TRIAL STATISTICAL ANALYSIS PLAN

c30253575-01

BI Trial No.:	1199-0337
Title:	A double blind, randomised, placebo-controlled trial to evaluate the dose-exposure and safety of nintedanib per os on top of standard of care for 24 weeks, followed by open label treatment with nintedanib of variable duration, in children and adolescents (6 to 17 year-old) with clinically significant fibrosing Interstitial Lung Disease
Investigational Product(s):	Ofev®, nintedanib
Responsible trial statistician(s):	[redacted] Phone: +[redacted]
Date of statistical analysis plan:	09 MAR 2022 SIGNED
Version:	1

1. TABLE OF CONTENTS

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

LIST OF TABLES

LIST OF FIGURES

2. LIST OF ABBREVIATIONS

See Medicine Glossary:
http://glossary

Term	Definition / description
AE	Adverse event
AESI	Adverse event of Special Interest
ADS	Analysis Dataset
ALK	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUCτ,ss	Area under the Plasma Concentration-Time Curve at Steady State
AUCτ,ss_D	Dose normalized AUCτ,ss
BI	Boehringer Ingelheim
bid	bis in die
[redacted]	
CDG	Customized Drug Groupings
cHP	Chronic Hypersensitivity Pneumonitis
CL/F_{ss}	Apparent Clearance of the Analyte in the Plasma at Steady-State following extravascular multiple dose administration
C_{max}	Maximum Concentration in Plasma
$C_{max,ss}$	Maximum Measured Concentration of the Analyte in Plasma at Steady State
CT	Computed Tomography
CTD	Connective Tissue Disease
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
Δ	Delta, i.e. difference
DBL	Database Lock
D_{LCO}	Diffusing Capacity of the Lung for Carbon Monoxide
DMARDs	Disease-Modifying Anti-Rheumatic Drugs
DRC	Disease Review Committee
DV domain	SDTM Protocol Deviations domain model
eCRF	electronic Case Report Form
EDMS	Electronic Document Management System

Term	Definition / description
EMA	European Medicines Agency
EOT	End of Treatment
FPI	First patient in (= first patient randomised)
FVC	Forced Vital Capacity
g	Gramm
[redacted]	
Hb	Haemoglobin
HRCT	High-Resolution Computer Tomography
ICH	International Conference on Harmonisation
ILD	Interstitial Lung Disease
INR	International Normalized Ratio
iPD	Important Protocol Deviation
IRT	Interactive Response Technology
LDH	Lactate dehydrogenase
m	Meter
MACE	Major Adverse Cardiovascular Events
MAP	Meta-analytic predictive
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligramm
min	Minute
ml	Milliliter
MCMC	Markov Chain Monte Carlo
MMRM	Mixed effect Model Repeat Measurement
N	Number
PedsQL™	Pediatric Quality of Life Questionnaire™
P-gp	Permeability Glycoprotein
PK	Pharmacokinetic(s)
PopPK	Population Pharmacokinetics
pred	Predicted
PT	Preferred Term
REML	Restricted Maximum Likelihood
REP	Residual Effect Period

Term	Definition / description
RS	Randomised Set
RPM	Report Planning Meeting
SCS	Screened Set
SD	Standard deviation
SE	Standard Error
SEM	Standard Error of the Mean
6MWT	Six-Minute Walk Test
SoC	Standard of Care
SOC	System organ class
SpO_2	Saturation of oxygen
TMF	Trial Master File
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
ULN	Upper Limit of Normal
[redacted]	
WHO-DD	World Health Organization Drug Dictionary

3. INTRODUCTION

As per ICH E9 (1) the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

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

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

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

4.1 ADDITIONS / NEW ANALYSES

In addition to the evaluations depicted in the CTP, the following evaluations will be added:

- Secondary endpoint analysis:

- Further endpoint analysis:

4.2 CHANGES

5. ENDPOINT(S)

In this section, more details are given regarding endpoints. Please note that for all endpoints and analyses, Section 6.7 should be consulted for baseline value definition.
Please note, that due to the design of the study, not all time points will be available for all patients.

Handling of missing data points is described in Section 6.6.

For endpoints where the "date of last contact" is utilized, the following will apply:

- The last contact date when the patient 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 an Adverse Event date is planned to be imputed for the analysis, the imputed date will also be used for the definition of "date of last contact"):
    - Date of last visit (e.g. for spirometry), date of last reported Adverse Event (AE) (excluding censored dates), date of last reported concomitant treatment, date of last laboratory sample, date of last drug intake, date of last reported dose change / interruption, end of study participation date (as documented on the End of Study eCRF page if the reason for not completing the planned observation period is NOT "Death"), vital status date (from the vital status eCRF page if the patient is known to be alive) and the latest of vital status date / last successful contact date (from the End of Study eCRF page if the patient was lost to follow-up).

5.1 PRIMARY ENDPOINT(S)

The primary PK endpoint is the AUCτ,ss based on sampling at steady state (at week 2 and week 26 visit).
For patients receiving nintedanib in Part A, PK profiles on week 2 and week 26 are planned to be collected. For the primary endpoint AUCτ,ss the AUCτ,ss at week 2 will be used. If the week 2 value is missing, then it will be replaced by available AUCτ,ss at week 26 (or later, if PK visit was postponed). For patients receiving placebo in Part A and nintedanib in Part B, AUCτ,ss evaluated based on
PK profiles at week 26 (or later, if PK visit was postponed) will be used (which corresponds to week 2 on active treatment).

The primary safety endpoint is the N (%) of patients with treatment-emergent adverse events at week 24, i.e., during the planned double-blind period of the trial.
Thus, the number of patients experiencing at least one adverse event during the double-blind period of the trial will be analyzed, see Section 7.8.

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

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

5.2.2 Secondary endpoint(s)

Endpoints will be used as defined in the CTP Section 2.1.3. Additional specifications are given below.

5.2.2.1 N (%) of patients with treatment-emergent pathological findings of epiphyseal growth plate on imaging at week 24, and week 52

Pathological findings which were already present at baseline imaging will NOT be considered treatment-emergent in this analysis, in spite identified after start of treatment, in order to be able to separate:

- findings that were identified on the follow-up MRI/x-ray and were already present on the baseline MRI/x-ray (i.e. not treatment-emergent)
- findings that were identified on the follow-up MRI/x-ray and were NOT already present on the baseline MRI/x-ray (i.e. treatment-emergent).

There are two possible kinds of predefined pathological findings for the growth plate recorded in the Safety Read Results:

- Pathological Findings at the Distal Femur
- Pathological Findings at the Proximal Tibia

A pathological finding of epiphyseal growth plate is defined as a pathological finding at the distal femur or the proximal tibia.

More precisely,

- Thickening of the epiphyseal growth plates
- Swelling of articular cartilage

will be captured as pathological findings.

Whereas,

- Narrowing of the lucent growth plate margin compared to the baseline time point (at post-baseline time points only)
- Metaphyseal lines
- Other findings

will only be captured as pathological findings if judged pathological.

Frequencies will be reported in a cumulative way over 24 and 52 weeks, respectively.

5.2.2.2 N (%) of patients with treatment-emergent pathological findings on dental examination or imaging at week 24, and week 52

Pathological findings which were already present at baseline imaging/examination will NOT be considered treatment-emergent in this analysis, in spite identified after start of treatment, in order to be able to separate:

- findings that were identified on the follow-up panoramic x-ray and were already present on the baseline panoramic x-ray (i.e. not treatment-emergent)
- findings that were identified on the follow-up panoramic x-ray and were NOT already present on the baseline panoramic x-ray (i.e. treatment-emergent).

For the dental examination, pathological findings will be identified through the dental examination eCRF pages where the question 'Is this a new abnormal finding' is answered with 'Yes' and thus, an AE page is filled in.
If a baseline pathological finding is reported with a post-baseline worsening, it will be counted as treatment-emergent from the time point of worsening.

For the dental imaging, a pathological finding is defined as at least one tooth being reported in the Safety Read Results with at least one of the following findings:

1. Change in root length (at post-baseline time points only)
    - "Stunted growth (e.g., premature closing of the apex/apices with a blunted root appearance)"
    - "Accelerated growth (abnormally long roots exceeding 2/3rd the total length of the tooth)"
2. Extra/Supernumerary teeth
3. Impacted permanent teeth
4. Additional findings ("cyst present", "abscess is present", "solid lesion is present", "bone abnormality is present")
5. Additional findings "other findings" (incl. comment)

Frequencies will be reported in a cumulative way over 24 and 52 weeks, respectively.

5.2.2.3 N (%) of patients with treatment-emergent adverse events over the whole trial

The analysis will include all adverse events during the double-blind and open-label periods of the trial, see Section 7.8.1.

5.2.2.4 Change in height, sitting height, leg length from baseline at week 24, and week 52, week 76, and week 100

The absolute change from baseline in height, the absolute change from baseline in sitting height and the absolute change from baseline in leg length will each be computed and evaluated separately.

As the sitting height has been measured incorrectly (i.e. total distance between the floor and the top of patient's head with the patient in a sitting position) at some sites (2), the main analysis of this endpoint will contain only the correctly measured (i.e. total distance between the sitting surface and the patients top of patient's head with the patient in a sitting position).

[redacted]

5.2.2.5 Change in Forced Vital Capacity (FVC) % predicted from baseline at week 24, and week 52

The absolute change from baseline in FVC % predicted (percent of predicted) at week 24 and week 52 will be used. The predicted values are calculated by the vendor according to Global Lungs Initiative (GLI) 2012 equations (4).

5.2.2.6 Absolute change from baseline in Pediatric Quality of Life Questionnaire (PedsQL) at week 24, and week 52

Health-related quality of life will be assessed using the PedsQL™ questionnaire. Depending on the age there are PedsQL™ Young Child Report (ages <8 years), Child Report (ages 8-12 years) and Report for Teens (ages >13.0 years). Furthermore, the respective Parent Reports are filled in by the parents of the child. For more details see CTP Section 5.6.1.
The questionnaire consists of 23 items and 4 dimensions: physical functioning, emotional functioning, social functioning and school functioning.
The PedsQL™ evaluation will primarily focus on the absolute change from baseline in the total score at week 24, and week 52.
In addition, the absolute change from baseline in the psychosocial health summary score (sum of emotional, social, and school functioning scales) and the absolute change from baseline in the physical health summary score (physical functioning score) will be presented.

A 5-point Likert response scale (0 = never; 1=almost never; 2=sometimes; 3=often; 4=almost always) is used in all cases except for the Young Child Report, where a 3-point scale (0=not at all; 2=Sometimes; 4=a lot) is used.

Items are reverse-scored and linearly transformed to a 0-100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0), so that higher scores indicate better health-related quality of life (HrQoL).
The specific instructions for deriving the PedsQL™ total score are provided in Appendix Section 9.1.

5.2.2.7 Change in oxygen saturation (SpO_2) on room air at rest from baseline at week 24, and week 52

Oxygen saturation on room air at rest will be analysed.

5.2.2.8 Change in 6-min walk distance from baseline at week 24, and week 52

The exercise capacity of the patient will be recorded as distance covered in 6 minutes on the respective eCRF page. Furthermore, continuous pulse oximetry (SpO_2) will be performed and additional measurements such as pulse rate and blood pressure conducted.

The 6-minute walk test evaluation will primarily focus on the absolute change from baseline in the distance walked. Oxygen saturation measured by SpO_2, vital signs and BORG CR-10 Scales of the patient will be presented as scatterplots (each parameter versus age).
Only one value per period (pre-test, during test, post-test and recovery) patient, parameter and visit will be shown: for pulse rate, blood pressure and BORG scales the highest; for oxygen saturation and walking time the lowest value.
For more details please refer to CTP Section 5.1.6.

5.2.2.9 Patient acceptability based on the size of capsules at week 24

The acceptability questionnaire will be filled in by the patient. Further, to collect the investigator / site staff impression about the patient's acceptability of the study medication intake, the treatment acceptability questionnaire for the investigator or investigational site staff will be completed by the investigator / site staff.

The answer to question 3 on the patient's questionnaire "How is the size of the capsule" of the "Acceptability Questionnaire for the patient" will be used with categories "OK (=acceptable)", "Large", "Very large".
On the investigator questionnaire, the question 3 "If the drug was not taken, was this due to (check all answers that you consider applicable for this patient at this point in time" and others will be assessed to retrieve more information on the acceptability and palatability of the capsules.

An analysis of patients not taking the 100 mg b.i.d. or 150 mg b.i.d. form, i.e. who take 4x25 mg b.i.d. or 6x25 mg b.i.d., will be conducted in order to examine the swallowability.

5.2.2.10 Patient acceptability based on the number of capsules at week 24

The answer to question 4 "How easy was to swallow the given number of capsules" of the "Acceptability Questionnaire for the patient" will be used with categories "I had no problem swallowing them (=acceptable)", "I swallowed them, but it was difficult", "I could not swallow them sometimes".

See also Section 5.2.2.9.

5.2.2.11 Time to first respiratory-related hospitalization over the whole trial

Time to first respiratory-related hospitalization assessment will be based on the date of hospitalization collected on a specific hospitalization eCRF page.

For those patients who experience a respiratory-related hospitalization, time to first respiratory-related hospitalization [days] will be computed as:

- Date of first respiratory-related hospitalization – date of first drug intake + 1

Patients who did not experience any event during their trial participation will be censored according to the mechanism for censoring as described in Table 5.2.2.11: 1.

Table 5.2.2.11: 1 Censoring Rules for Time to first respiratory-related hospitalization over the whole trial

Rule #	Situation	Outcome (event or censored)	Date of event or censoring
1	Patient had a documented respiratory-related hospitalization and the date of the event is known	Event	Date of event
2	Patient had a documented respiratory-related hospitalization and the date of the event is unknown	Event	Imputed date of event (imputation see Section 6.6.2.2)
3	Patient did not have a documented respiratory-related hospitalization (no matter whether the patient is alive or died or patient status is unknown)	Censored	Date of last contact when the patient was known to be alive and event free

5.2.2.12 Time to first acute Interstitial Lung Disease (ILD) exacerbation or death over the whole trial

For those patients who either experience acute ILD exacerbations or who die due to any cause at any point in the study, time to first acute ILD exacerbation or death [days] will be computed as:

- Date of first documented acute ILD exacerbation or death (whichever occurs earlier) – date of first drug intake + 1

Patients who did not experience any event during their trial participation will be censored according to the mechanism for censoring as described in Table 5.2.2.12: 1.

Table 5.2.2.12: 1 Censoring Rules for Time to first acute ILD exacerbation or death over the whole trial

Rule #	Situation	Outcome (event or censored)	Date of event or censoring
1	Patient had a documented acute ILD exacerbation or died and the date of the event is known	Event	Earliest Date of event

Table 5.2.2.12: 1 Censoring Rules for Time to first acute ILD exacerbation or death over the whole trial (continued)

Rule #	Situation	Outcome (event or censored)	Date of event or censoring
2	Patient had a documented acute ILD exacerbation or died and the date of the event is unknown	Event	Imputed date of event (imputation see Section 6.6.2.2)
3	Patient did not have a documented acute ILD exacerbation and is alive	Censored	Date of last contact when the patient was known to be alive and event free
4	Patient status is unknown	Censored	Date of last contact when the patient was known to be alive and event free

5.2.2.13 Time to death over the whole trial

Date of death for an individual patient will be obtained from either the AE reporting page for patients with AEs leading to death or the information from the vital status assessment eCRF page. The start date of time at risk is the date of first drug intake, and, in general, patients who did not die during the trial will be censored at the last known date when the patient was alive.

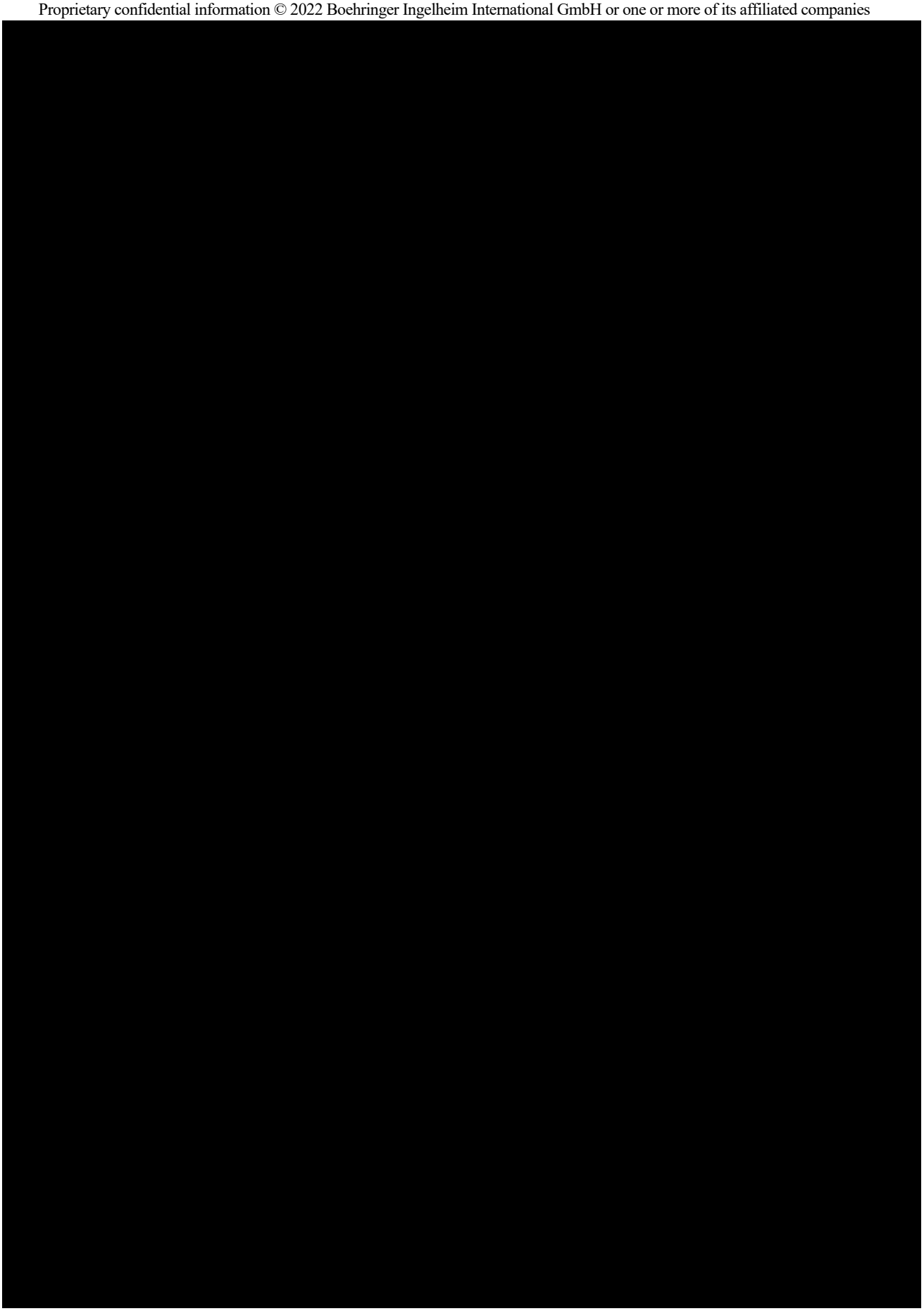
For patients with known date of death (regardless of the cause of death) at any point within the trial, the time to death will be computed as:

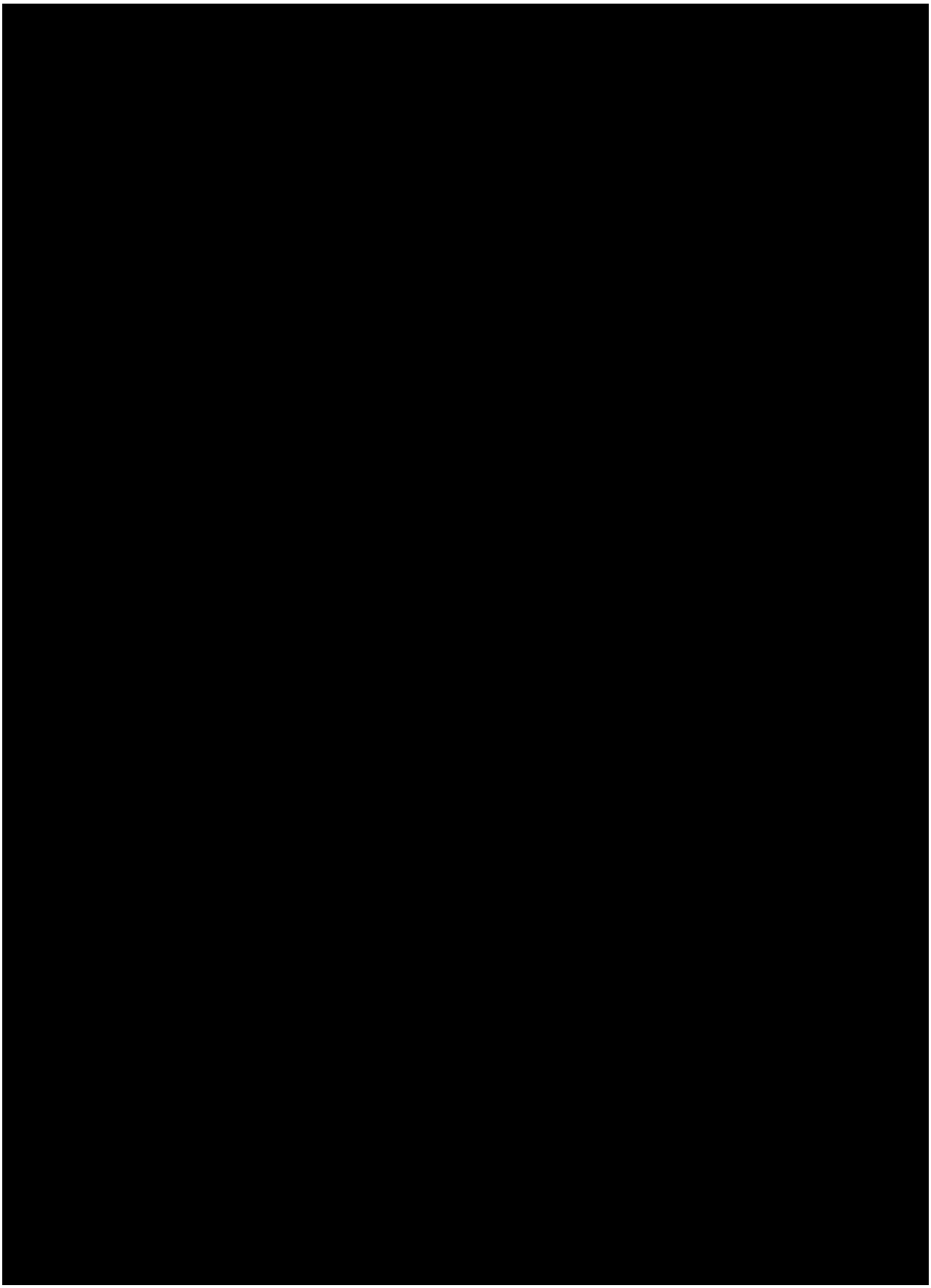
- Date of death – date of first drug intake + 1

Patients who did not experience any event during their trial participation will be censored according to the mechanism for censoring as described in Table 5.2.2.13: 1.

