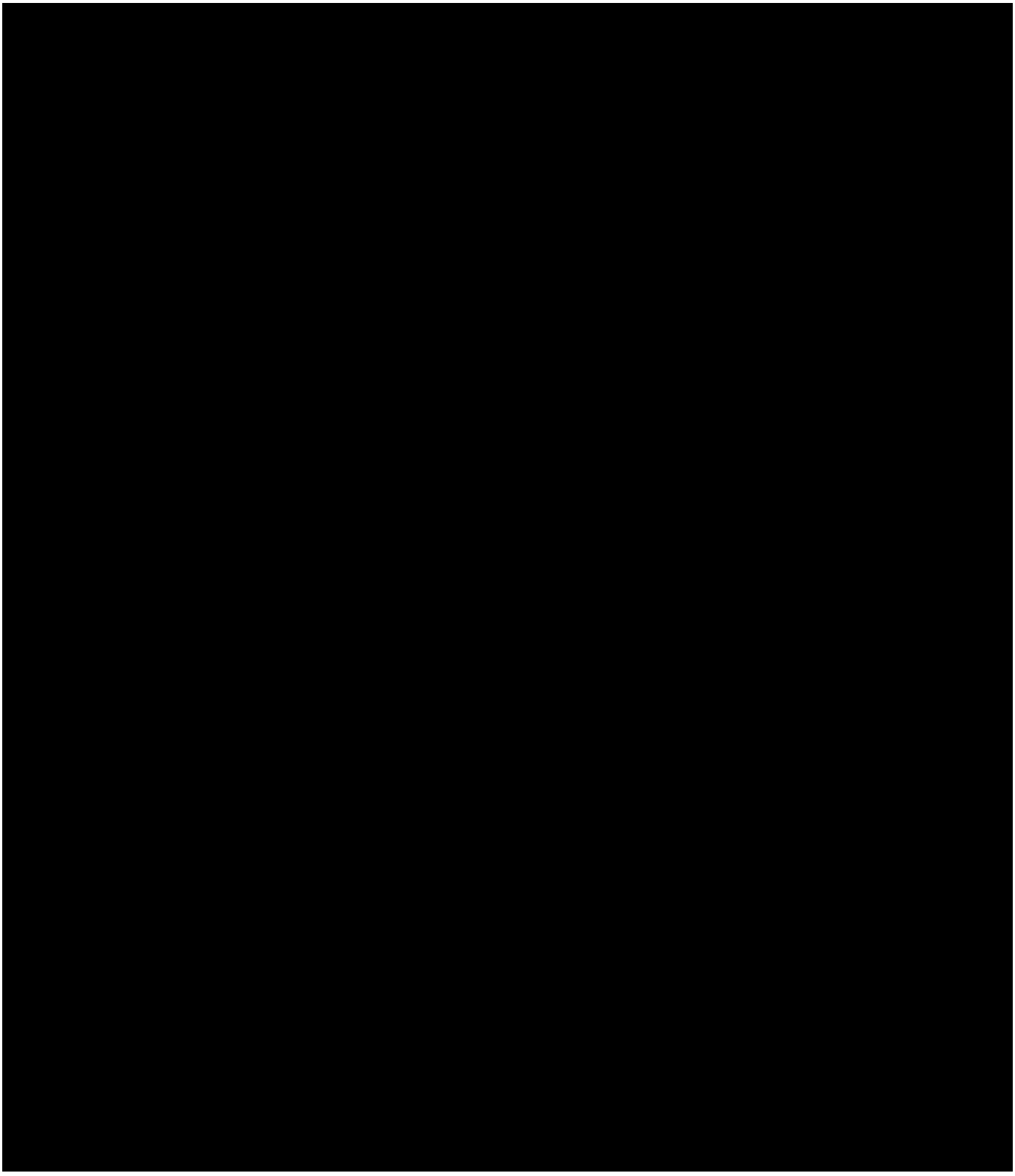

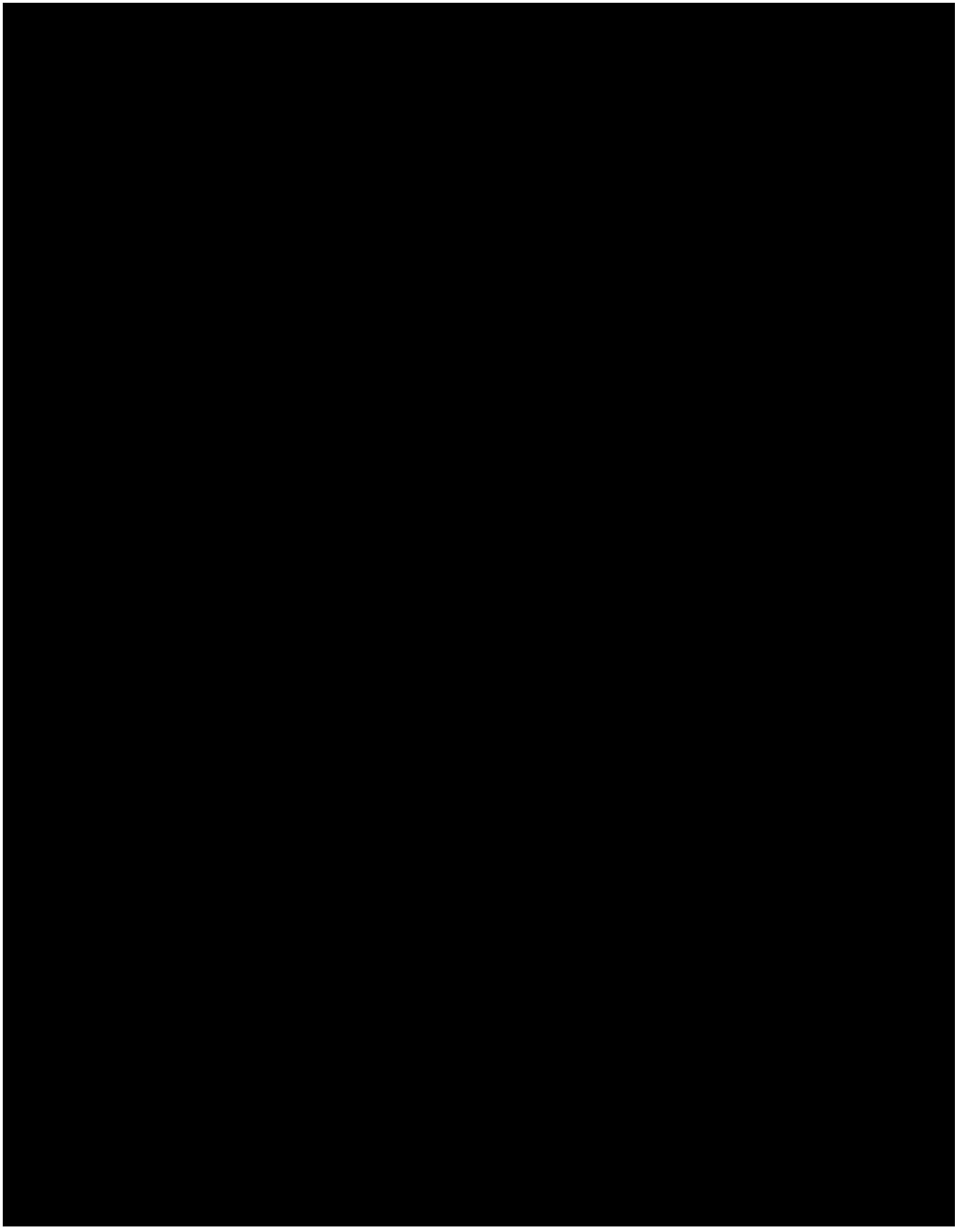

