TRIAL STATISTICAL ANALYSIS PLAN

Global ID_Version:	**228892_204952_2.0**
BI Trial No.:	1199-0378
Title:	An open-label trial of the long-term safety and tolerability of nintedanib per os, on top of standard of care, over at least 3 years, in children and adolescents with clinically significant fibrosing Interstitial Lung Disease (InPedILD®-ON). Including global Protocol Amendments 1-5 and Local EU Amendment 1
Investigational Product(s):	Ofev®, nintedanib
Responsible trial statistician(s):	[redacted] Phone: [redacted]
Date of statistical analysis plan:	14 MAY 2025
Version:	2
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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse event
AESI	Adverse event of Special Interest
ALK	Alkaline Phosphatase
ALT	Alanine Aminotransferase
[redacted]	
AST	Aspartate Aminotransferase
[redacted]	
BI	Boehringer Ingelheim
[redacted]	
BMI	Body Mass Index
[redacted]	
CKD-EPI	Chronic Kidney Disease - Epidemiology Collaboration
[redacted]	
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
[redacted]	
DBL	Database Lock
[redacted]	
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EDMS	Electronic Document Management System
eGFR	estimated Glomerular Filtration Rate
EMA	European Medicines Agency

Term	Definition / description
EoT	End of Treatment
[redacted]	
GGT	Gamma-Glutamyl-Transferase
[redacted]	
Hb	Haemoglobin
[redacted]	
ICE	Intercurrent Event
ICH	International Conference on Harmonisation
ILD	Interstitial Lung Disease
INR	International Normalised Ratio
iPD	Important Protocol Deviation
IRT	Interactive Response Technology
ISF	Investigator Site File
KMED	Knowledge Management in Medicine
[redacted]	
LLN	Lower Limit of Normal
[redacted]	
MACE	Major Adverse Cardiovascular Events
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	
N	Number
[redacted]	
PD	Protocol Deviation

Term	Definition / description
[redacted]	
PK	Pharmacokinetic(s)
[redacted]	
PKS	Pharmacokinetics Set
[redacted]	
PT	Preferred Term
pt-yrs	patient-years
[redacted]	
REP	Residual Effect Period
SAE	Serious Adverse Event
SAS	Statistical Analyses Software as developed by SAS Institute
SCS	Screened Set
SD	Standard deviation
[redacted]	
SSc	Systemic Sclerosis
[redacted]	
SOC	System Organ Class
[redacted]	
TMF	Trial Master File
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
ULN	Upper Limit of Normal
[redacted]	

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.

InPedILD®-ON is the open label extension of InPedILD® trial 1199.0337 which is also referred to as parent trial in this document.

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

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

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

- Further endpoint analysis:

[redacted]

For patients who had a lung transplant during the trial, results after the lung transplant will not be considered for the analyses of

[redacted]

No safety data collected after a lung transplant will be excluded from the analyses.

As per CTP amendments 3 (29 Nov 2023) and 5 (27 Nov 2024) some additional timepoints have been added to some further safety and efficacy endpoints due to prolongation of the trial from 2 to 3 years:

[redacted]

5. ENDPOINTS

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.

Handling of missing data points is described in Section 6.6.

For endpoints or other variables where derived "last contact date" is utilised, e.g. time-to-event analyses, the following will apply:

The derived last contact date when the 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):

- Last visit date (including start or end date of a non-elective hospitalisation),
- Last reported Adverse Event (AE) date (excluding end dates when AE outcome is fatal or unknown),
- Last reported concomitant therapy date,
- Last laboratory sample date,
- Last reported trial drug intake date,
- Last reported dose change / interruption date,
- Last spirometry assessment,
- End of study participation date (as documented on End of Study eCRF page if reason for not completing the planned observation period is NOT "Death" or "Lost to Follow-up").
- Last vital status date (as documented on Vital Status eCRF page if the patient is known to be alive),
- Last successful contact date (as documented on End of Study eCRF page if reason is "Lost to Follow-up")

5.1 PRIMARY ENDPOINT

The primary endpoint is the incidence of treatment emergent adverse events over the whole trial. Thus, the number of patients experiencing at least one adverse event during the course of this extension trial will be analysed, see Section 7.8.