Table 5.2.2.13: 1 Censoring Rules for Time to death over the whole trial

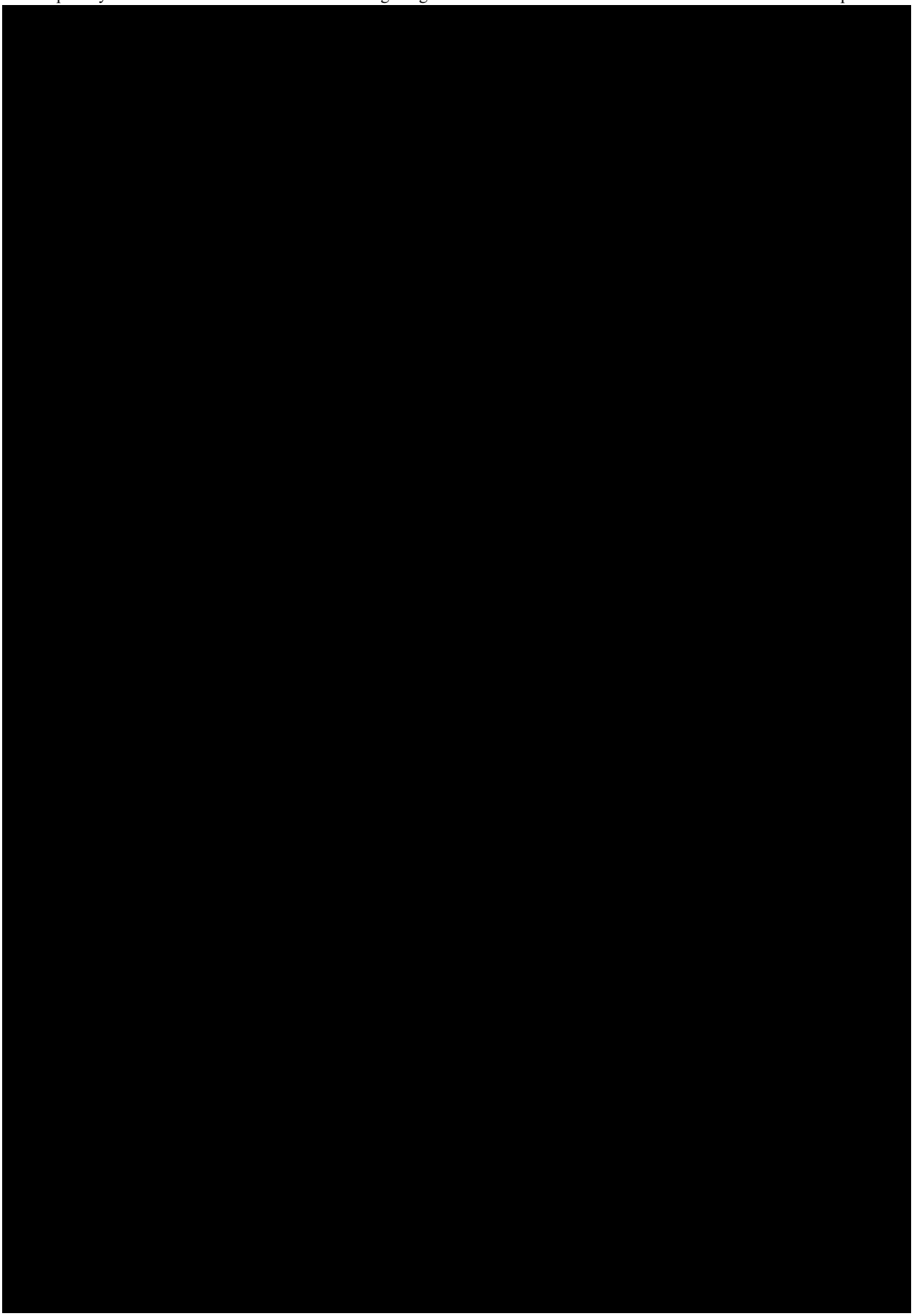
Rule #	Situation	Outcome (event or censored)	Date of event or censoring
1	Patient died and date of Death is known	Event	Date of event
2	Patient died and date of Death is unknown	Event	Imputed date of event (imputation see Section 6.6.2.2)
3	Patient is alive	Censored	Date of last contact when the patient was known to be alive
4	Patient status is unknown	Censored	Date of last contact when the patient was known to be alive

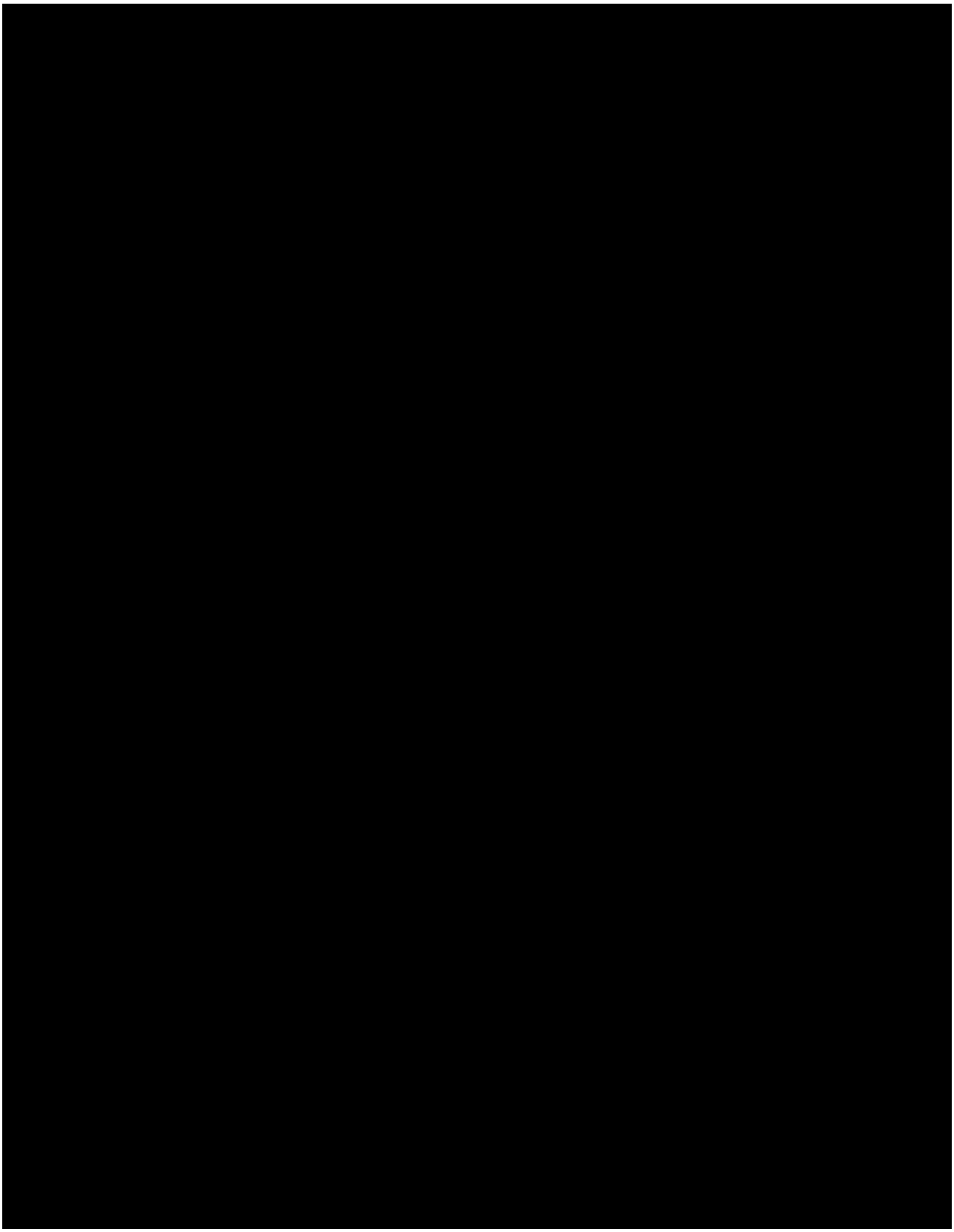




5.4.1.1 Demographic data

- Gender (Male; Female)
- Ethnicity (Hispanic/Latino; Not Hispanic/Latino)
- Race: single race respondents, multiple race respondents (all combinations ticked), and all race categories regardless of how many race categories were ticked
- Age [years] at time of informed consent (transferred by IRT)*
- Age at time of informed consent (transferred by IRT) in categories [years] (≥6 and <12; ≥12 and <18)*
- Weight [kg] at baseline and historical weight (up to 2 years prior to screening) as continuous variable and in classes (<13.5; ≥13.5 and <23; ≥23 and <33.5; ≥33.5 and <57.5; ≥57.5)
- Height [cm] (standing and sitting) at baseline and historical (up to 2 years prior to screening)
- Tobacco consumption (Never, Current, Former)
- Pack years (for patients who tick “Current” or “Former” in the variable “Tobacco consumption”) as continuous variable





5.4.3 Exposure

The date of first administration is recorded at visit 2 (day 1) for the blinded period and at visit 6 (week 24) for the open-label period of the trial. The blinded exposure period ends with the first documented intake of the open-label treatment (day of visit excluded). Vice versa, the open-label exposure period begins with the first documented intake of the open-label treatment (day of visit included).
If the open-label exposure period is not started, then the double-blind exposure period ends with the day of last intake of blinded treatment.
All of the following definitions regarding exposure will be calculated separately for the double-blind period, the nintedanib exposure period and over the whole trial.

Duration of exposure [weeks] will be calculated as

$$\frac{\textit{Date of last administration - date of first administration during respective period + 1[days]}}{7}$$

Treatment interruptions between date of first administration and date of last administration during the respective period will not be subtracted from this duration of exposure.

Duration of exposure will be summarized as continuous variable [weeks] and in categories:

- Double-blind period:
  - <=2 weeks (14 days)
  - >2 to <=6 weeks (42 days)
  - >6 to <=12 weeks (84 days)
  - >12 to <=18 weeks (126 days)
  - >18 to <=24 weeks (168 days)
  - >24 weeks (168 days)

- Nintedanib exposure period:
  - <=2 weeks (14 days)
  - >2 to <=6 weeks (42 days)
  - >6 to <=12 weeks (84 days)
  - >12 to <=24 weeks (168 days)
  - >24 to <=36 weeks (252 days)
  - >36 to <=52 weeks (364 days)
  - >52 to <=64 weeks (448 days)
  - >64 to <=76 weeks (532 days)
  - >76 weeks (532 days)

Further categories might be defined if needed.

Duration of exposure on dose assigned according to weight range [weeks] will be calculated per period as

$$\frac{\textit{Sum of durations on-treatment with dose effectively taken according to weight range [days]}}{7}$$

Duration of exposure on reduced dose due to AE [weeks] will be calculated per period as

$$\frac{\textit{Sum of durations on-treatment with reduced dose effectively taken due to AE [days]}}{7}$$

Calculating the duration of exposure on dose assigned according to weight range and on reduced dose due to AE, time periods with treatment interruptions as well as on dose reduced due to other reasons will be excluded.
In case the weight of the patient on reduced dose reduces in a way to match this lower dose level, the duration of exposure on reduced dose ends.

Summary of dose changes will be presented, containing

- N (%) of patients with at least one dose reduction
- Number of dose reductions
- Reasons for dose reductions
- N (%) of patients with at least one dose increase
- Number of dose increases
- Reasons for dose increases

Off-treatment duration [weeks] will be calculated per period as

$$\frac{\textit{Sum of all treatment interruption durations between date of first administration and date of last administration during the respective period [days]}}{7}$$

Total dose [g] will be calculated as

*Sum of durations of exposure on x g in respective period [days] *2 * x g,*

with x in 0.025, 0.05, 0.075, 0.1, 0.15.

Dose intensity [%] will be calculated as the amount of drug received during respective period multiplied by 100% and divided by the amount of drug that would have been administered, i.e. dose xx mg bid (depending on the body weight) over the respective period (or until study discontinuation).

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

- <=30%
- >30 to <=50%
- >50 to <=90%
- >90 to <100%
- >= 100%

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

- Time to first dose reduction (not due to weight-based adjustment) [days]

- Time to first treatment interruption [days]
- Time to premature treatment discontinuation [days]

Time-to-event [days] for exposure-related analyses is derived based on first study drug intake in the respective study period as

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

For the above mentioned time-to-event analyses patients with no such event occurred during the respective period will be censored according to the mechanism for censoring as described in Table 5.4.3: 1.

Table 5.4.3: 1 Censoring rules for exposure-related time-to-event analyses

Rule #	Situation	Outcome (event/censored)	Date of event/censoring
1	Patient had a documented event during the respective period and the date of the event is known	Event	Earliest date of event
2	Patient had a documented event during the respective period and the date of the event is unknown	Event	Imputed date of event (as defined in Section 6.6.3.3)
3	Patient had no documented event during the respective period and already terminated study drug (last intake on End of treatment eCRF page available)	Censored	Date of last study drug intake
4	Patient neither had a documented event nor terminated study drug during respective period	Censored	Date of last study drug intake or end date of respective period, whichever is earlier

5.4.4 Liver enzyme and bilirubin elevations

The analysis of liver enzyme and bilirubin elevation will be done separately for each period (double-blind period, nintedanib exposure period, over the whole trial).
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 patients presenting signs of hepatic injury will be summarised, based on the following definition for signs of hepatic injury:

- ALT and/or AST >=8 fold ULN
- ALT and/or AST >=3 fold ULN and total bilirubin >=2 fold ULN [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 9.4: 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.

5.4.4.1 Time-to-event analyses for liver enzyme elevations

- Time to liver enzyme and bilirubin elevation (ALT and/or AST >= 3xULN and bilirubin >= 2xULN)
- Time to liver enzyme elevation (ALT and/or AST >= 5xULN)
- Time to liver enzyme elevation (ALT and/or AST >= 3xULN)

Time to first occurrence of the above described liver enzyme elevations [days] will be analyzed as

Date of event/censoring – Date of first treatment intake + 1 day.

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

Table 5.4.4.1: 1 Censoring rules for time to first occurrence of liver enzyme elevations

Rule	**Situation**	**Outcome**	**Date of event/censoring**
1	Patient had a documented event during treatment or REP[1] of respective period	Event	Earliest date of event
2	Patient had no documented event during treatment or REP[1] of respective period.	Censored	Earliest date of • end date of REP of respective period, • date of last contact when patient was known to be alive and event free, • date of death.

[1] See Sec. 6.1 for definition of Residual Effect Period (REP)

These times to onset of first event will also be summarized in categories:

- Double-blind period:
  - <=2 weeks (14 days)
  - >2 to <=6 weeks (42 days)
  - >6 to <=12 weeks (84 days)
  - >12 to <=18 weeks (126 days)
  - >18 to <=24 weeks (168 days)
  - >24 weeks (168 days)
  - Censored

- Nintedanib exposure period, over the whole trial:
  - <=2 weeks (14 days)
  - >2 to <=6 weeks (42 days)
  - >6 to <=12 weeks (84 days)
  - >12 to <=24 weeks (168 days)
  - >24 to <=36 weeks (252 days)
  - >36 to <=52 weeks (364 days)
  - >52 to <=64 weeks (448 days)
  - >64 to <=76 weeks (532 days)
  - >76 weeks (532 days)
  - Censored

Further categories might be defined if needed.

5.4.5 Vital signs

Weight minimum relative change from baseline will be summarized as continuous variable and in categories:

- Relative decrease of more than 10% (excl.)
- Relative decrease of between 5% (excl.) and 10% (incl.)
- Relative decrease of between 0% (excl.) and 5% (incl.)
- Relative increase (>=0%)

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

For treatment specifications, please refer to CTP Section 4.

The following trial periods will be defined: screening, post-randomization, blinded treatment period (with sub-periods treatment period, off-treatment, residual effect period and follow-up), open-label treatment period (with sub-periods treatment period, off-treatment, residual effect period and follow-up), nintedanib exposure period (with sub-periods treatment period, off-treatment, residual effect period and follow-up), and post-study as follows
(Note: As described below, the last day of each of the following periods is excluded from the respective period. It defines the first day of the subsequent period):

- Screening: from informed consent to randomization

- Post-randomization (optional[a]): from randomization to first randomized trial drug intake in blinded treatment period

- Double-blind period:
    - Blinded treatment period: from first randomized trial drug intake (or re-start of treatment if interruption) to last blinded trial drug intake (or the day before start date of interruption, if interruption) plus one day
    - Blinded off-treatment (optional[a]): from start date of interruption to re-start of blinded treatment
    - Residual Effect Period: the Residual Effect Period (REP) of nintedanib for the pediatric program is 28 days. This is the period from the last blinded trial drug intake plus one day to last blinded trial drug intake plus 28 days plus one day or the day of first open-label treatment administration (whichever occurs earlier)
    - Blinded follow-up (optional[a]): from last blinded trial drug intake plus 29 days up to the beginning of post-study period. This period is only created if last blinded trial drug intake took place more than 28 days before trial completion, or for patients having prematurely discontinued the blinded treatment and still continuing the trial

- Nintedanib exposure period:
    - Nintedanib treatment period: from first nintedanib intake (or re-start of treatment if interruption) to last nintedanib intake (or the day before start date of interruption, if interruption) plus one day
    - Nintedanib off-treatment (optional[a]): from start date of interruption to re-start of nintedanib treatment
    - Nintedanib residual effect period: from the last nintedanib intake plus one day to last nintedanib intake plus 28 days plus one day
    - Nintedanib follow-up (optional[a]): from last nintedanib intake plus 29 days up to the beginning of post-study period. This period is only created if last trial drug intake took place more than 28 days before trial completion, or for

patients having prematurely discontinued the treatment and still continuing the trial

- Over the whole trial:
  - Whole trial treatment period: from first randomized trial drug intake (or re-start of treatment if interruption) to last study drug intake (or the day before start date of interruption, if interruption) plus one day
  - Whole trial off-treatment (optional[a]): from start date of interruption to re-start of treatment
  - Whole trial residual effect period: from the last trial drug intake plus one day to last trial drug intake plus 28 days plus one day
  - Whole trial follow-up (optional[a]): from last trial drug intake plus 29 days up to the beginning of post-study period. This period is only created if last trial drug intake took place more than 28 days before trial completion, or for patients having prematurely discontinued the treatment and still continuing the trial

- Open-label period:
  - Open-label treatment period: from first open-label nintedanib intake (or re-start of treatment if interruption) to last open-label nintedanib intake (or the day before start date of interruption, if interruption) plus one day
  - Open-label off-treatment (optional[a]): from start date of interruption to re-start of open-label treatment
  - Open-label residual effect period: from the last open-label trial drug intake plus one day to last open-label trial drug intake plus 28 days plus one day
  - Open-label follow-up (optional[a]): from last open-label trial drug intake plus 29 days up to the beginning of post-study period. This period is only created if last open-label trial drug intake took place more than 28 days before trial completion, or for patients having prematurely discontinued the open-label treatment and still continuing the trial

- Post-study period: from the latest of
  - last trial drug intake plus 29 days
  - end of study participation date (from the End of Study page of the eCRF)
  - follow-up visit
  - early end of treatment visit plus 1 day .

  This period is not created if date of first trial drug intake in extension trial is before last trial drug intake plus 28 days.

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

Assessments on day of first open-label intake will be handled as follows:

- Assessments with time record: period is assigned based on time stamp (if time lies prior to open-label start then double-blind period; otherwise, open-label period)
- Assessments without time record: assigned to double-blind period, even if interruption prior to open-label start (if interruption longer than REP, then assessment falls into double-blind follow up period and thus, will not be evaluated anymore).
- Exception: AEs and concomitant medications with start date on day of open-label start will be assigned to the open-label period.

Further details will be specified in the ADS plan.

If in the double-blind period an interruption is not followed by a re-start of blinded treatment then this is counted as (early) discontinuation of the blinded treatment period.
Over the whole trial, this will be counted as whole trial off-treatment period.

For safety analyses, data up to the end of the double-blind residual effect period / whole trial residual effect period / nintedanib residual effect period will be considered on-treatment.

For on-treatment efficacy analyses, data up to the day after last trial drug intake (included) will be considered.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Handling of iPDs in analysis is included in the DV domain specifications and stored within the TMF in EDMS.

6.3 SUBJECT SETS ANALYZED

The following analysis sets are defined for this trial:

- Screened set (SCS):
  This patient set includes all patients having signed informed consent.

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

- Treated Set (TS):
  The Treated Set (TS) consists of patients who are randomized to a treatment group and receive at least one dose of study medication.

- Pharmacokinetic parameter analysis set (PKS):
  This set includes all patients in the treated set (TS) who provide at least one PK endpoint that was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the CTP Sec. 7.2.1.). Thus, a patient will be included in the PKS, even if he/she contributes only one PK parameter value for one period to the statistical assessment. Descriptive and model based analyses of PK parameters will be based on the PKS.

Analyses for PK endpoints will be based on the PKS. All other analyses will be based on the TS except for disposition.

Table 6.3: 1 Patient sets analyzed

	Patient set		
Class of endpoint	SCS	TS	PKS
Primary endpoint PK			X
Primary endpoint Safety		X	
Secondary endpoints		X	
Further endpoints Efficacy		X	
Further endpoints PK			X
Safety endpoints		X	
Demographic/baseline characteristics		X	
Disposition	X		

Note that the number of patients with available data for an endpoint may differ. For details, see Section 6.6

[redacted]

6.5 POOLING OF CENTRES

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

6.6 HANDLING OF MISSING DATA AND OUTLIERS

In general, missing data will not be imputed. Exceptions are detailed in the subsequent subsections.

6.6.1 Primary endpoint

Missing data and outliers of PK data are handled according to (7). For patients receiving nintedanib in Part A, PK profiles on week 2 and week 26 are planned to be collected. For the primary endpoint AUCτ,ss the AUCτ,ss at week 2 will be used. If the week 2 value is missing, then it will be replaced by available AUCτ,ss at week 26 (or later, if PK visit was postponed).

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

6.6.2 Secondary and further endpoints

6.6.2.1 Change from baseline endpoints

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

Item-level data for the PedsQL™ questionnaires will be handled according to the instructions provided by the instrument developer (see Appendix Section 9.1).

If no FVC measurement prior to first trial drug intake is available, the baseline FVC value will be imputed with the earliest FVC value obtained after (but on the same day as) the first trial drug intake.

[redacted]

According to (7), other missing biomarker data (NOS - no sample available, NOR - no valid result, NOA - not analysed) will not be imputed.

Data below or above the limit of quantification (BLQ or ALQ) for biomarkers will be handled as follows:

- BLQ data will be replaced by 0.5 LLOQ (lower limit of quantification). Hereby LLOQ will be the maximum used lower reference limit for classification of BLQs. All values lower than LLOQ will be imputed (regardless of whether they are classified as BLQ or not).
- ALQ data will be replaced by ULOQ (upper limit of quantification), if ULOQs are available and are greater than observed study values (i.e. the highest solution will be applied for the measurement). Otherwise, ALQ data will be excluded from the analysis.

6.6.2.2 Time-to-event endpoints

In the analyses of the time-to-event endpoints, missing or incomplete data will be managed by standard survival analysis techniques (i.e. censoring). If a patient has no event then he will be censored as described in Section 5.2.2.
A missing or incomplete date of death will be imputed/completed that the derived date is the earliest possible date which is on or after date of onset of the fatal AE, and on or after treatment start (in case this AE is treatment-emergent), and on or after derived date of last contact.
For the time to first respiratory-related hospitalization, or time to first acute ILD exacerbation, in case of partially missing dates, the following imputation will be done:

- If day is missing, then imputed day will be the 15th of the month
- If day and month are missing, then imputed date will be the 1st of July of the (non-missing) year
- If year is missing, date will not be imputed

6.6.2.3 Categorical endpoints

In the analyses of the binary endpoints, multiple imputation will be used to handle missing data at week 24. For week 52 and later, data will not be imputed and only observed values will be used.

The following process describes the multiple imputation for spirometry data (FVC % pred. and SpO_2) and for PedsQL™ point data. Therefore, the words “data” and “value” stand for the data and value of the respective kind of data to be imputed.

In a first step non-monotone missing data will be imputed m = 100 times using MCMC (Markov Chain Monte Carlo) to generate m data sets of longitudinal data with monotone missingness pattern. Such a missingness pattern is the pre-requisite for subsequently applying sequential imputation and means that once a patient has a missing value at a particular time point, the corresponding values at all subsequent time points also have missing values. The seemingly large number of imputations (m=100) is chosen to minimize the standard error of those estimates that are produced to fill the missing values. The seed number will be set to

1199337. For this step all available data of the respective kind will be used, restricted to one value per patient and analysis time window according to selection process described in Section 6.7 below.
In a second step a regression model including baseline value and measurements at all post-baseline analysis visits scheduled (see Table 6.7: 1 and Table 6.7: 6, respectively) by treatment, will be used to complete the imputation in each dataset.
For each imputed complete dataset, the proportion of non-responders (and the corresponding standard error) will be used for the analysis. The results will be pooled following the standard multiple imputation procedure (9).
Patients with missing baseline value will be excluded from the analysis.

6.6.2.4 Endpoints based on MRI/x-ray

Patients will complete the baseline MRI/x-ray within the first 2 weeks after randomization. As for the imaging variables we do not expect a change through treatment within the first two weeks wherefore a measurement within the first two weeks can still be considered as baseline in this special case. The same holds for dental examination.

6.6.2.5 6-min walk test (6MWT)

In case the earliest assessment of the 6MWT is on treatment start day after treatment start time, then the whole 6MWT (pre-, during and after) assessment can still be counted as baseline assessment.

6.6.3.3 Exposure

6.6.3.3.1 Permanent trial drug discontinuation

A missing or incomplete date of last trial drug 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 patient will be missing in these cases as well.

[redacted]

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

As a general rule, the last assessment/measurement observed prior to start of trial medication will be used as baseline. If the time of the assessment/measurement was not captured, and it was on the same day trial medication started, it will be assumed that it was taken prior to the intake of trial medication. For the nintedanib-exposure period, the last measurement prior to the first nintedanib intake was defined as the baseline measurement.

Visit windowing will be performed as described in the following tables, 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.