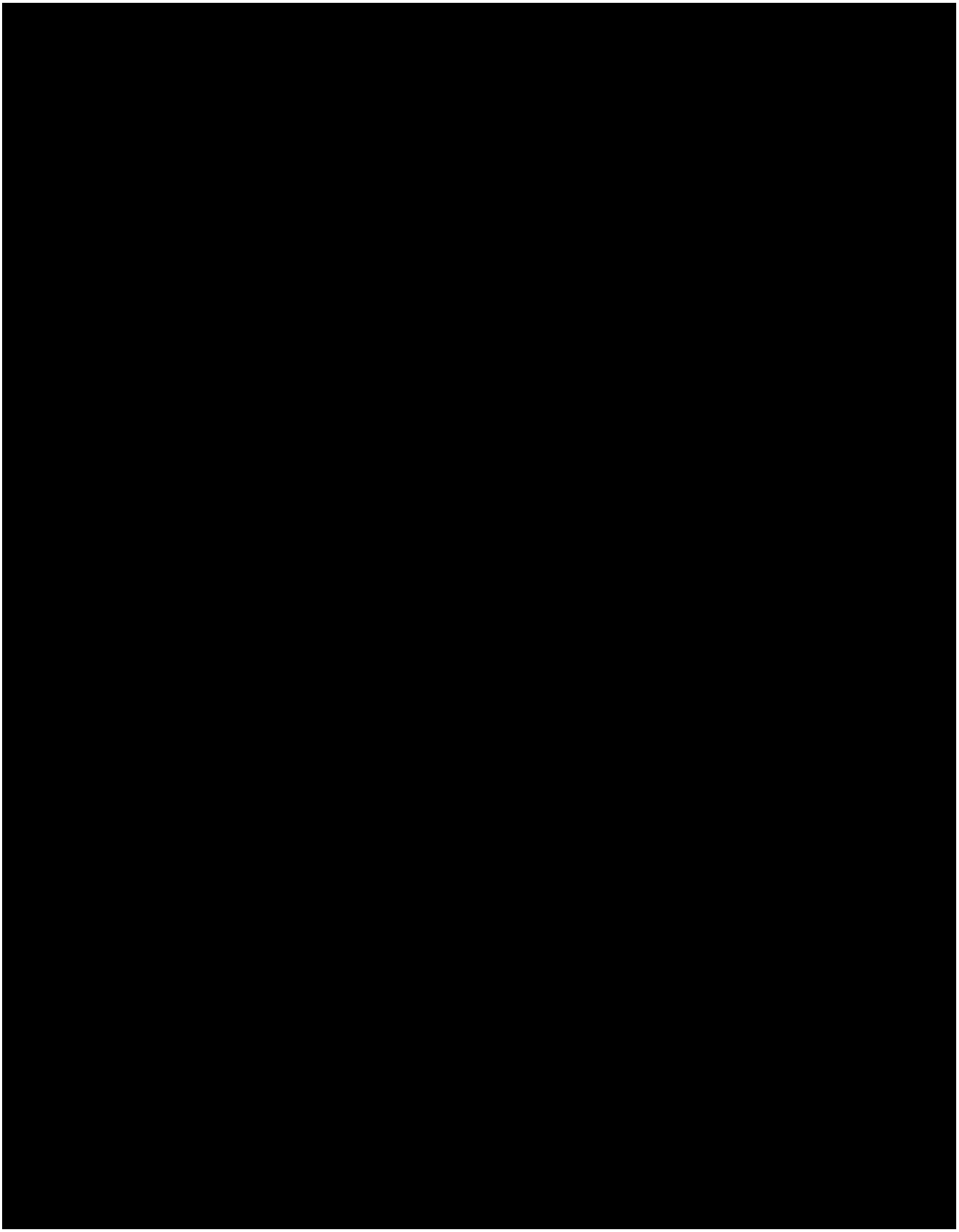