Exception:
to account for the short timespan between planned visit 6 (with first open-label intake) and visit 7, a special rule is applied to analyses by visit (not cumulative across visits) in case assignment to visit windows leads to missing values at visit 6 or subsequent visit to take possible multiple measurements in the respective other time window into account.
If such an assessment lies in analysis visit window of visit 7, but not later than 1 month after the planned day of visit 7 and still within the double-blind period, then it is allocated to the analysis visit 6.

Similarly, if such an assessment lies in analysis visit window of visit 6, but after the planned day of visit 6 and not within the double-blind period, then it is allocated to the subsequent visit where this assessment is planned.

If after windowing of visits at baseline, two or more values fall within the same baseline interval, then the last value prior to first drug intake will be taken into account. If after windowing of post-baseline visits, two visits fall in the same interval, then the measurement closest to the planned visit will be taken into account. If only on-treatment values are to be considered, this rule will be applied to on-treatment assessments only. In case two measurements are equidistant from the planned visit, then the last one will be picked.

Table 6.7: 1 Time windowing rules for FVC, SpO_2, missed school days, vital signs (syst. and diast. blood pressure, pulse rate) and laboratory tests (incl. LDH)

Time window of actual day[1,2]			Allocated to		
Start day	End day (included)	Length of the time-window [days]	Visit number	Visit name	Planned day of the visit
-84	1	85	2	Baseline	1
2	29	28	3	2 weeks	15
30	64	35	4	6 weeks	43
65	127	63	5	12 weeks	85
128	176	49	6	24 weeks	169
177	218	42	7	26 weeks	183
219	309	84	8	36 weeks	253
310	407	112	9 (p)	52 weeks	365 (V_p)
(V_p + 1) + (V_{p+1} - V_p)/2	V_{p+1} + (V_{p+2} - V_{p+1})/2	(V_{p+2} - V_p)/2	p+1		V_{p+1} = V_p + 12 x 7
…	...	…	…	Every 12 weeks thereafter	…

V_p denotes the planned day of the visit
[1] First trial drug intake date is taken into account as reference to calculate time windows
[2] Only for LDH biomarker analyses: Biomarker values are only considered up to + 7 days after last drug intake.

Table 6.7: 2 Time windowing rules for weight

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
-84	1	85	2	Baseline	1
2	29	28	3	2 weeks	15
30	64	35	4	6 weeks	43
65	127	63	5	12 weeks	85
128	211	84	6	24 weeks	169
212	309	84	8	36 weeks	253
310	407	112	9 (p)	52 weeks	365 (V_p)
(V_p + 1) + (V_{p+1} - V_p)/2	V_{p+1} + (V_{p+2} - V_{p+1})/2	(V_{p+2} - V_p)/2	p+1		V_{p+1} = V_p + 12 x 7
…	...	…	…	Every 12 weeks thereafter	…

V_p denotes the planned day of the visit
[1] First trial drug intake date is taken into account as reference to calculate time windows

Table 6.7: 3 Time windowing rules for height and leg length

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
-84	1	85	2	Baseline	1
2	127	126	5	12 weeks	85
128	211	84	6	24 weeks	169
212	309	98	8	36 weeks	253
310	449	140	9 (p)	52 weeks	365 (V_p)
(V_p + 1) + (V_{p+1} - V_p)/2	V_{p+1} + (V_{p+2} - V_{p+1})/2	(V_{p+2} - V_p)/2	p+1		V_{p+1} = V_p + 24 x 7
…	...	…	…	Every 24 weeks thereafter	…

V_p denotes the planned day of the visit
[1] First trial drug intake date is taken into account as reference to calculate time windows

Table 6.7: 4 Time windowing rules for dental examination and bone imaging

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
-84	15	99	2	Baseline[2]	1
16	127	112	5	12 weeks	85
128	211	84	6	24 weeks	169
212	309	98	8	36 weeks	253
310	449	140	9	52 weeks	365 (V_p)
450	617	168	11 (p)	76 weeks	533
(V_p + 1) + (V_{p+1} - V_p)/2	V_{p+1} + (V_{p+2} - V_{p+1})/2	(V_{p+2} - V_p)/2	p+1	100 weeks	V_{p+1} = V_p + 24 x 7
…	...	…	…	Every 24 weeks thereafter	…

V_p denotes the planned day of the visit
[1] First trial drug intake date is taken into account as reference to calculate time windows
[2] For assessments in baseline window: if available prior to first trial drug intake, use the latest one of those. If only assessments available after first trial drug intake, use the one closest to the planned day as baseline value.

Table 6.7: 5 Time windowing rules for dental imaging

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
-84	15	99	2	Baseline[2]	1
16	267	252	6	24 weeks	169
268	533	266	9 (p)	52 weeks	365 (V_p)
(V_p + 1) + (V_{p+1} - V_p)/2	V_{p+1} + (V_{p+2} - V_{p+1})/2	(V_{p+2} - V_p)/2	p+1		V_{p+1} = V_p + 48 x 7
…	...	…	…	Every 48 weeks thereafter	…

V_p denotes the planned day of the visit
[1] First trial drug intake date is taken into account as reference to calculate time windows
[2] For assessments in baseline window: if available prior to first trial drug intake, use the latest one of those. If only assessments available after first trial drug intake, use the one closest to the planned day as baseline value.

Table 6.7: 6 Time windowing rules for data from PedsQL questionnaire, 6MWT, Borg CR-10 scale®

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
-84	1	85	2	Baseline	1
2	267	266	6	24 weeks	169
268	463	196	9	52 weeks	365

[1] First trial drug intake date is taken into account as reference to calculate time windows
This time windowing will be applied to the following data: PedsQL and 6MWT, Borg CR-10 scale

Table 6.7: 7 Time windowing rules for data from acceptability questionnaire

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
2	92	91	3	2 weeks	15
93	309	217	6	24 weeks	169

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

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 (10).
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 patient 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 randomized treatment group (placebo or nintedanib) and overall (total).

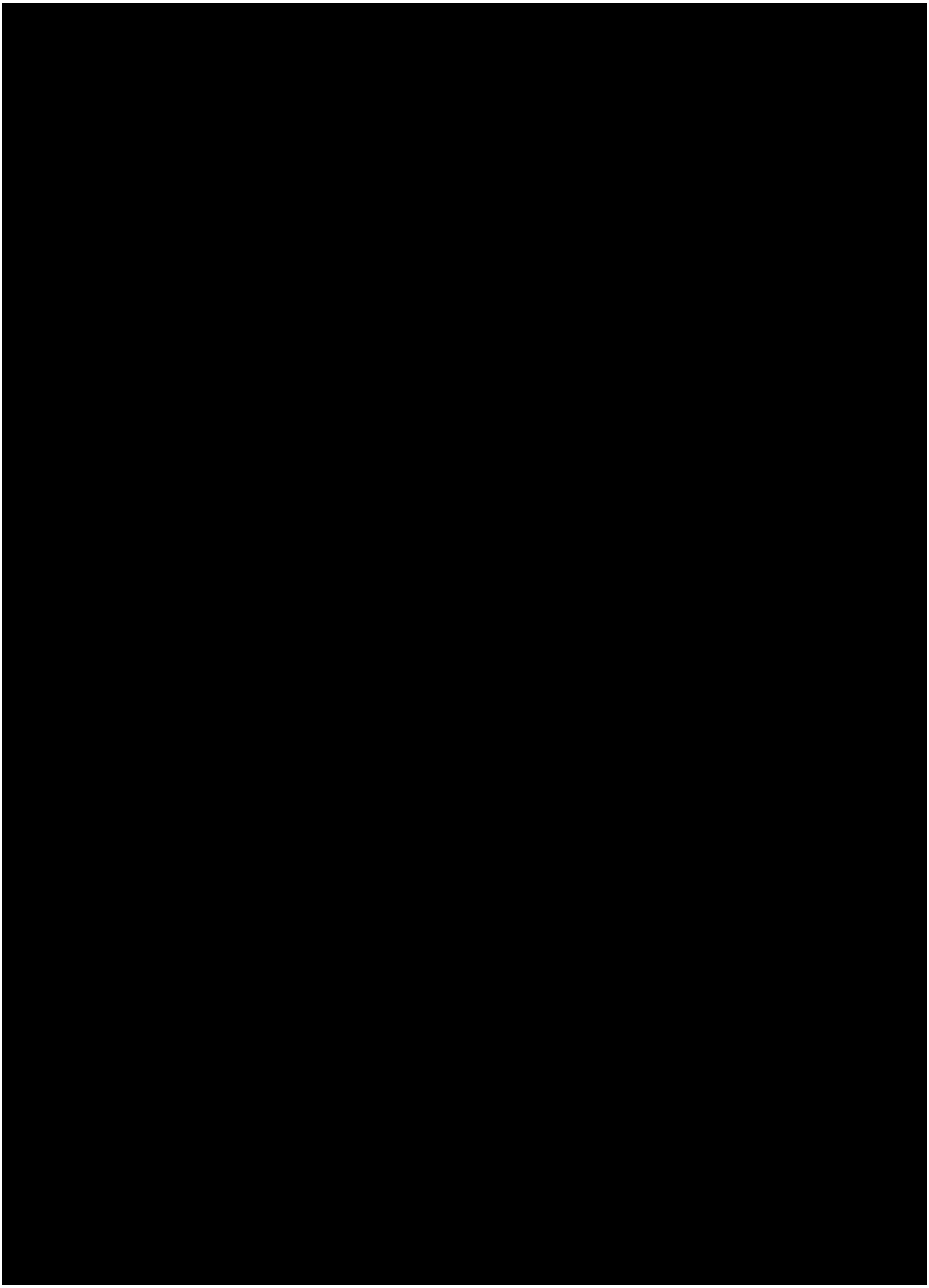
For efficacy and safety end point analyses by time point, as well as for the safety analyses of Part A, patients switching during Part A to Part B will be censored at the time point of the switch and for the safety analyses of Part A (due to the definition of the double-blind period). Patients who started directly in Part B will be analyzed as a separate cohort, in addition to those randomized to nintedanib and those randomized to placebo.
All analyses performed after DBL1 will be repeated after DBL2 to include newly emerging data.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report. A table in the CTR will present the number of patients screened, randomised and treated. The number of patients prematurely discontinuing their study treatment will be shown with the reasons for discontinuation. The number and percent of patients completing the end of treatment visit and the number of patients with treatment ongoing will also be presented. Please note there will be ongoing patients at the time of the data cut-off for the primary analysis; at the time point when the final analysis will take place there will not be any more ongoing patients in this trial. Where percentages are shown, the denominator will be the number of patients treated in each treatment group.

Descriptive statistics as well as frequency counts will be provided for all demographic and baseline characteristics depicted in Section 5.4.1. The CTR tables will show the relevant descriptive statistics (number and percent within categories; other descriptive statistics for continuous variables) by treatment arm.

[redacted]



7.4 PRIMARY ENDPOINT(S)

The primary endpoints are the PK endpoint AUCτ,ss based on sampling at steady state (at week 2 and week 26) and the safety-endpoint N (%) of patients with treatment-emergent adverse events at week 24.

7.4.1 Primary analysis of the primary endpoint(s)

7.4.1.1 PK endpoint

AUCτ,ss based on sampling at steady state will be calculated as specified in the CTP Sections 7.2.1 and 7.2.2. For patients receiving nintedanib in Part A, PK profiles on week 2 and week 26 are planned to be collected. For the primary endpoint AUCτ,ss the AUCτ,ss at week 2 will be used. If the week 2 value is missing, then it will be replaced by available AUCτ,ss at week 26 (or later, if PK visit was postponed). For patients receiving placebo in Part A and nintedanib in Part B, AUCτ,ss evaluated based on PK profiles at week 26 (or later, if PK visit was postponed) will be used as primary endpoint (which corresponds to week 2 on active treatment). See also Section 6.6.1.

To account for potential dose reductions, AUCτ,ss will be dose normalized by the actual dose taken by the patient corresponding to that PK sampling. The dose normalized AUCτ,ss for nintedanib (AUCτ,ss_D) will be summarised descriptively.

AUCτ,ss will additionally be derived using population PK modelling (for all patients with at least one valid PK sample). Details of the analysis will be reported separately in the popPKPD report, but the main AUCτ,ss results also will be included in the CTR.
The 95% CI of nintedanib CL/Fss will be calculated according to company standards.
All PK analyses will be based on the pharmacokinetic analysis set (PKS), see Section 6.3.

7.4.1.2 Safety endpoint

Only descriptive analyses will be performed. The number and frequency of patients with treatment-emergent adverse events by primary system organ class (SOC) and preferred term (PT) during the double-blind period, as described in Section 7.8.1, will be displayed.

7.5 SECONDARY ENDPOINT(S)

Please note that any p-value presented will be considered nominal in nature and no adjustment for multiplicity will be made.

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)

7.5.2.1 Continuous (change from baseline) endpoints

The continuous secondary endpoint analysis will be based on the TS (according to randomised treatment), using available data from all visits (after time-windowing) from Part A and Part B and the estimate and contrast between treatments at the applicable endpoint visits will be used.
The analysis of continuous secondary endpoints is a restricted maximum likelihood (REML) based approach using a Mixed effect Model for Repeated Measures (MMRM). The analysis will include the fixed, categorical effects of treatment at each visit, age-group and the fixed continuous effects of baseline at each visit. Visit will be treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements.

Patients will be analyzed according to the age group stratum to which they belong to based on the data entered in the eCRF, which may not necessarily coincide with data used for randomisation.

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Significance tests will be based on least-squares means (two-sided 95% confidence intervals will be presented). The primary treatment comparison will be the contrast between treatments at the endpoint visit.

In the event of non-convergence, the following methods will be attempted (in order) to overcome it:

1. Add the ‘singular=1e-10’ option in the model statement – This raises the threshold at which columns are declared linearly dependent (from typically 1e-12).
2. Set ‘maxiter=100’ in the Proc Mixed statement – This increases the number of convergence iterations used from a default of 50.
3. Set ‘scoring=4’ to specify use of the Fisher scoring algorithm in the first 4 iterations.
4. Exclude all visits > 24 weeks and report weeks > 24 data only descriptively (ANOVA) using observed data.
5. Include the statement ‘performance nothread’ – this removes multi-threading from the calculations.
6. Provide starting values for covariance parameters using a ‘parms’ statement. Estimates will be obtained from using a simpler covariance matrix.
7. Should none of the previous methods work, the covariance matrix will be changed from unstructured to Toeplitz with heterogeneous variances (TOEPH). Should this also not converge, a standard Toeplitz matrix (TOEP) will be fitted. Finally, if convergence still does not occur, then an order-1 autoregressive matrix (AR(1)) will be fitted.

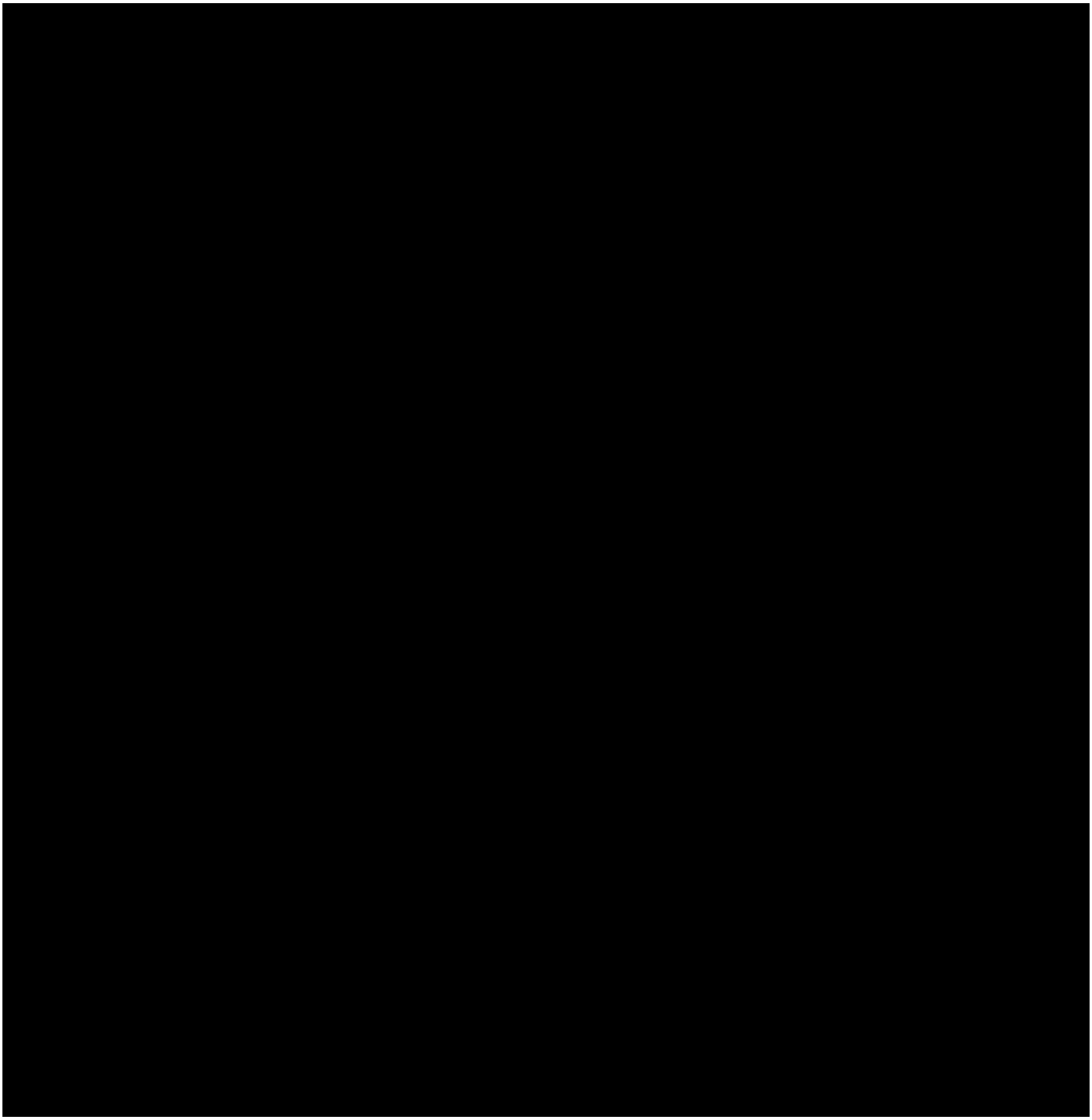
Additionally, a descriptive analysis for all time points will be done.

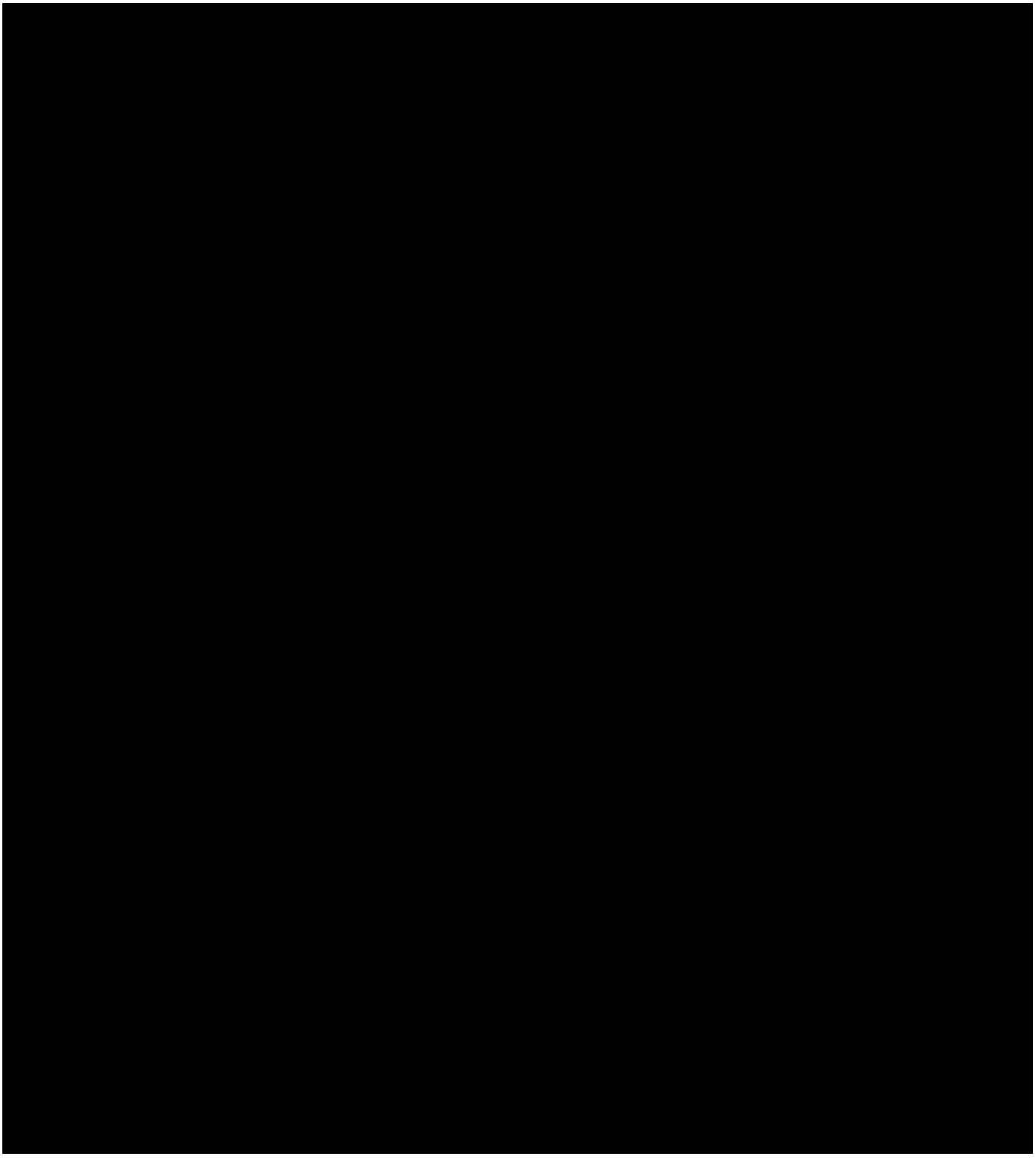
7.5.2.2 Time-to-event endpoints

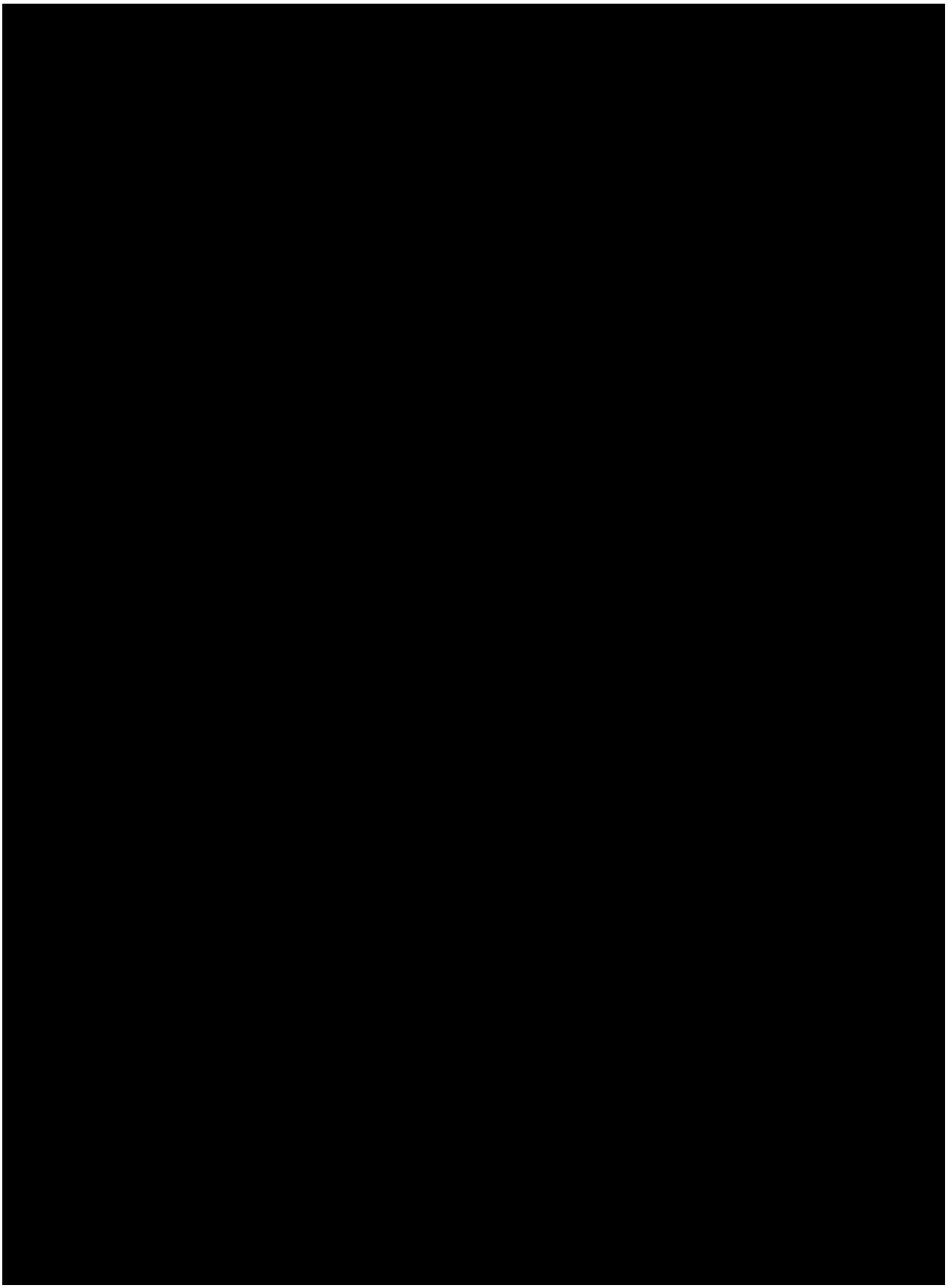
Separate Kaplan-Meier plots will be presented by randomised treatment group and overall (total group) for time-to-event endpoints defined in Section 5.2.2. Kaplan Meier estimates and confidence intervals (using Greenwood variance formula) for the cumulated time-to-event rate will be calculated at 24 weeks and at 52 weeks. Q1, median and Q3 of the time to event will be presented, if reached. No statistical test will be performed.

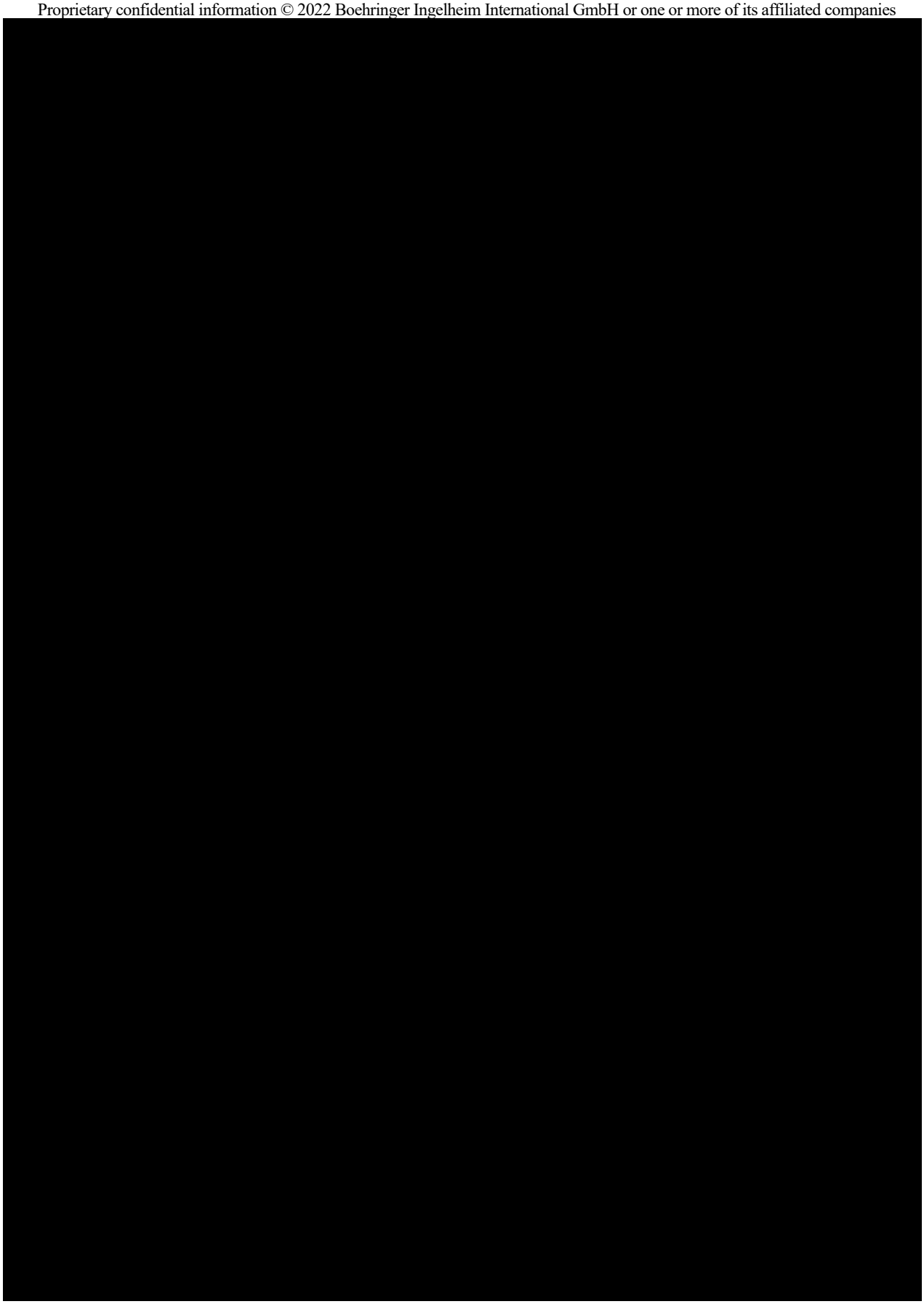
7.5.2.3 Categorical endpoints, safety and tolerability endpoints

Only descriptive analyses in the form of frequency tables will be performed.









[redacted]

7.8 SAFETY ANALYSIS

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. The analyses of AEs will be descriptive in nature.

All analyses of AEs will be based on the number of patients with AEs and NOT on the number of AEs. To account for the variable length of exposure to treatment in both study periods tables will be presented including count and percentage of patients with AE and the incidence rates of AEs with time at risk and rate per 100 patient years. Please refer to Section 7.8.1.1 for further details on the derivation of time at risk and exposure-adjusted incidence rates.

Since this study consists of a double-blind, placebo-controlled part and an open-label part with nintedanib treatment only, three treatment periods will be used for analysis and definition of "treatment-emergent":

1. **Double-blind period**: Analyses of AEs will be presented by treatment group and overall. Only adverse events with onset or worsening on or after date of treatment start until end of double-blind period (defined as the day before first intake of open-label nintedanib or last double-blind drug intake + residual effect period, whichever is earlier) will be considered as treatment-emergent and will be included in the analysis. Adverse events will be counted under the treatment as randomized for the double-blind period.

2. Nintedanib exposure period: Analyses of AEs will be presented by randomized treatment group and overall. All adverse events with onset or worsening on or after first intake of nintedanib (double-blind or open-label period) until last intake of nintedanib (double-blind or open-label period) + residual effect period will be considered as treatment-emergent and will be included in the analysis.

3. Over the whole-trial: Analyses of AEs will be presented by treatment group and overall. All adverse events with onset or worsening on or after date of treatment start until last drug intake + residual effect period will be considered as treatment-emergent and will be included in the analysis. Adverse events will be counted under the treatment as randomized for the double-blind period.

In case an AE starts on first day of open-label treatment, it is assigned to the open-label period (and not to the double-blind period).
For further details on summarization of AE data, please refer to (8, 17).

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

According to ICH E3 (18), 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).

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, bleeding and hepatic injury, pathological findings identified on bone imaging and stunted growth identified on dental imaging are considered as protocol-specified AEs of special interest (AESIs), and are ticked as such in the eCRF.

Analysis of AEs in double-blind period:
An overall summary of AEs will be presented by treatment group and overall for the double-blind period of the study.
The following tables will also present number and percentages of patients with respective AEs and in addition the incidence rates of AEs with time at risk and rate per 100 patient years by treatment and overall. Please refer to Section 7.8.1.1 for further details on the derivation of time at risk and exposure-adjusted incidence rates.
The frequency of patients with adverse events, will be summarized by primary system organ class (SOC) and preferred term (PT). 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).

Separate tables will also be provided for patients 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
- AEs grouped by safety topic

Adverse event groupings by safety topic have been defined outside the trial protocol, which will be continuously updated at project level (19). 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 the respective DBL will be used in the CTR.
The frequency of patients with adverse events within these groupings will be summarized by system, safety topic, subcategory (if applicable) and preferred term. These displays will focus on patients with any adverse event, patients with serious adverse events and patients with investigator defined drug-related adverse events.
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).

Analysis of AEs during nintedanib exposure period:
All tables as described for double blind period will be repeated for AEs during nintedanib exposure period for nintedanib treatment only.

Analysis of AEs over the whole-trial:
All tables as described for double blind period will be repeated for AEs in the whole-trial period presenting results by treatment group and overall.

7.8.1.1 Adjudicated adverse events

An independent adjudication committee will review all fatal cases and adjudicate cause of death to respiratory, cardiovascular or other. The adjudication committee will also review all AEs categorized as MACE according to the definition in the adjudication charter.
In addition to standard safety analyses, the frequency of patients with AEs leading to death will be summarized by treatment, adjudicated cause of death (Cardiovascular, Respiratory or Other), and PT.
The frequency of patients with AEs categorized as MACE (that is all AEs categorized as MACE and therefore sent for adjudication) will be summarized by treatment and outcome of adjudication (adjudicated as MACE or adjudicated as not MACE). The frequency of patients with AEs adjudicated as MACE will also be summarized by treatment and PT.

7.8.1.2 Exposure adjusted analysis of adverse events 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 trial.

Time at risk:
For a specific AE, the total AE time at risk [years] is defined as

$$\frac{\sum \textit{Time at risk (days) across all contributing patients}}{365.25}$$

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

- *Date of first onset of the AE – date of first study drug intake +1 day*

for patients with the specific AE,

- *End of time at risk – date of first study drug intake + 1 day*

for patients without the specific AE.

The end of time at risk is defined as the minimum of

- end date of the double-blind, whole-trial and nintedanib exposure treatment period, respectively (incl. REP)
- date of last contact (for definition see Sec. 5)
- date of death
- date of the (interim) database lock.

For the double-blind treatment period, end of time at risk is the day before start of open-label period, in case the patient started open-label treatment before end of double-blind REP.

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

$$\frac{100 \times \textit{(Number of patients with specific AE)}}{\textit{Total specific AE time at risk [years]}}$$

The 95% confidence intervals for incidence rates are derived using the method described by Rothman and Greenland (2008) (20).

7.8.1.3 Adverse events with additional information collection

Diarrhea, 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 diarrhea information has been completed for an adverse event then the adverse event will be considered as diarrhea 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 patients with AEs with additional information collection will be summarized by treatment group and overall, primary SOC and PT and separately for diarrhea, bleeding and ILD. The additional information collected will also be summarized at the AE level (occurrence level) rather than at the patient level separately for diarrhea, bleeding and ILD. These analyses will be provided by analysis periods and treatment group and overall, where applicable.

For the time to first onset of diarrhea, bleeding or ILD, respectively, Kaplan-Meier plots by treatment will be created taking into account the respective data over the whole trial. Kaplan-Meier plots of the double-blind period and the nintedanib exposure period will be created as well. The same censoring rules as for time to first liver enzyme elevation trial will be used, see Section 5.4.4.1 for details.

7.8.1.4 Pathological findings of epiphyseal growth plate on imaging, on dental examination or dental imaging

Adverse events identified based on imaging or dental examination will be reported in the Adverse Event page of the eCRF and will be listed in the standard AE tables and listings.

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 (21). The variables to be recorded are listed in Table 7.8.2.1: 1 and Table 7.8.2.1: 2 below (see also Section 5.2.3 of the CTP).

Table 7.8.2.1: 1 Safety laboratory tests at regular site visits

The laboratory tests at regular site visits will include:

Category	Laboratory test
Haematology	Red blood cell count (RBC) Haemoglobin (Hb) Haematocrit (Hct) Mean corpuscular volume White blood cell count including differential count Platelet count
Biochemistry	Aspartate aminotransferase (AST) Alanine transaminase (ALT) Gamma-glutamyl transferase (GGT) Alkaline phosphatase (ALK) Creatine kinase (CK) Lactate dehydrogenase (LDH) Total protein Total bilirubin Creatinine Glucose (non fasting, V1 and V2 only) Uric acid Thyroid stimulating hormone ß-HCG (at all visits requiring blood sampling for laboratory tests –in all and only female patients)*

Table 7.8.2.1: 1 Safety laboratory tests at regular site visits (continued)

Category	**Laboratory test**
Electrolytes	Sodium Potassium Calcium Chloride Inorganic phosphorus
Coagulation	International normalized ratio (INR) Activated partial thromboplastin time (aPTT) Prothrombin time (PT)
Urinalysis	pH, glucose, erythrocytes, leukocytes, protein, nitrite (semi-quantitative measurements; -, +, ++, +++)

*Pregnancy test is required in all female patients every 4-6 weeks (in Poland: every 4 weeks), either at home or at site. ß-HCG test on blood will be conducted at all visits on blood collected for laboratory tests. Locally provided urine dipstick pregnancy tests will be dispensed for use between clinic visits starting from Visit 4.

Table 7.8.2.1: 2 Safety laboratory tests at intermediate ‘a’-visits

The laboratory tests at intermediate ‘a’-visits will include:

Category	Laboratory test
Biochemistry	Total protein, creatinine, electrolytes and liver function (AST, ALT, GGT, alkaline phosphatase, and total bilirubin)
Urinalysis	pH, glucose, erythrocytes, leukocytes, protein, nitrite (semi-quantitative measurements; -, +, ++, +++)

As described in Section 7.2.5 of the CTP, laboratory data will be analyzed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be summarized. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

Data will be received from a central laboratory, the respective reference ranges will be provided in the ISF.
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).

Analyses of laboratory variables will be displayed by treatment and overall for the double-blind period, for the nintedanib exposure period and over the whole trial; please refer to Table 6.7: 1 for time windowing definition.

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 for the double-blind period, for the nintedanib exposure period and over the whole trial by treatment group and overall, including:

- Summary table of liver enzyme elevation
- Summary of signs of hepatic injury (see Section 5.4.4)
- Summary table of individual maximum liver enzyme and bilirubin elevations
- Time to first onset and number of patients with liver enzyme elevation. The time to onset of first liver enzyme and bilirubin elevation [days] will be summarized according to both, quartiles from Kaplan-Meier curve
- Kaplan-Meier plot of time to first liver enzyme elevation. No statistical test will be performed. Separate plots will be presented by treatment group.
- Single time course profiles of liver enzymes and other laboratory parameters (ALT, AST, alkaline phosphatase, total bilirubin, absolute eosinophils, eosinophils/ leukocytes, GGT) for all patients (maximum individual elevations given in Section 5.4.4).
- Graphical displays of potential Hy's law cases

7.8.3 Vital signs

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

7.8.4 ECG

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

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.	*c37069138*: "sitting-height-measurement-note-to-file-2021-09-15"; TMF.
3.	Philip H. Quanjer, Multi-ethnic reference values for spirometry for the 3–95 year age range: The global lung function 2012 equations. [R15-0845]
4.	Onis MD, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann. Development of a WHO growth reference for school-aged children and adolescents. Bulletin of the World health Organization, 85. 2007; 660-667 [R21-1869]
5.	*Website:* https://www.who.int/tools/growth-reference-data-for-5to19-years/indicators/height-for-age (access date: 29 April 2021).
6.	Cole TJ, Green PJ. Smoothing reference centile curves: The LMS method and penalized likelihood. Statistics in Medicine. 1192. 1992;11:1305-1319 [R21-0301]
7.	*001-MCS-30-476:* "TMCP Data Analysis", current version, Group "TMCP", IDEA for CON.
8.	*KMED-BDS-HTG-0035:* "Handling of Missing and Incomplete AE Dates", current version KMED.
9.	Rubin, DB. Multiple Imputation for Nonresponse in Surveys. New York: John Wiley & Sons. 1987 [R12-2378]
10.	*BI-KMED-BDS-HTG-0045*: "Reporting of clinical trials and project summaries", current version; KMED.
11.	Bonella F, Maher TM, Cottin V, Valenzuela C, Wijsenbeek M, Voss F, et al. Consistent effect of nintedanib on reducing decline in forced vital capacity (FVC) across interstitial lung diseases (ILDs). 33rd Ann Mtg and Expo of the Academy of Managed Care Pharmacy (AMCP), Virtual, 12 - 16 Apr 2021 (Poster). 2021. [P21-03717]
12.	Best N, Price RG, Pouliquen IJ, Keene ON. Assessing efficacy in important subgroups in confirmatory trials: An example using Bayesian dynamic borrowing. Pharm Stat. 2021; 20(3): 551-562 [R21-1783]
13.	Schmidli H, Gsteiger S, Roychoudhury S, O'Hagan A, Spiegelhalter D, Neuenschwander B. Robust meta-analytic-predictive priors in clinical trials with historical control information. Biometrics. 2014; 70(4): 1023-32 [R16-0281]
14.	*c38440025:* "8-08-other-expert-elicitation-workshop-briefing-2021-09-09"; TMF.
15.	*c38440027:* "8-08-other-expert-elicitation-workshop-presentations-2021-09-09" ; TMF.
16.	*c38440031:* "8-08-other-expert-elicitation-workshop-results-2021-09-14"; TMF.
17.	*BI-KMED-BDS-HTG-0066*: "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version KMED.

18.	*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.
19.	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.
20.	Rothman KJ, Greenland S, Lash TL. Modern epidemiology. 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2008 [R10-1239]
21.	*BI-KMED-BDS-HTG-0042*: "Handling, Display and Analysis of Laboratory Data", current version; KMED.
22.	Varni JW, Scaling and scoring of the Pediatric Quality of Life Inventory PedsQL. Mapi Research Trust; 2017. http://www.pedsql.org/PedsQL-Scoring.pdf (access date: 11 May 2021) [R21-1786]
23.	Neuenschwander B, Capkun-Niggli G, Branson M, Spiegelhalter DJ. Summarizing historical information on controls in clinical trials. Clin Trials. 2010; 7(1): 5-18 [R16-0278]
24.	Neuenschwander B, Schmidli H. Use of Historical Data. In: Lesaffre E, Baio G, Boulanger B (editors). Bayesian Methods in Pharmaceutical Research. 2020, CRC Press [R21-1784]
25.	Weber S (2020). RBesT: R Bayesian Evidence Synthesis Tools. R package version 1.6-1. Website: https://cran.r-project.org/web/packages/RBesT/RBesT.pdf (access date: 11 May 2021) [R21-1785]

9. ADDITIONAL SECTIONS

9.1 PEDSQL SCORING INSTRUCTIONS

The Reports of the PedsQL™ 4.0 Generic Core Scales (22) for:
- Young Children (ages 5-7),
- Children (ages 8-12),
- Teens (ages 13-18),
and respective parent reports, are composed of 23 items comprising 4 dimensions.

1. On the PedsQL Generic Core Scales, for ease of interpretability, items are reversed scored and linearly transformed to a 0-100 scale, so that higher scores indicate better HRQOL (Health-Related Quality of Life).

2. To reverse score, transform the 0-4 scale items to 0-100 as follows: 0=100, 1=75, 2=50, 3=25, 4=0.

3. To create Scale Scores, the mean is computed as the sum of the items over the number of items answered (this accounts for missing data). If more than 50% of the items in the scale are missing, the Scale Score should not be computed. Imputing the mean of the completed items in a scale when 50% or more are completed is generally the most unbiased and precise method. To do this, count the number of missing values in the scale (call it nmiss). Next, sum the item scores and divide by the number of items in the scale minus nmiss.

4. To create the Psychosocial Health Summary Score, the mean is computed as the sum of the items over the number of items answered in the Emotional, Social, and School Functioning Scales. The Physical Health Summary Score is the same as the Physical Functioning Scale Score.

5. To create the Total Scale Score, the mean is computed as the sum of all the items over the number of items answered on all the Scales.

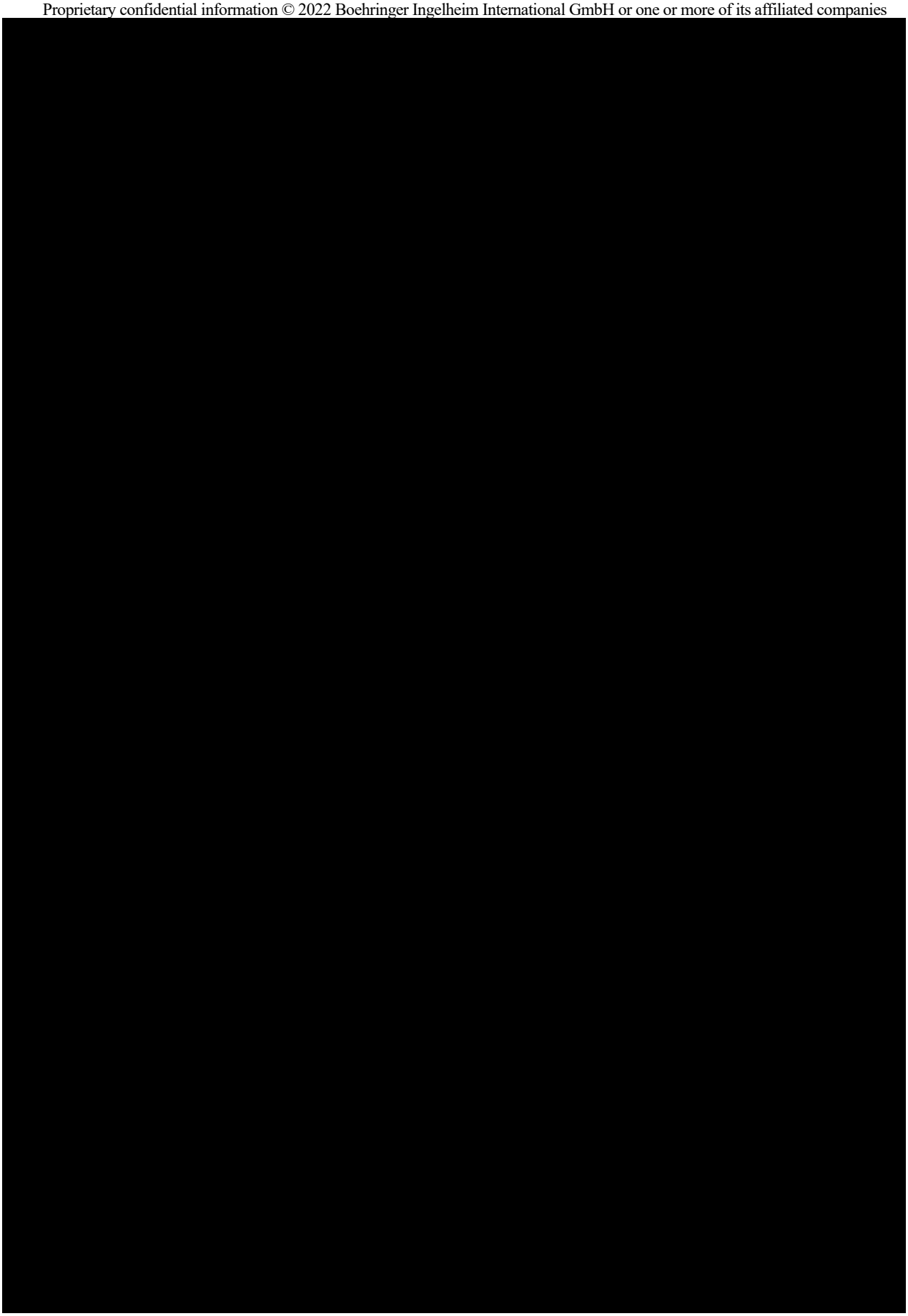
DESCRIPTION OF THE QUESTIONNAIRE:

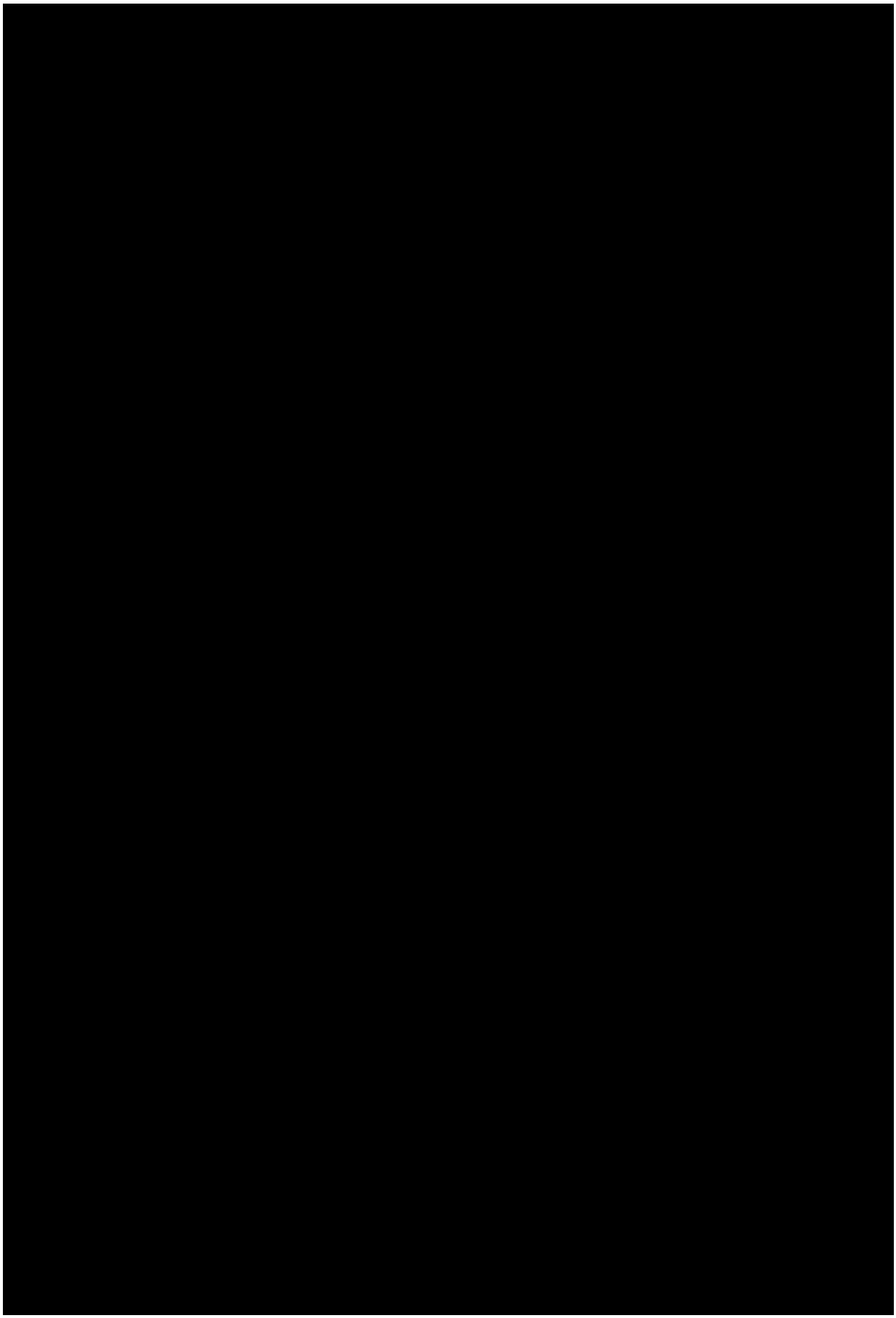
Dimensions	Number of Items	Cluster of Items	Reversed scoring	Direction of Dimensions
Physical Functioning	8	1-8	1-8	Higher scores indicate better HRQOL.
Emotional Functioning	5	1-5	1-5	
Social Functioning	5	1-5	1-5	
School Functioning	5	1-5	1-5	

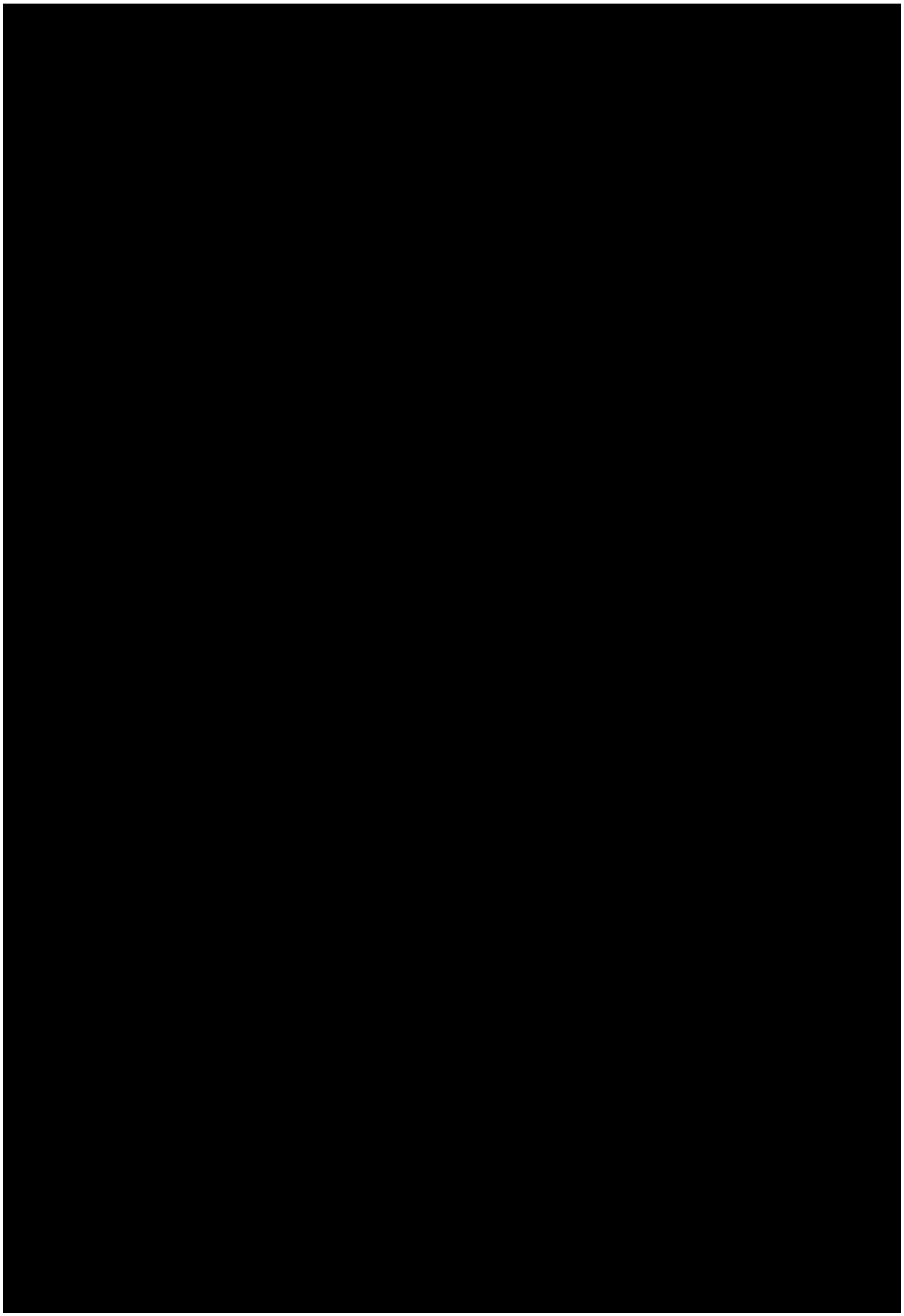
SCORING OF DIMENSIONS:

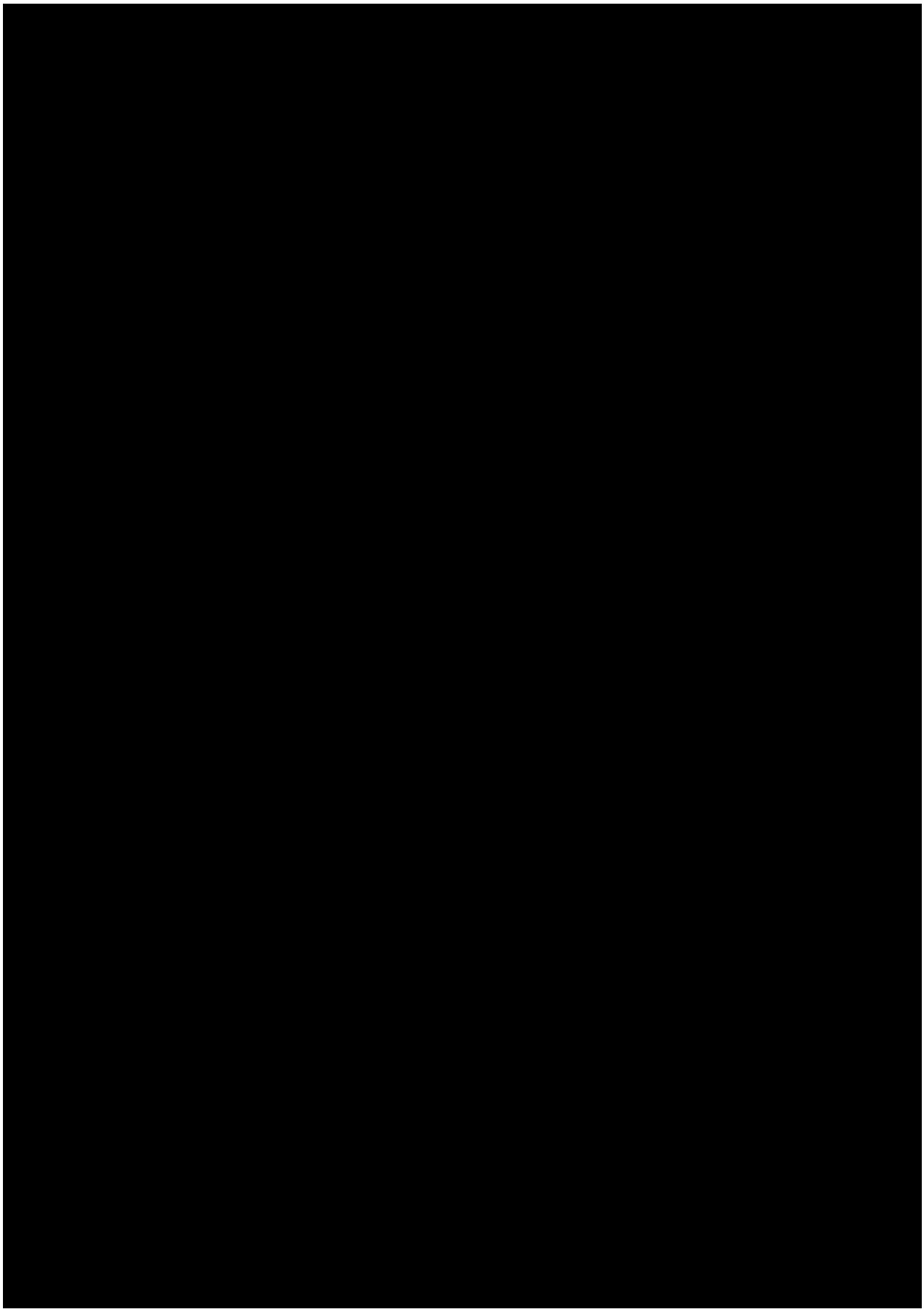
Item Scaling	5-point Likert scale from 0 (Never) to 4 (Almost always) 3-point scale: 0 (Not at all), 2 (Sometimes) and 4 (A lot) for the Young Child (ages 5-7) child report
Weighting of Items	No
Extension of the Scoring Scale	Scores are transformed on a scale from 0 to 100.
Scoring Procedure	**Step 1: Transform Score** Items are reversed scored and linearly transformed to a 0-100 scale as follows: 0=100, 1=75, 2=50, 3=25, 4=0. **Step 2: Calculate Scores** Score by Dimensions: • If more than 50% of the items in the scale are missing, the scale scores should not be computed, • Mean score = Sum of the items over the number of items answered. Psychosocial Health Summary Score = Sum of the items over the number of items answered in the Emotional, Social, and School Functioning Scales. Physical Health Summary Score = Physical Functioning Scale Score **Total Score**: Sum of all the items over the number of items answered on all the Scales.
Interpretation and Analysis of Missing Data	If more than 50% of the items in the scale are missing, the Scale Scores should not be computed. If 50% or more items are completed: Impute the mean of the completed items in a scale.

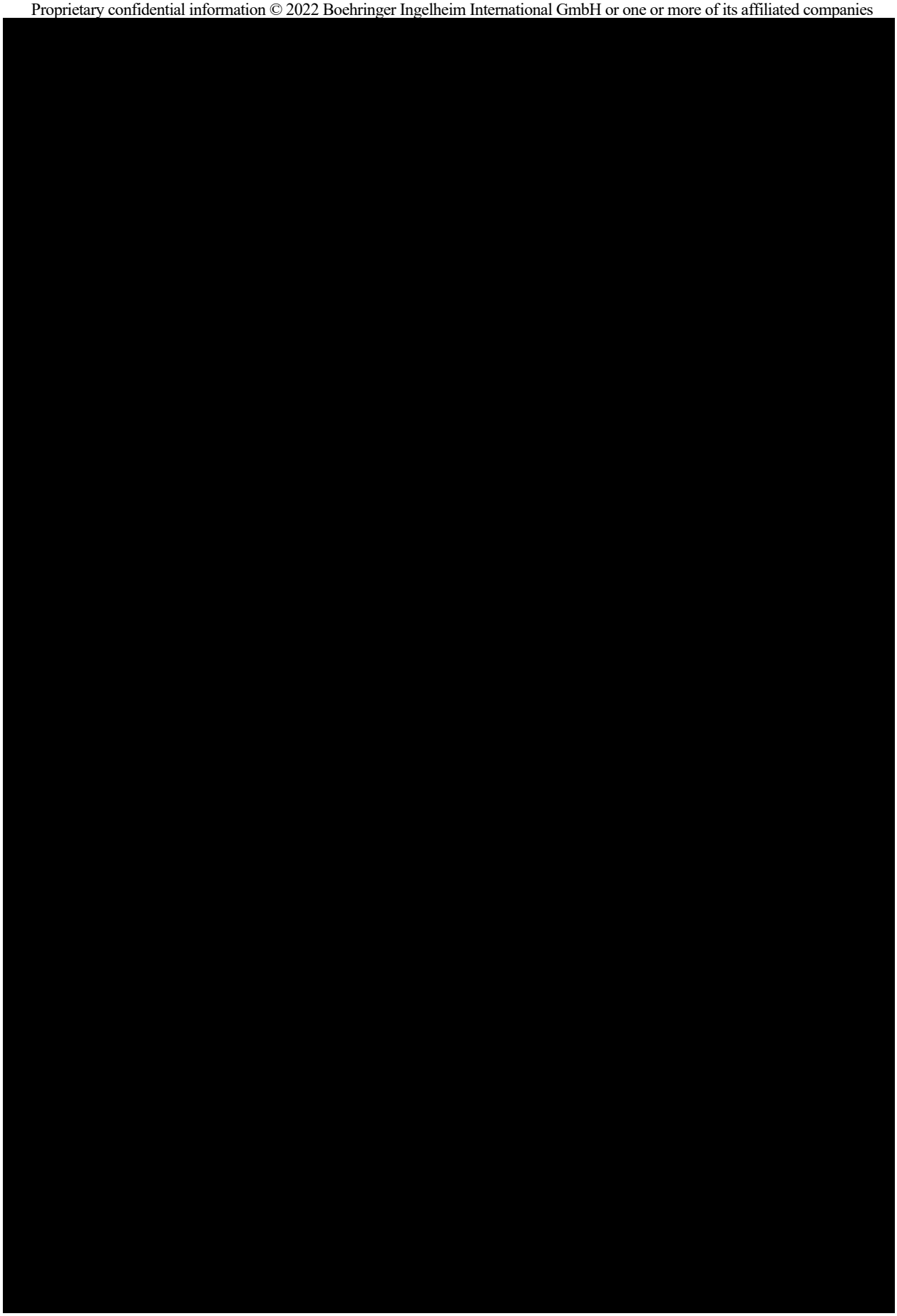
Figure 9.1: 1 Description of the PedsQL questionnaire