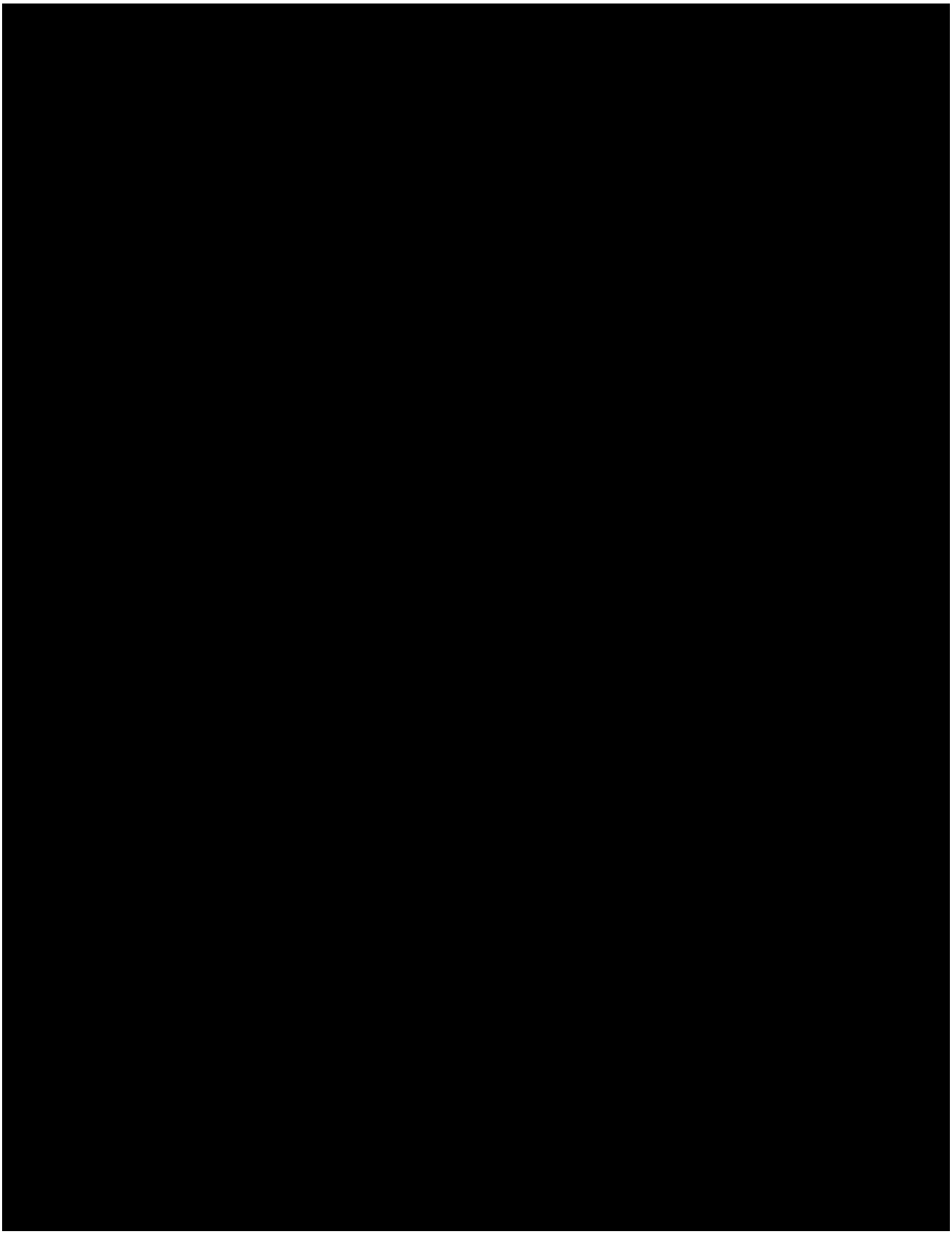

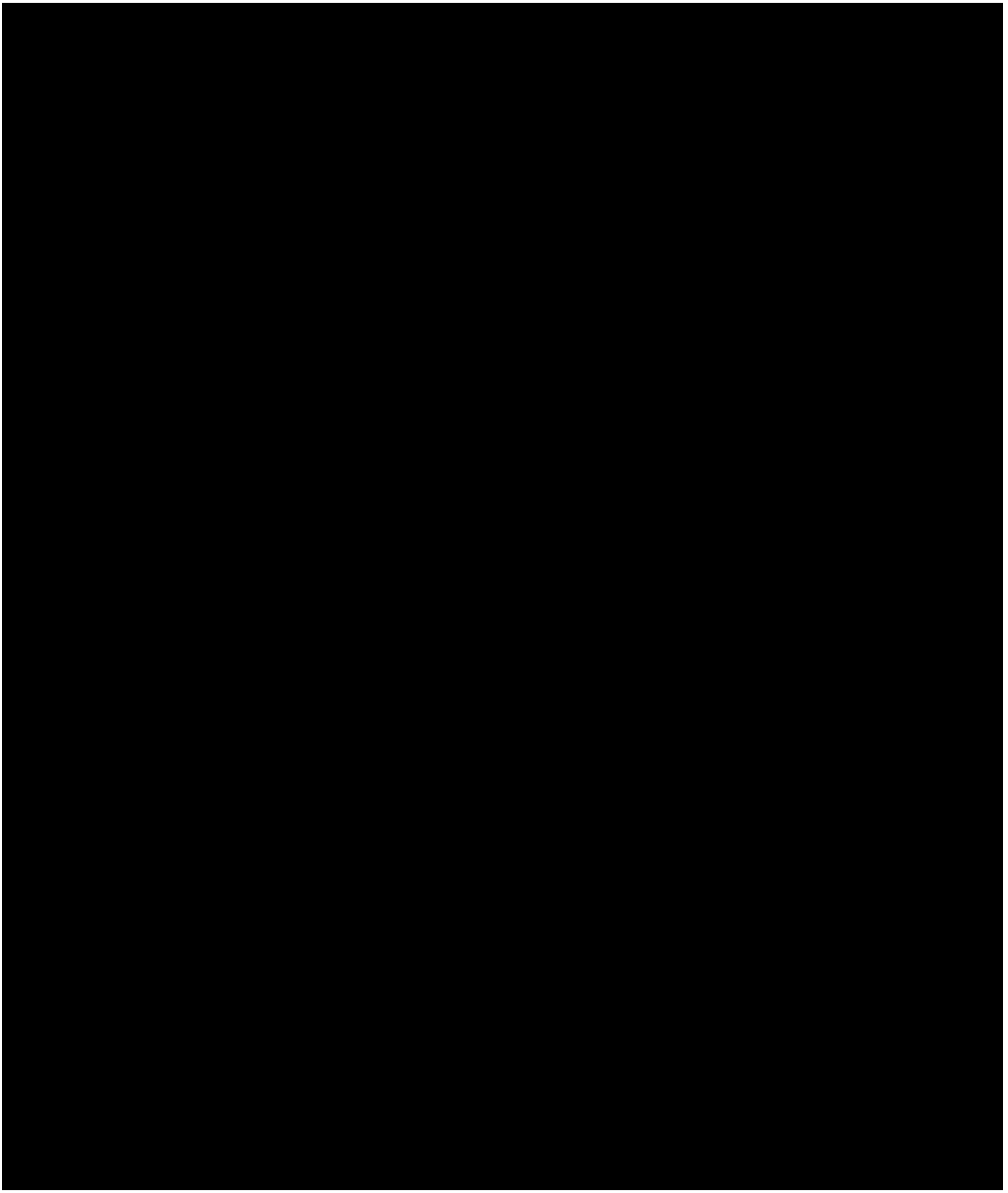

11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1.0	**07-JUN-24**	[redacted]	None	This is the final TSAP.