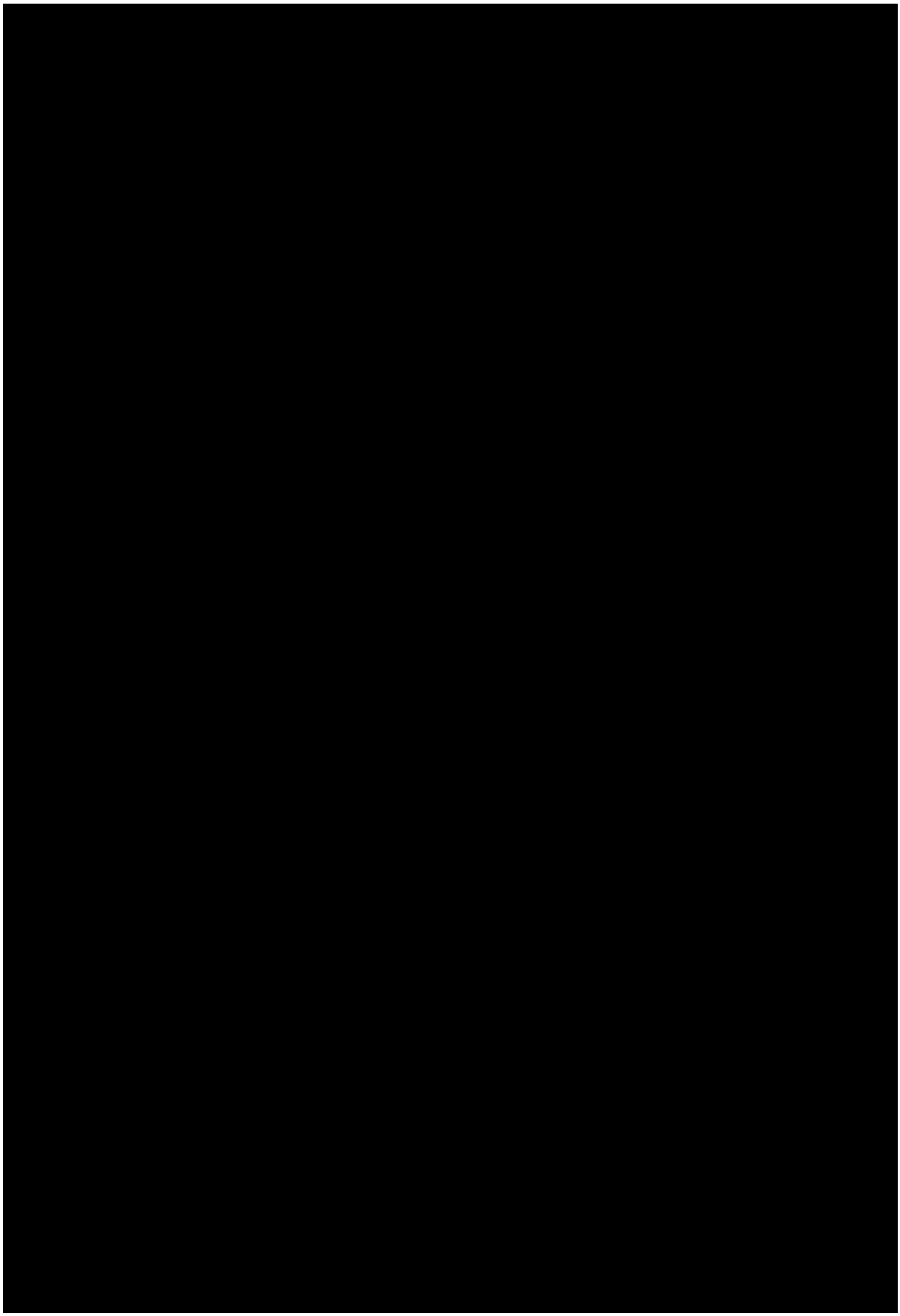


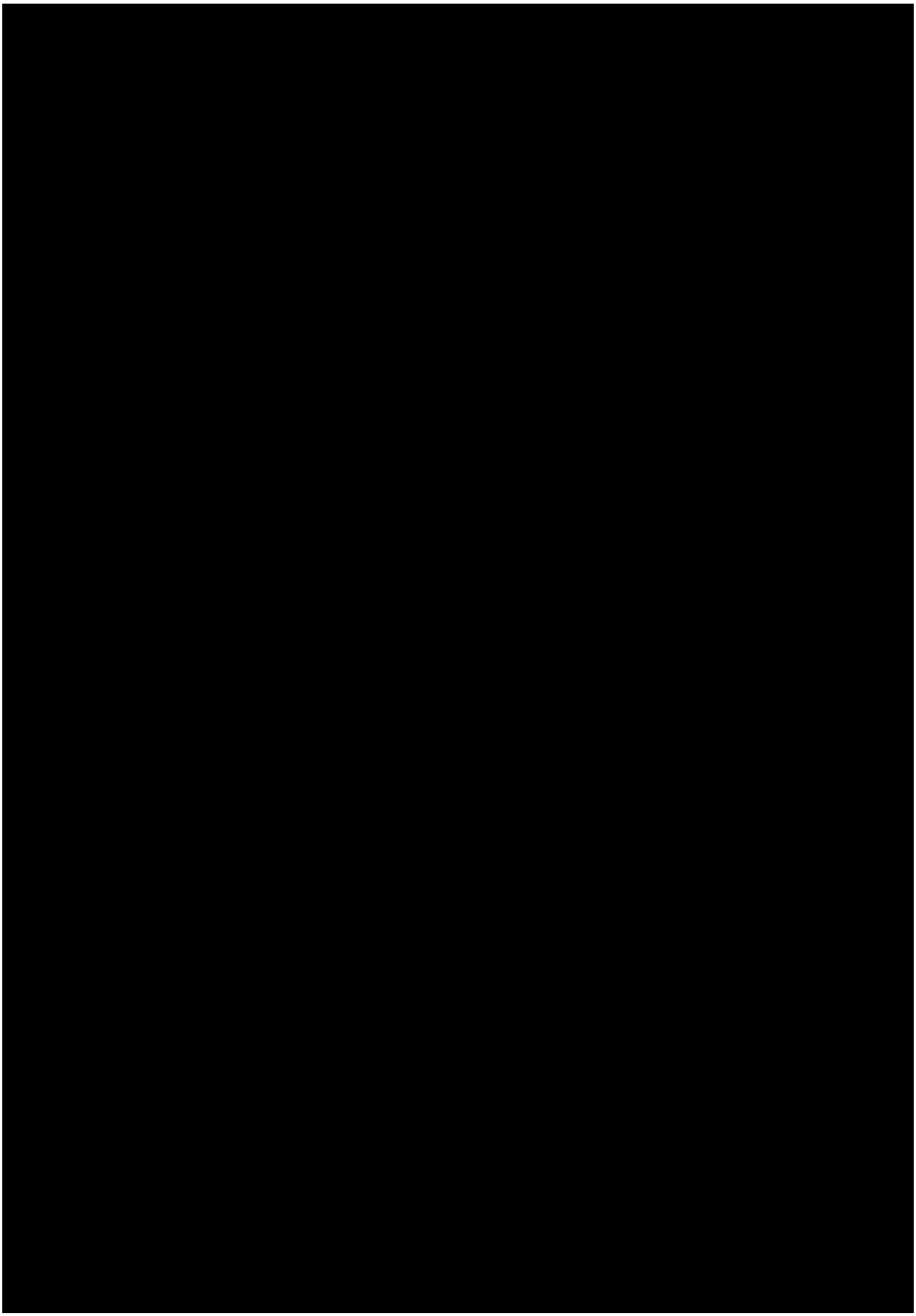


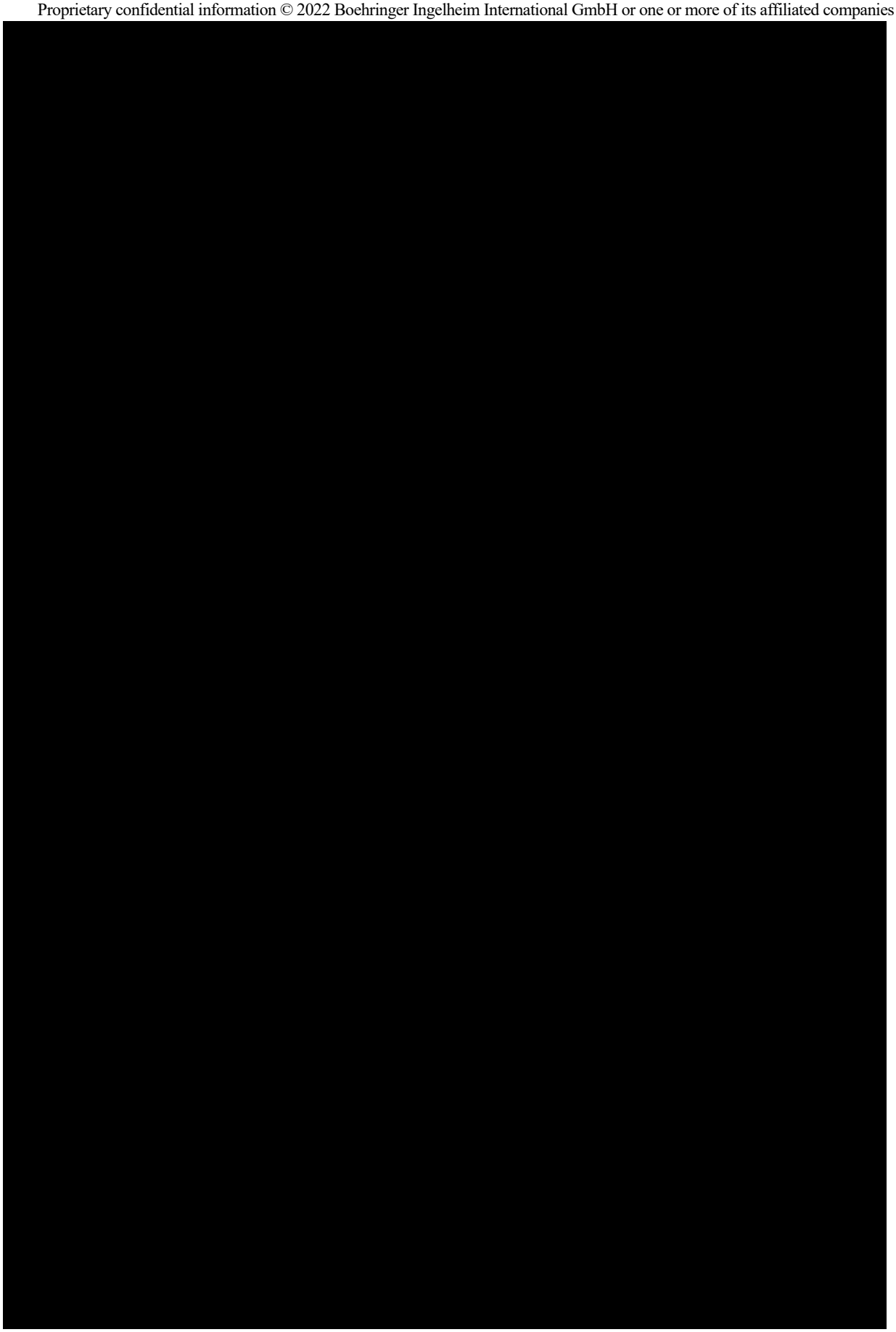


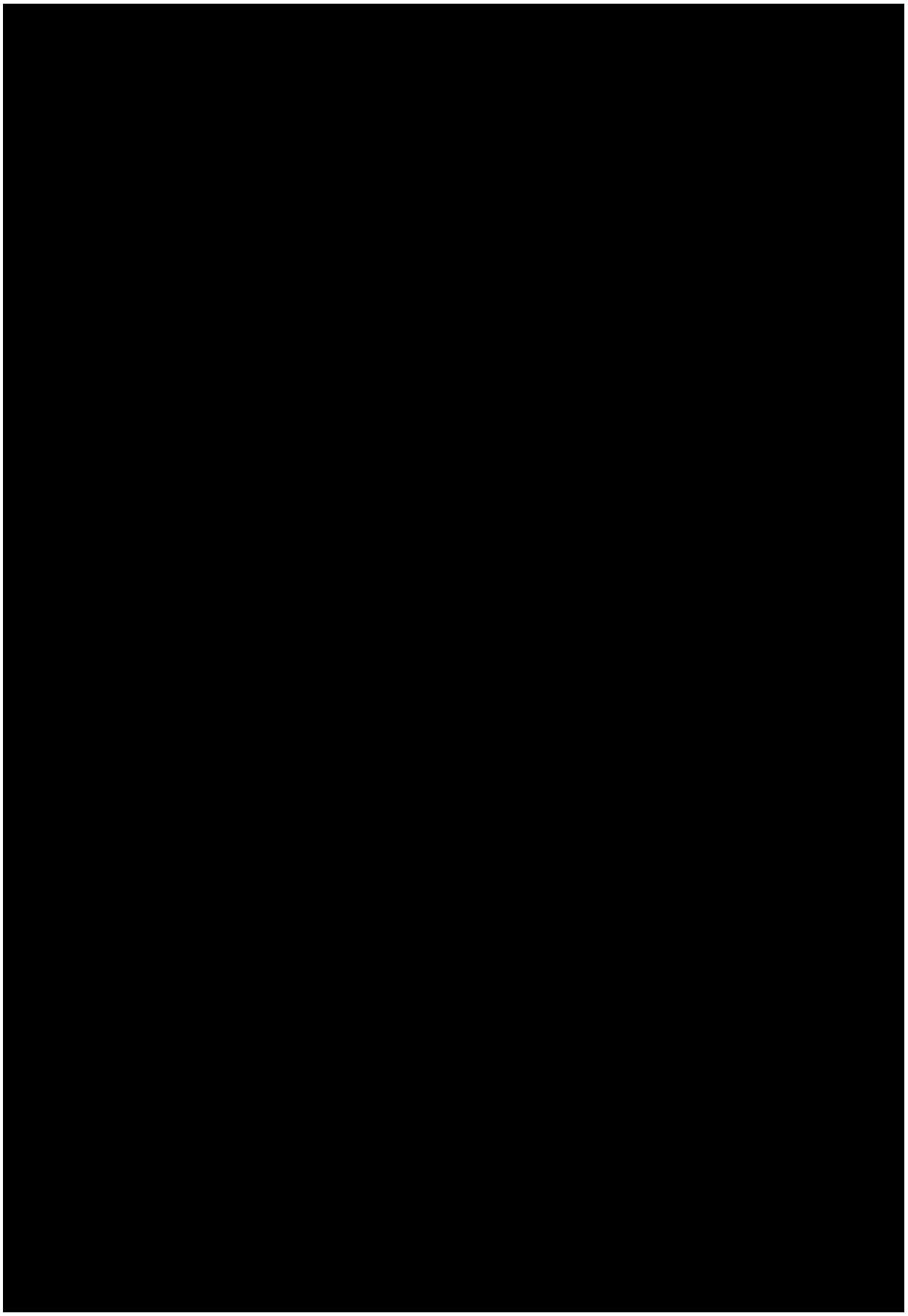


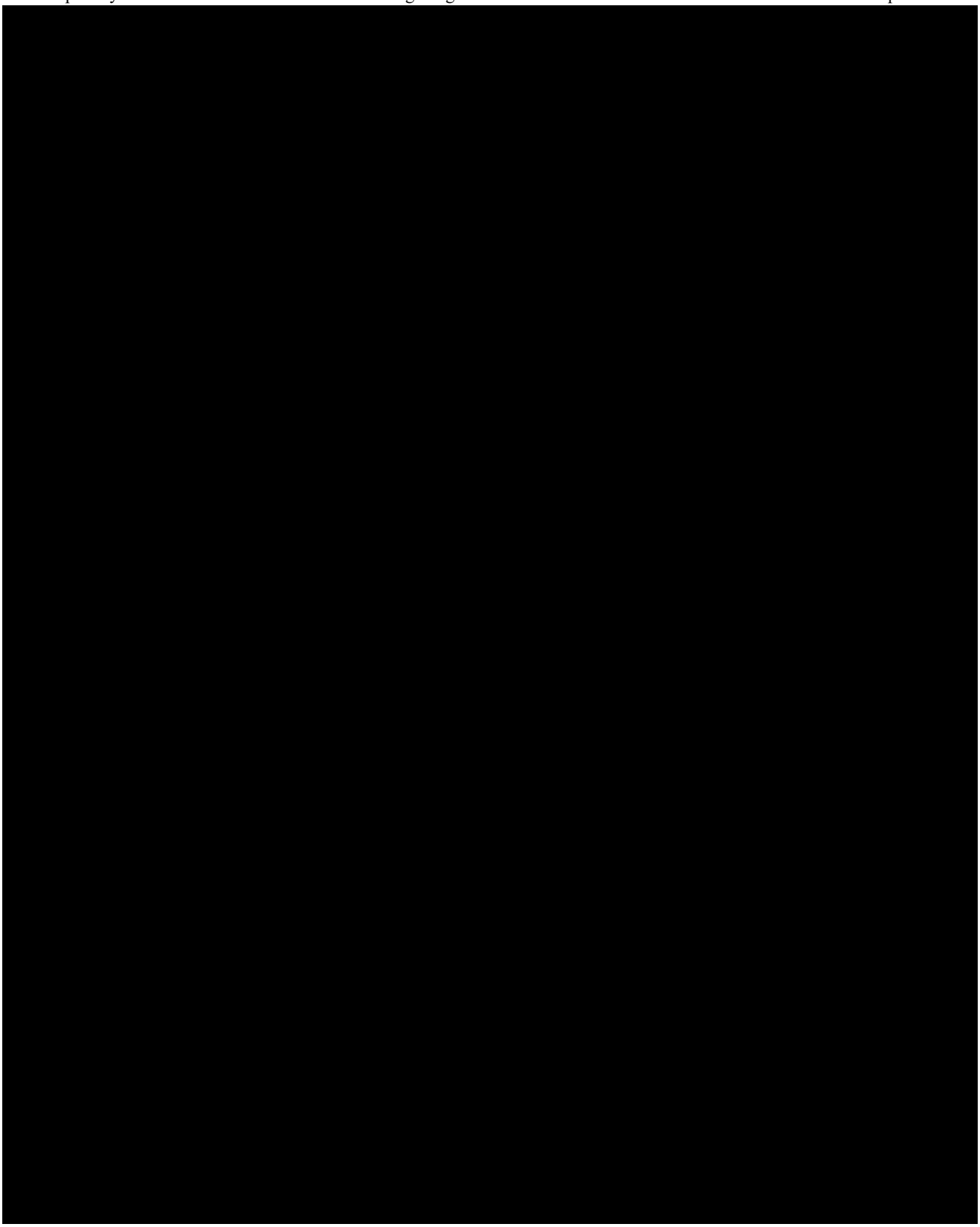


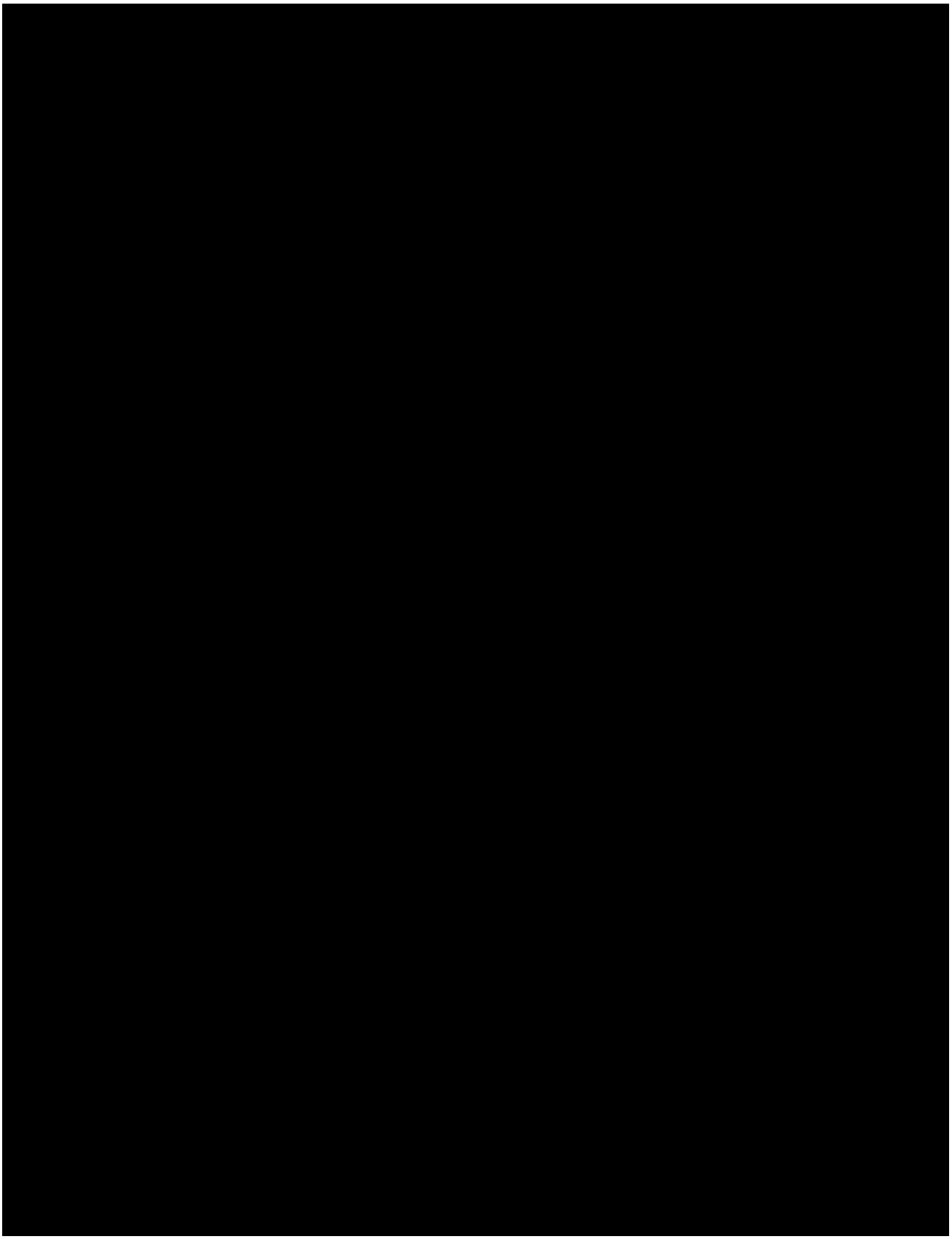


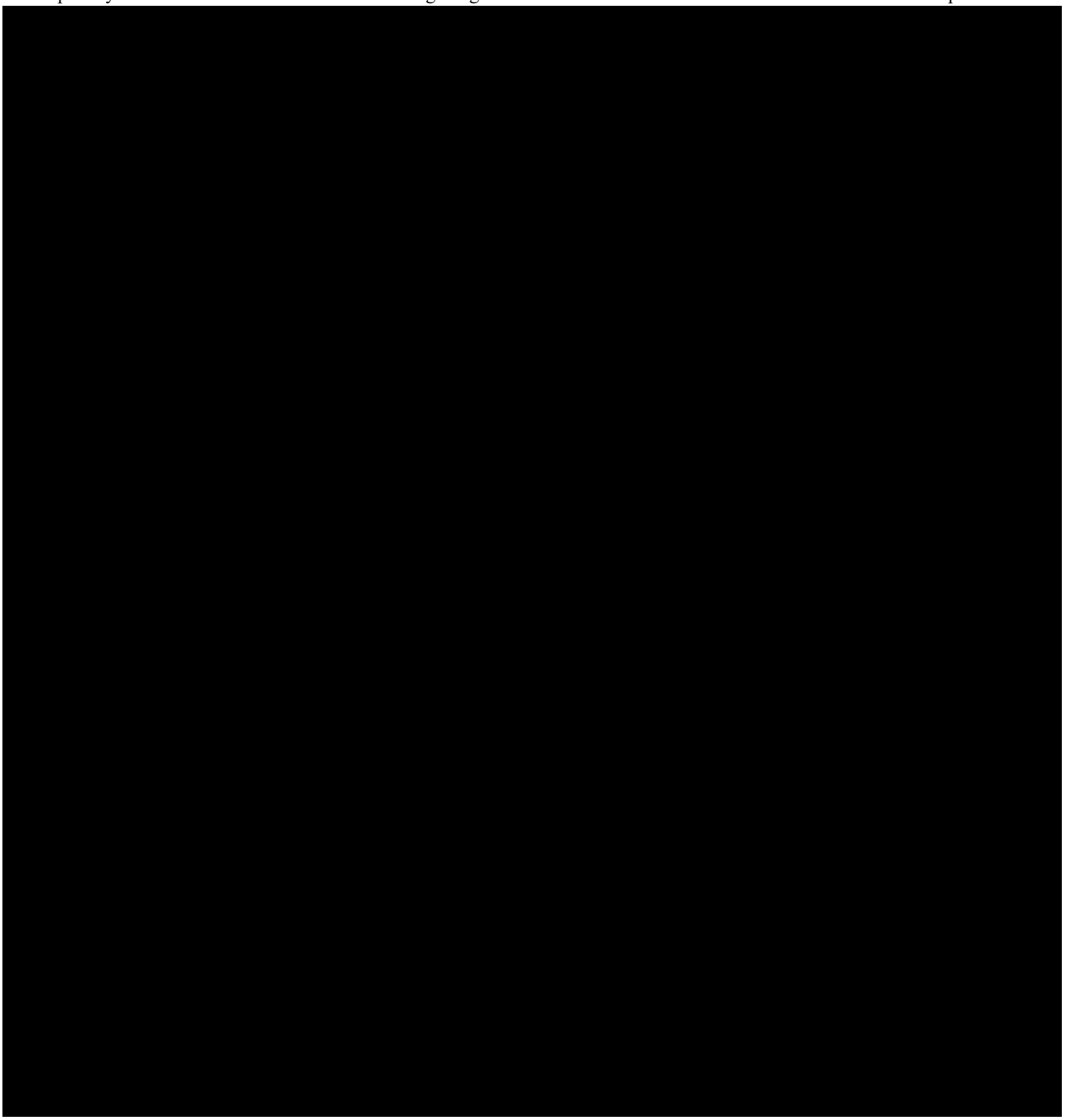










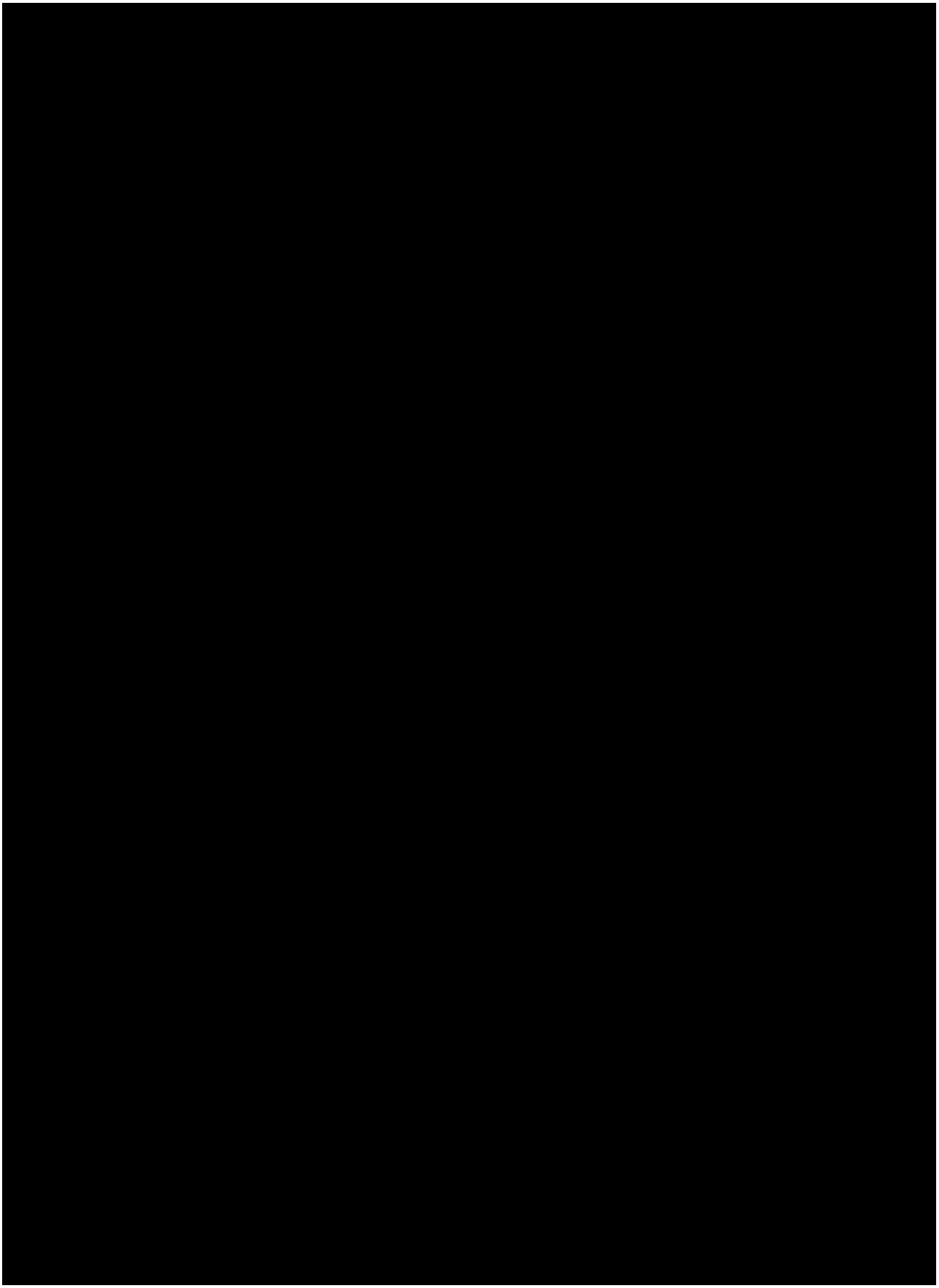


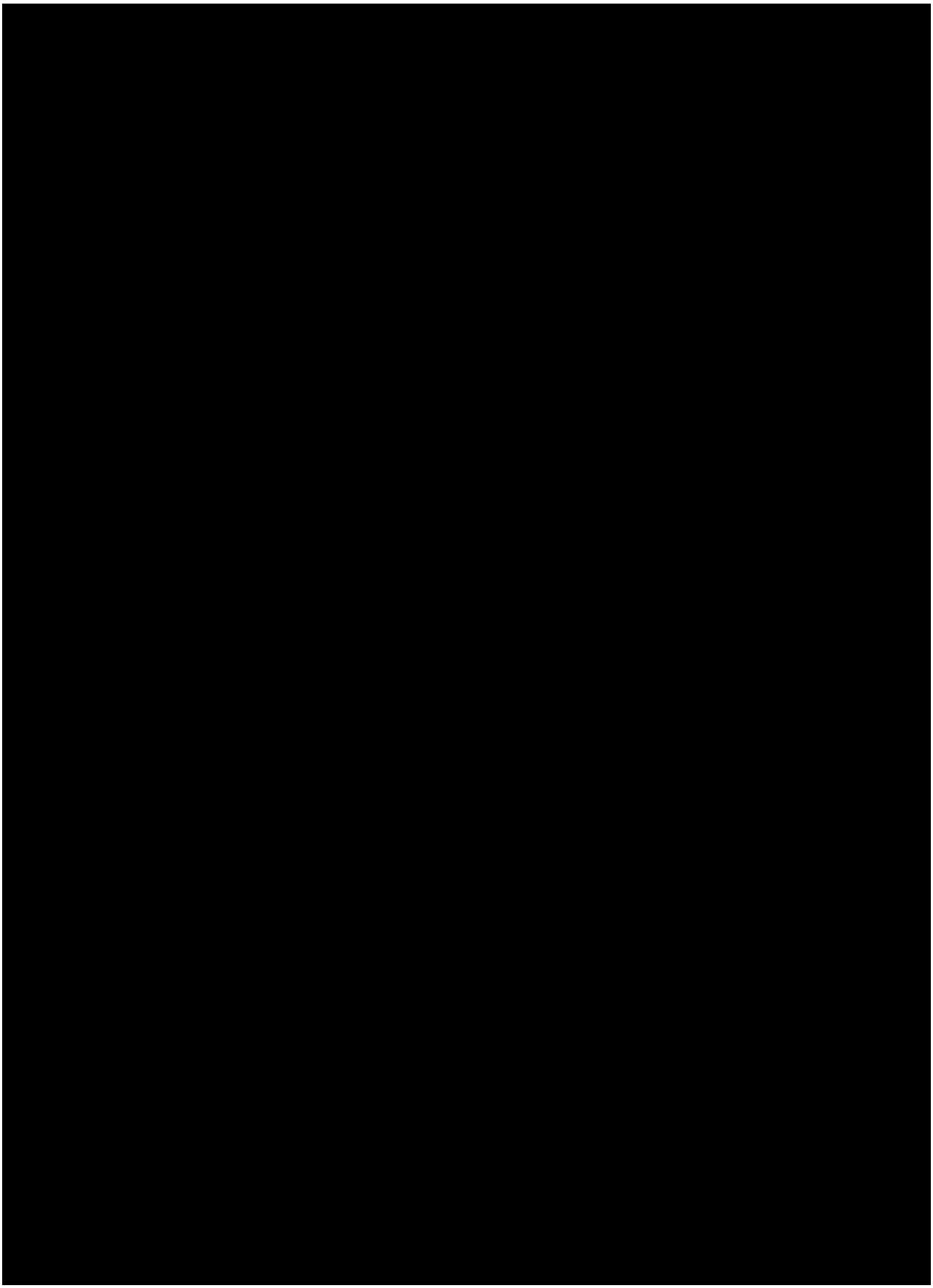
9.4 LIST OF POTENTIAL TERMS FOR HEPATIC INJURY DERIVATION

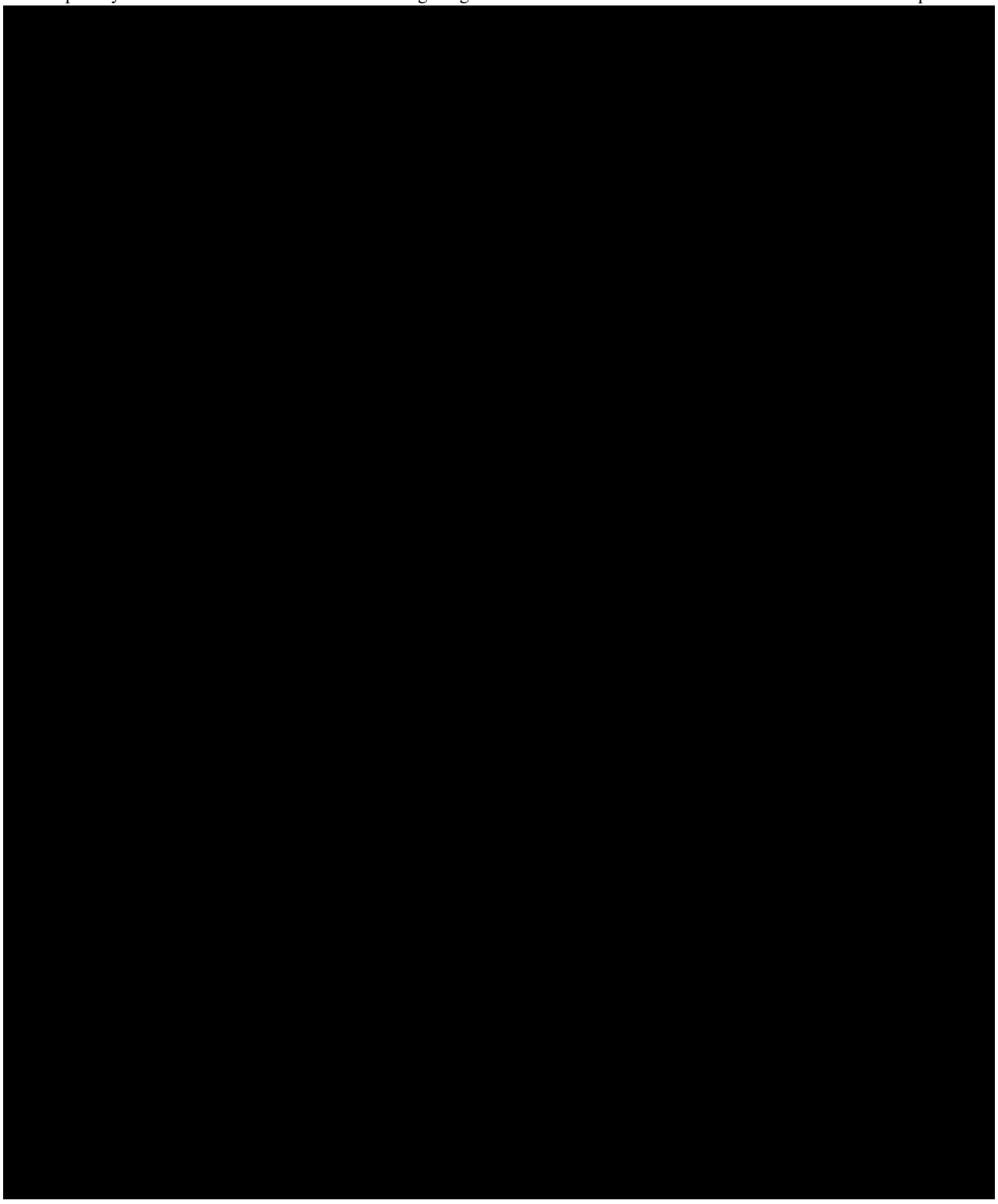
The table below shows the list of potentially relevant MedDRA preferred terms to support the derivation of a potential hepatic injury.

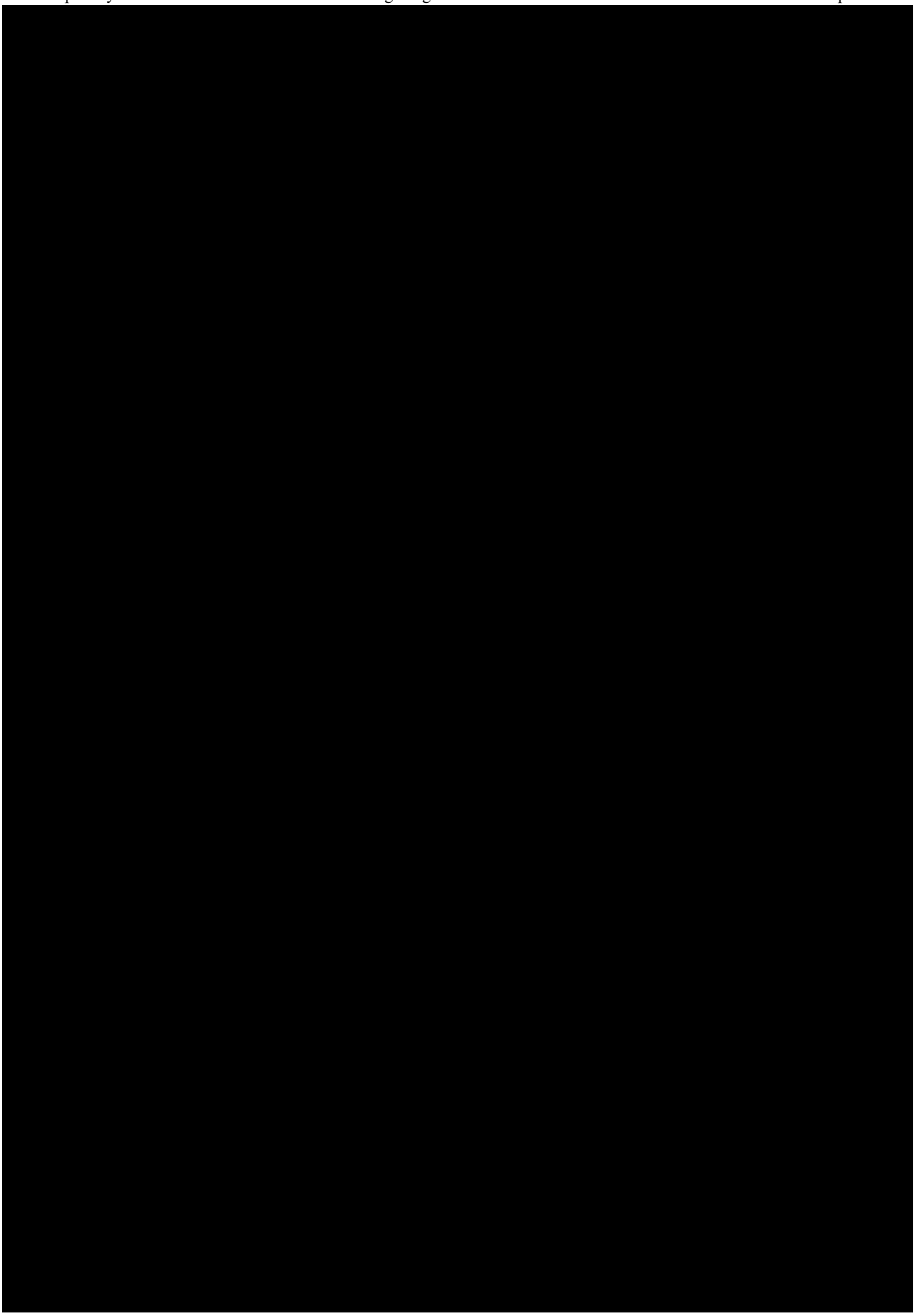
Table 9.4: 1 List of potentially relevant MedDRA preferred terms

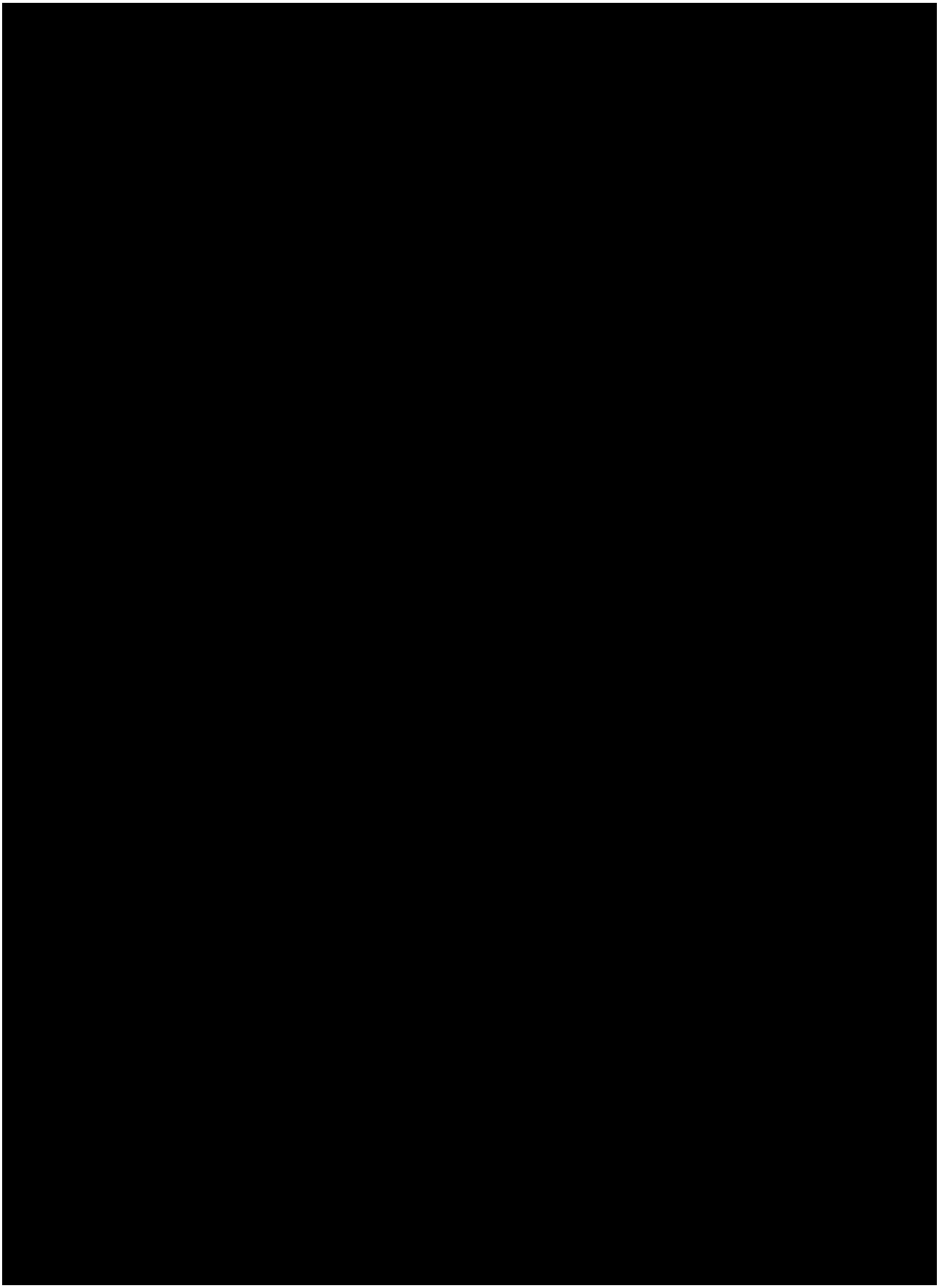
Symptom	Selection via	MedDRA decode	MedDRA code
Vomiting	Preferred Term	Vomiting	10047700
Fatigue	Preferred Term	Fatigue	10016256
Nausea	Preferred Term	Nausea	10028813
Right upper abdominal quadrant pain or tenderness	High Level Term	Gastrointestinal and abdominal pains (excl oral and throat)	10017926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

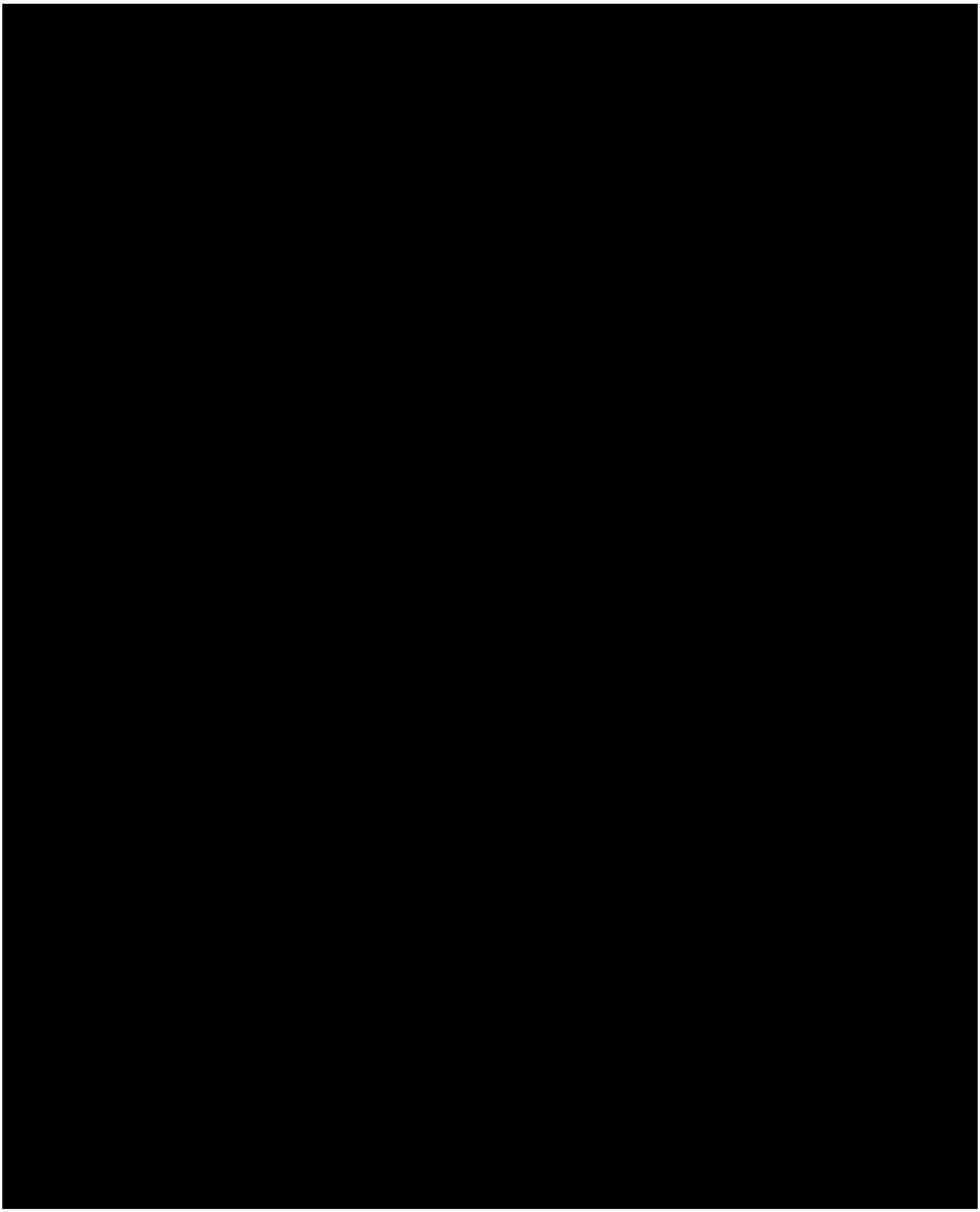


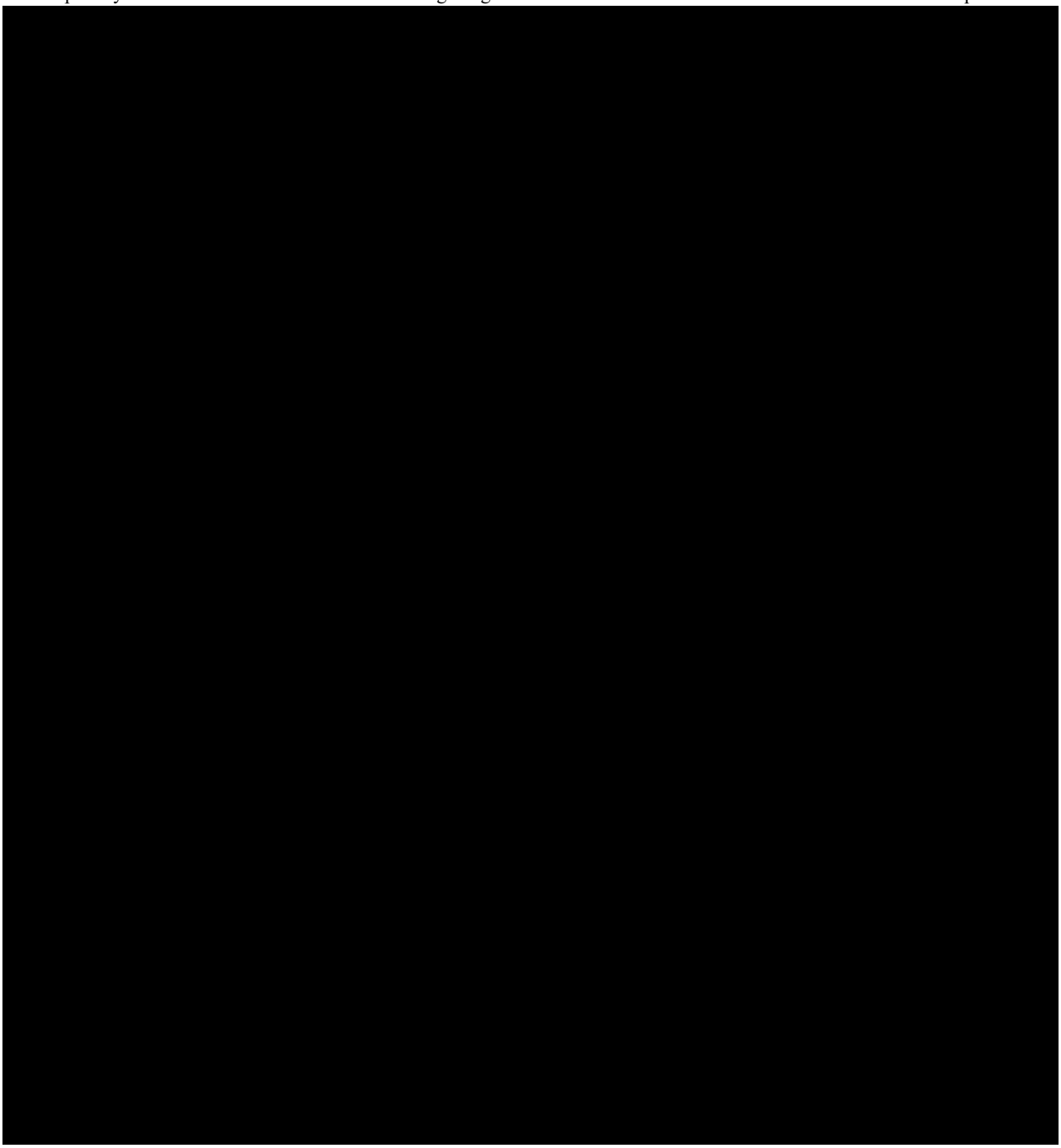


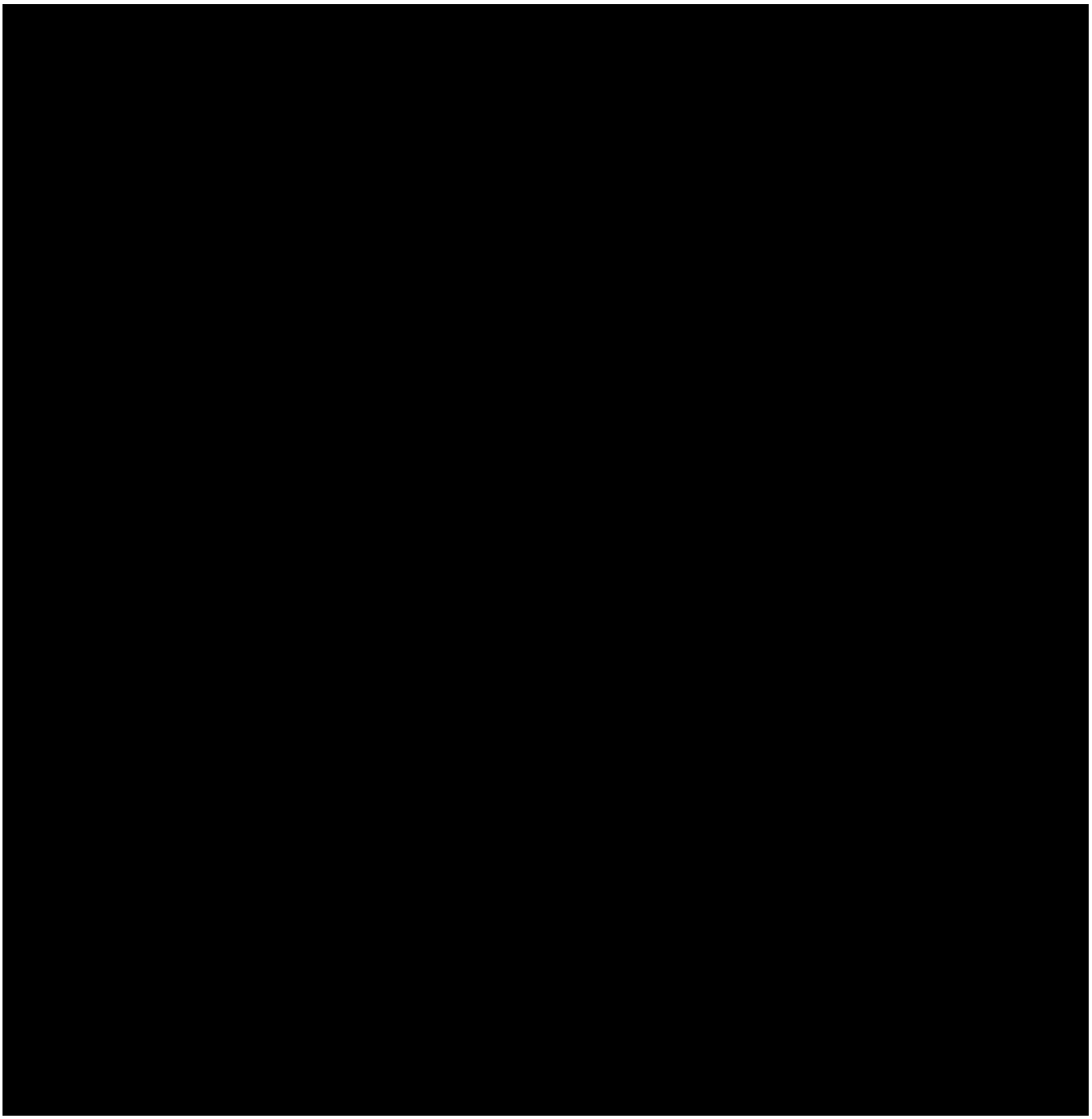


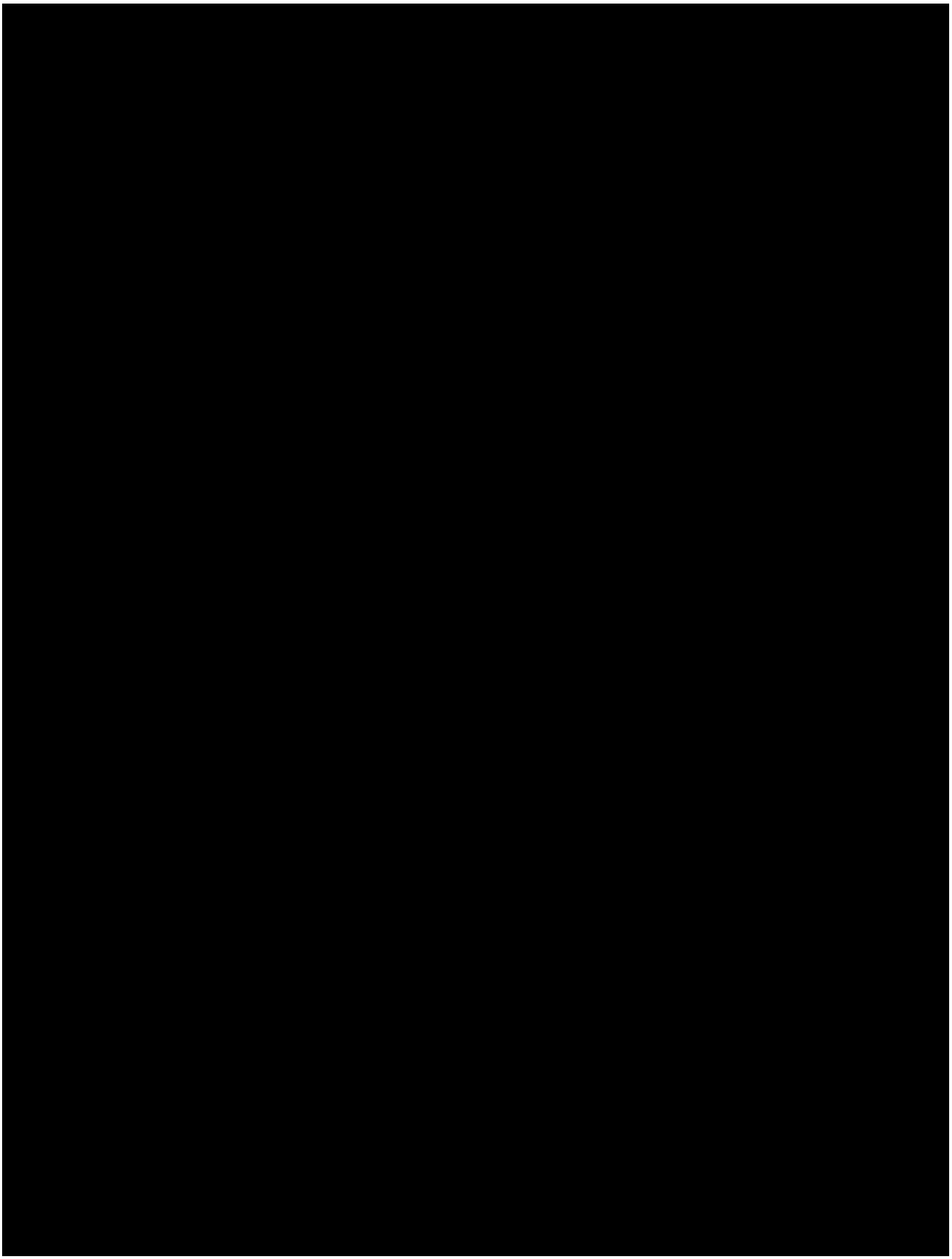


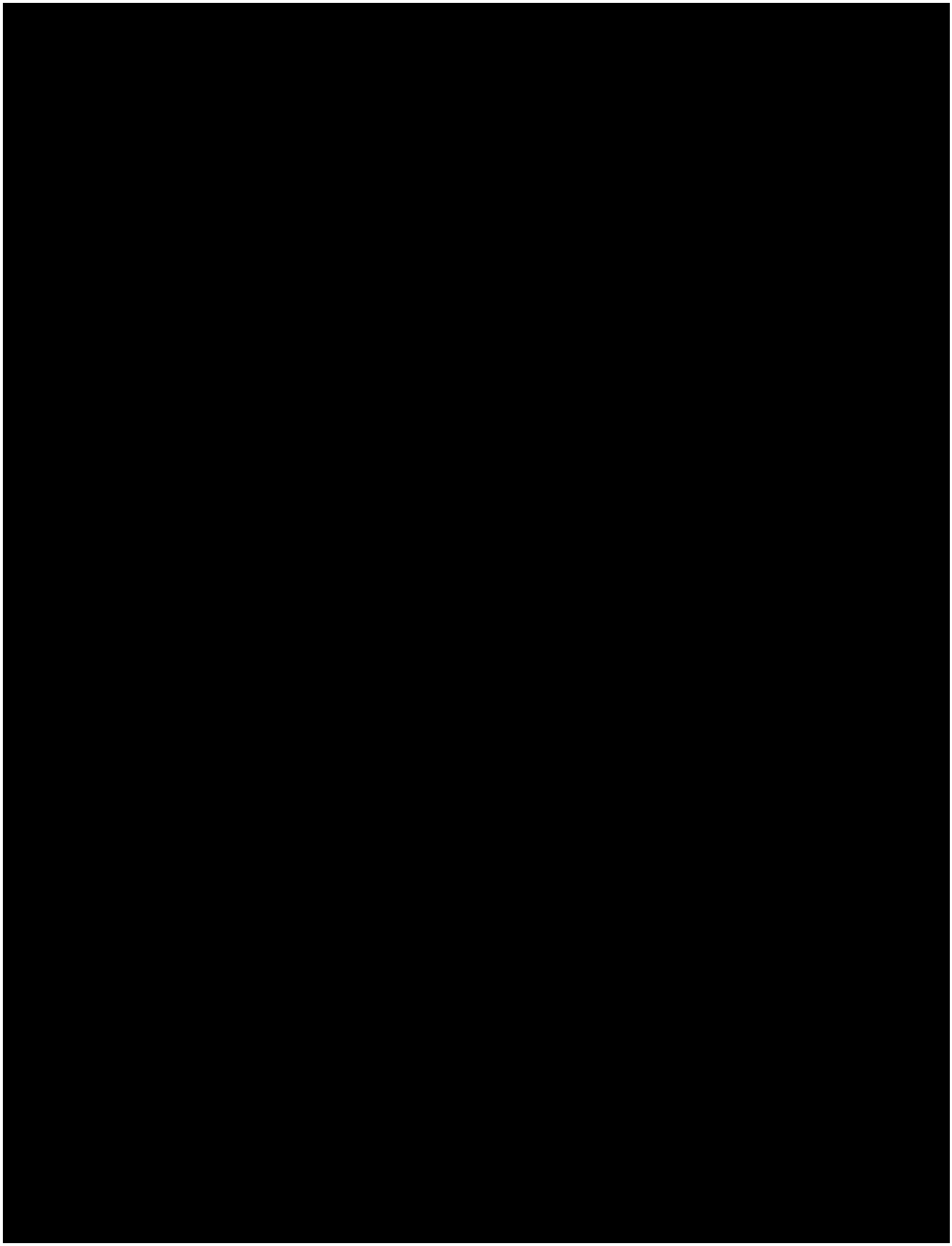


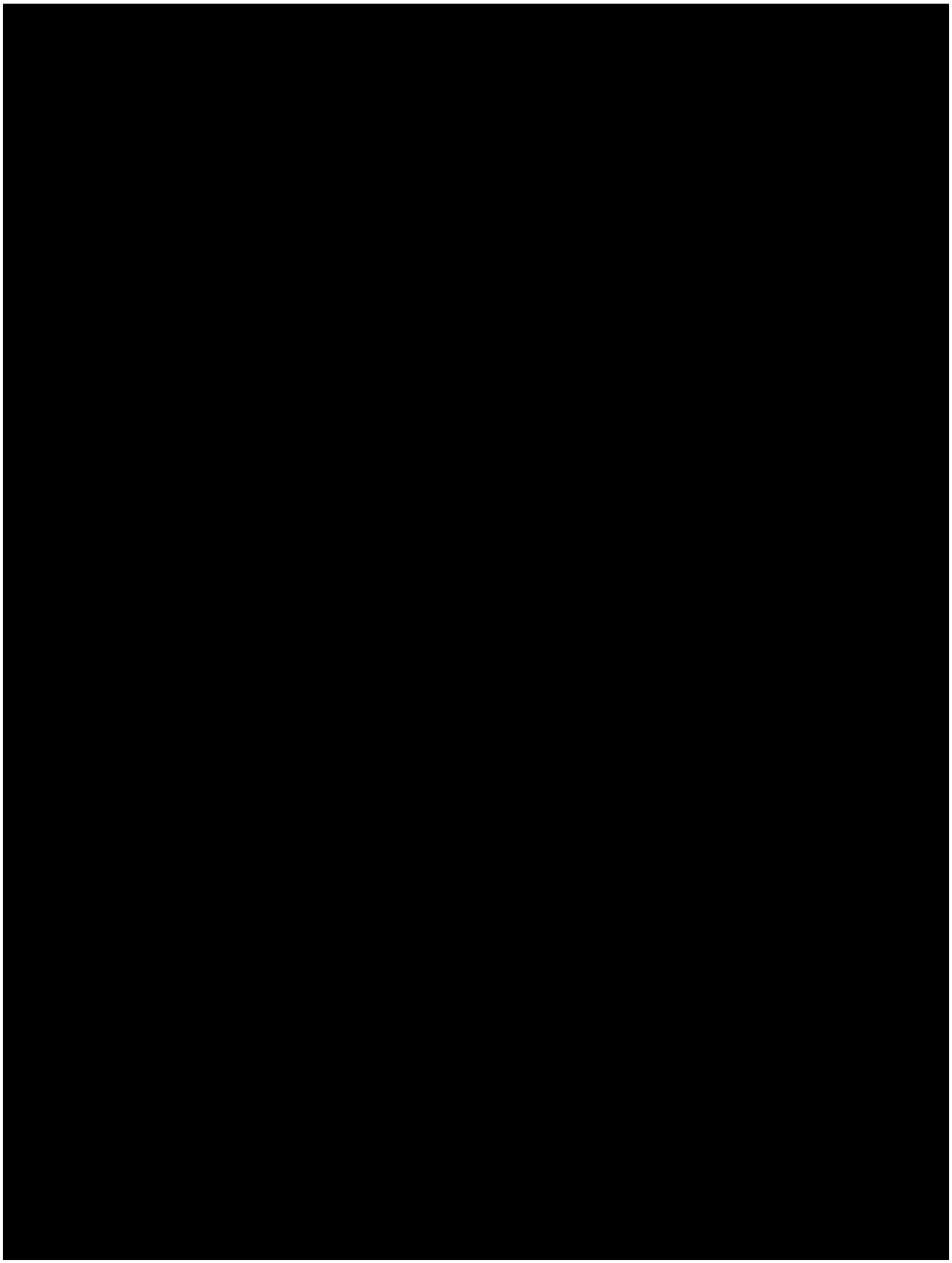


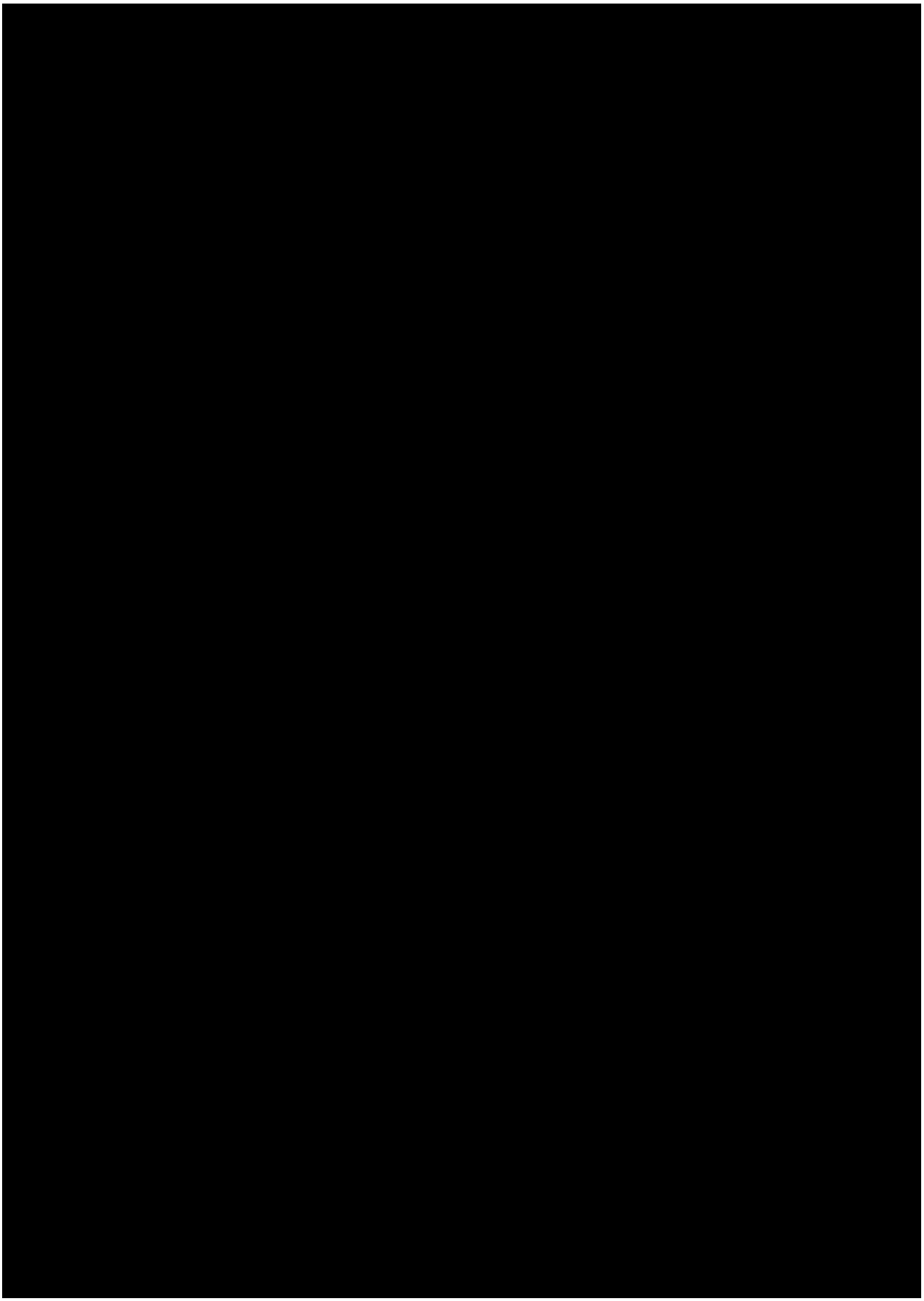


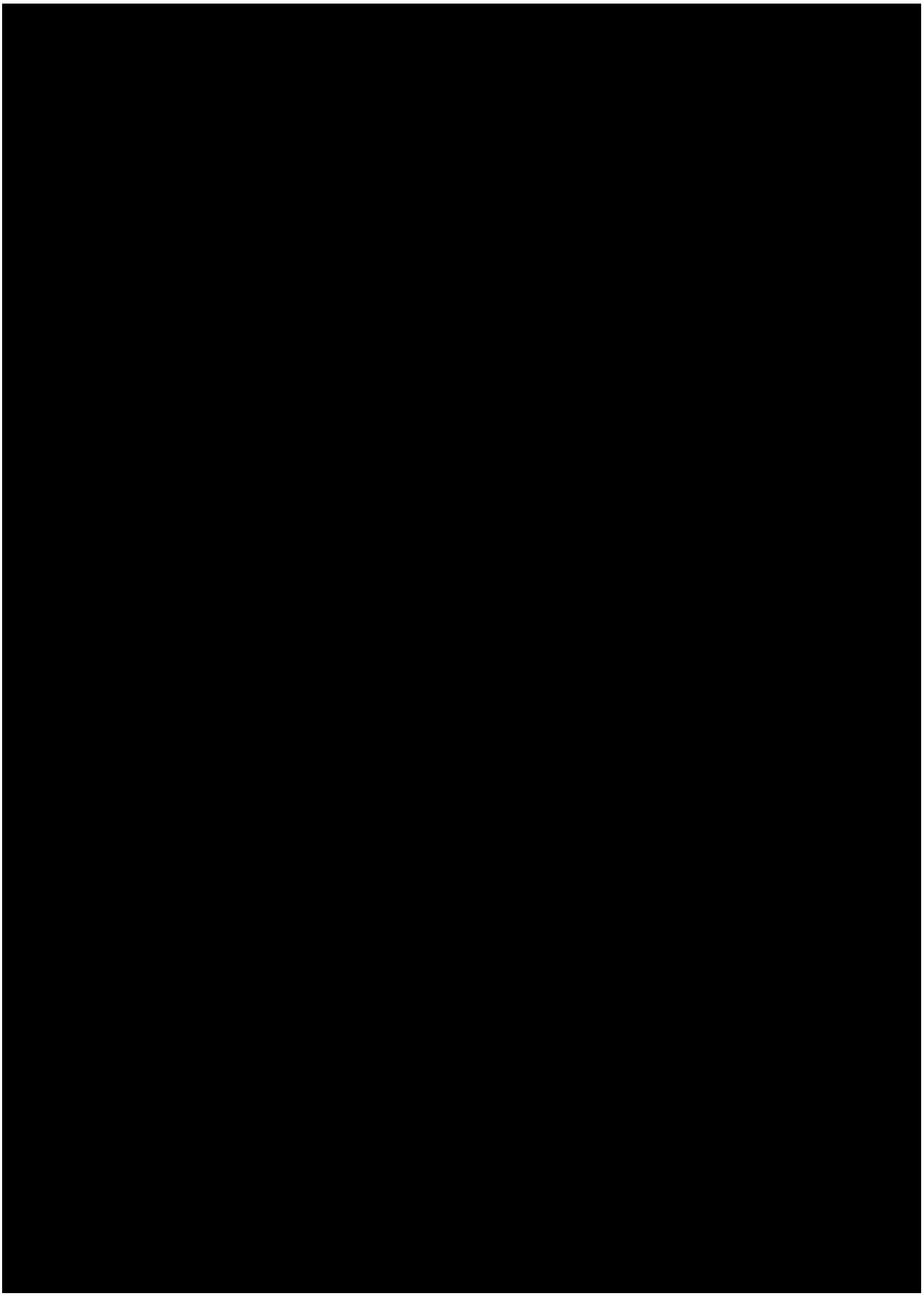


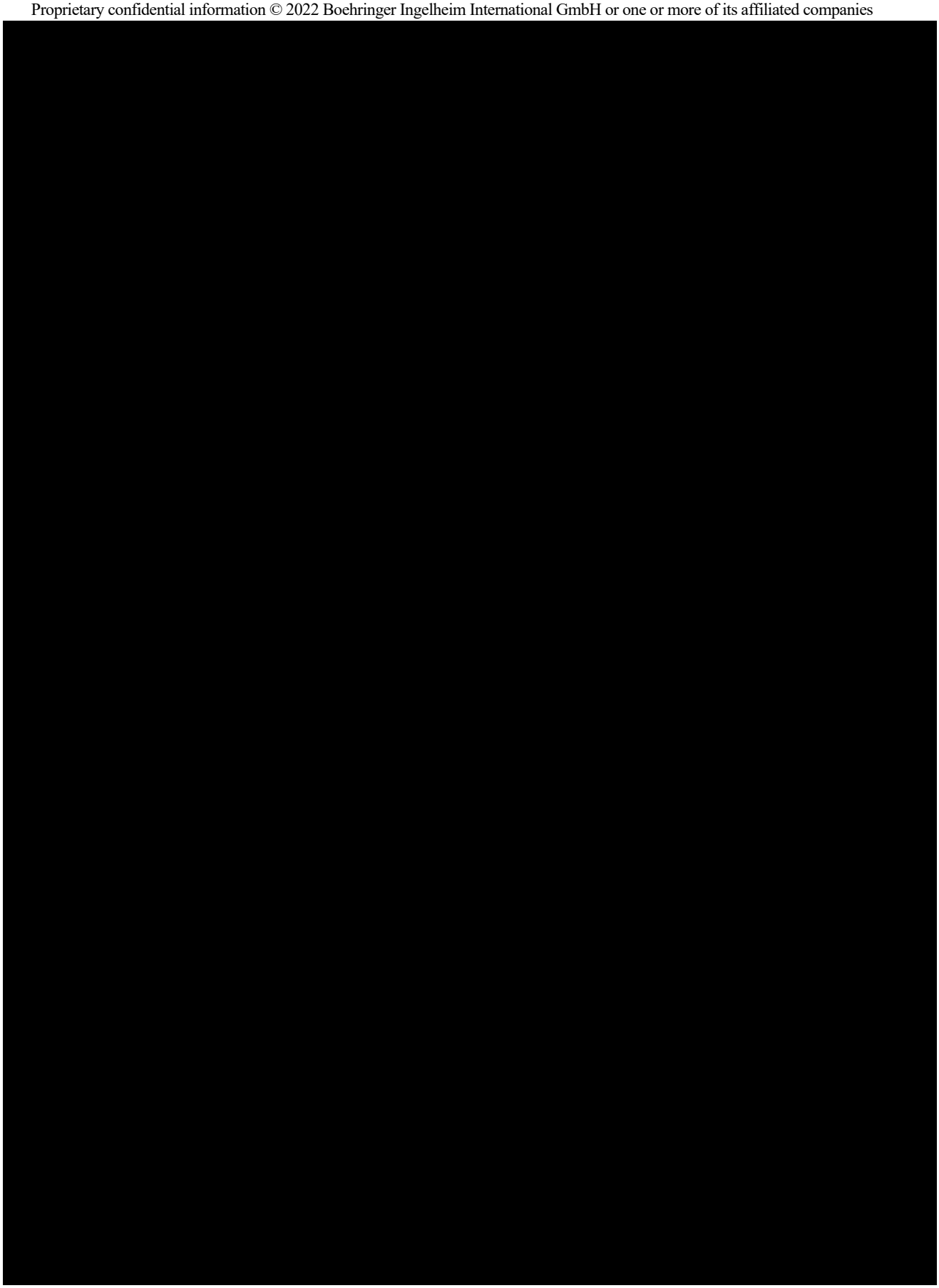


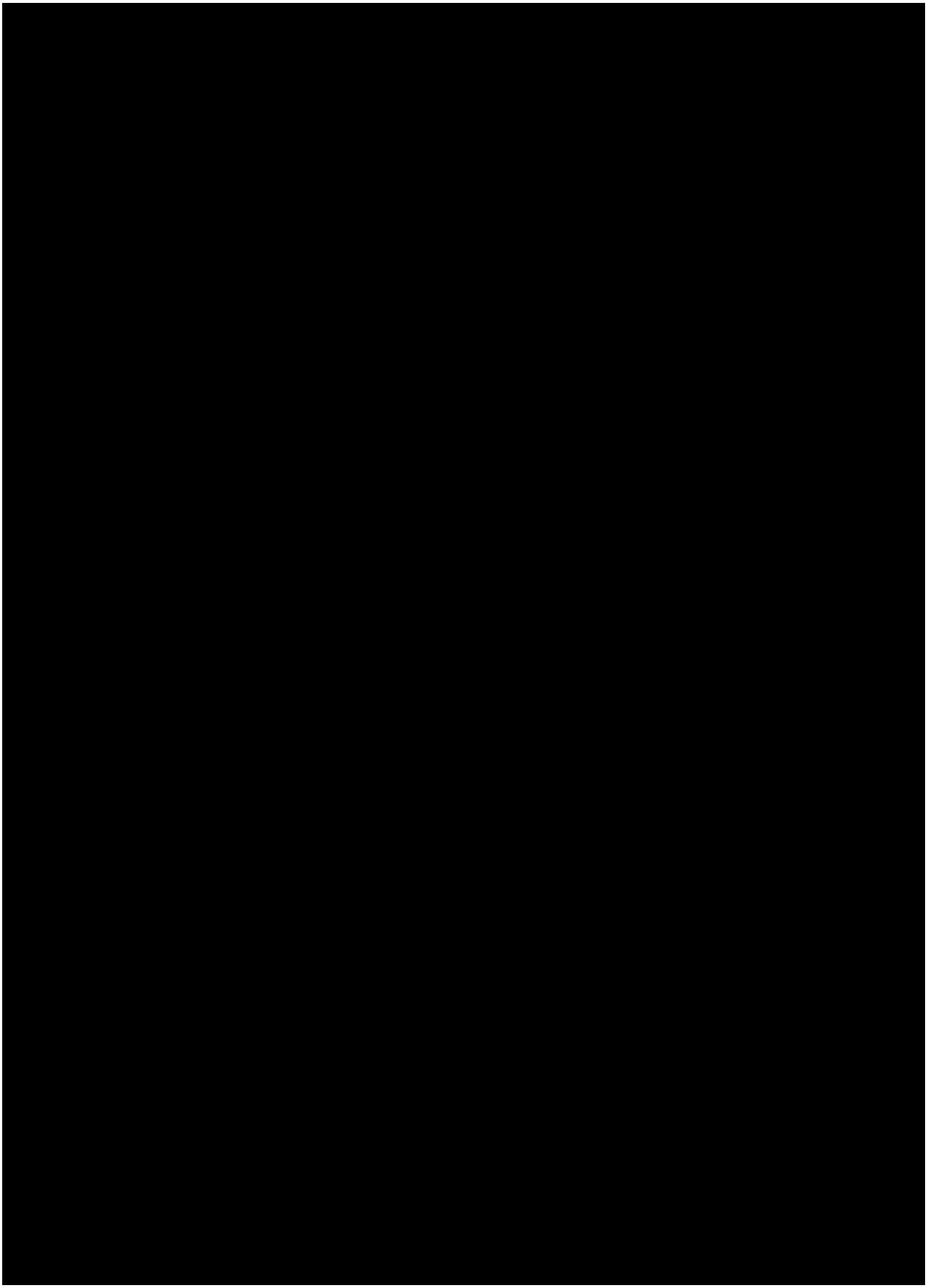












10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	**09 MAR 22**	[redacted]	None	This is the final TSAP.