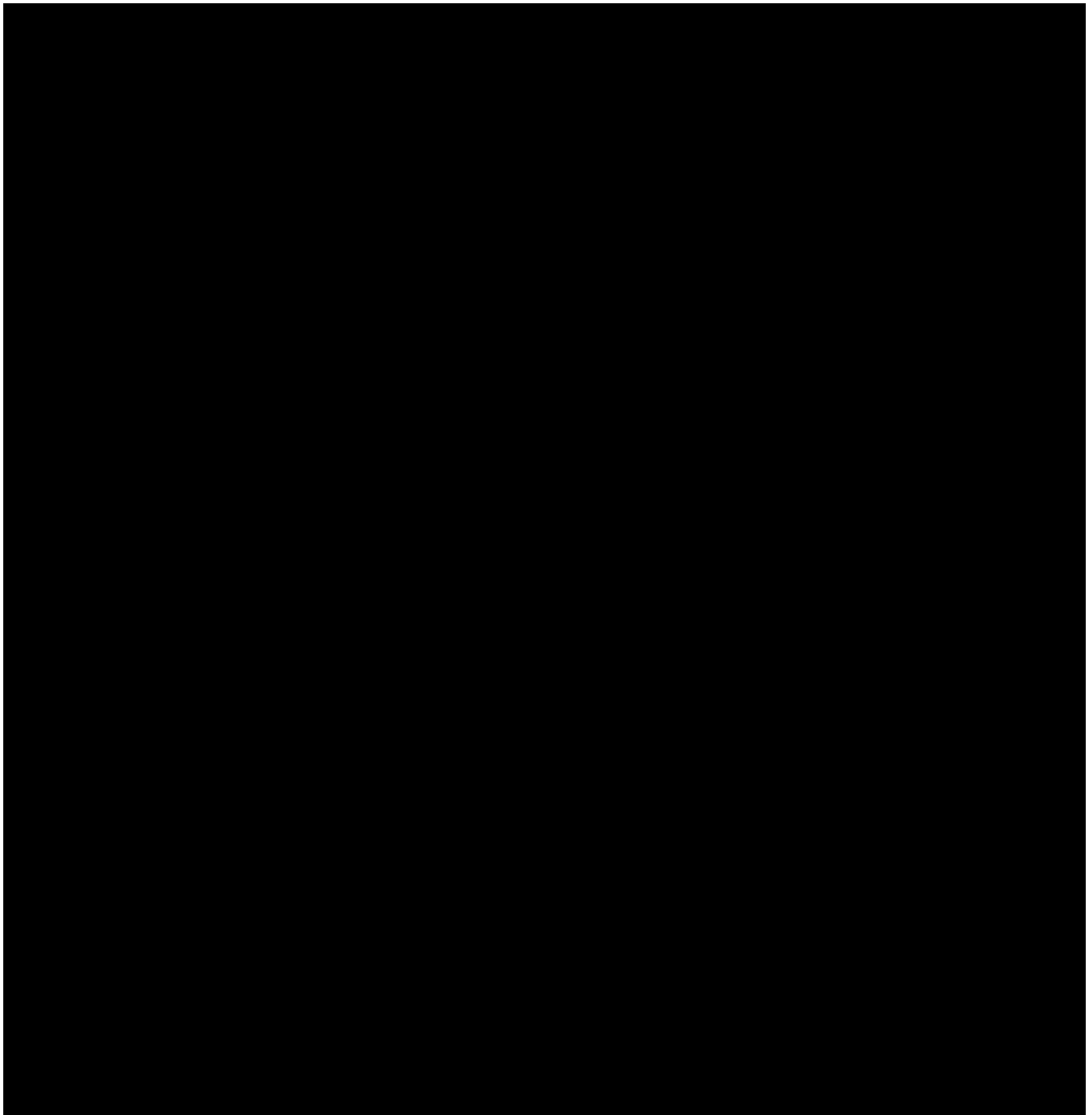
5.2 SECONDARY ENDPOINT(S)

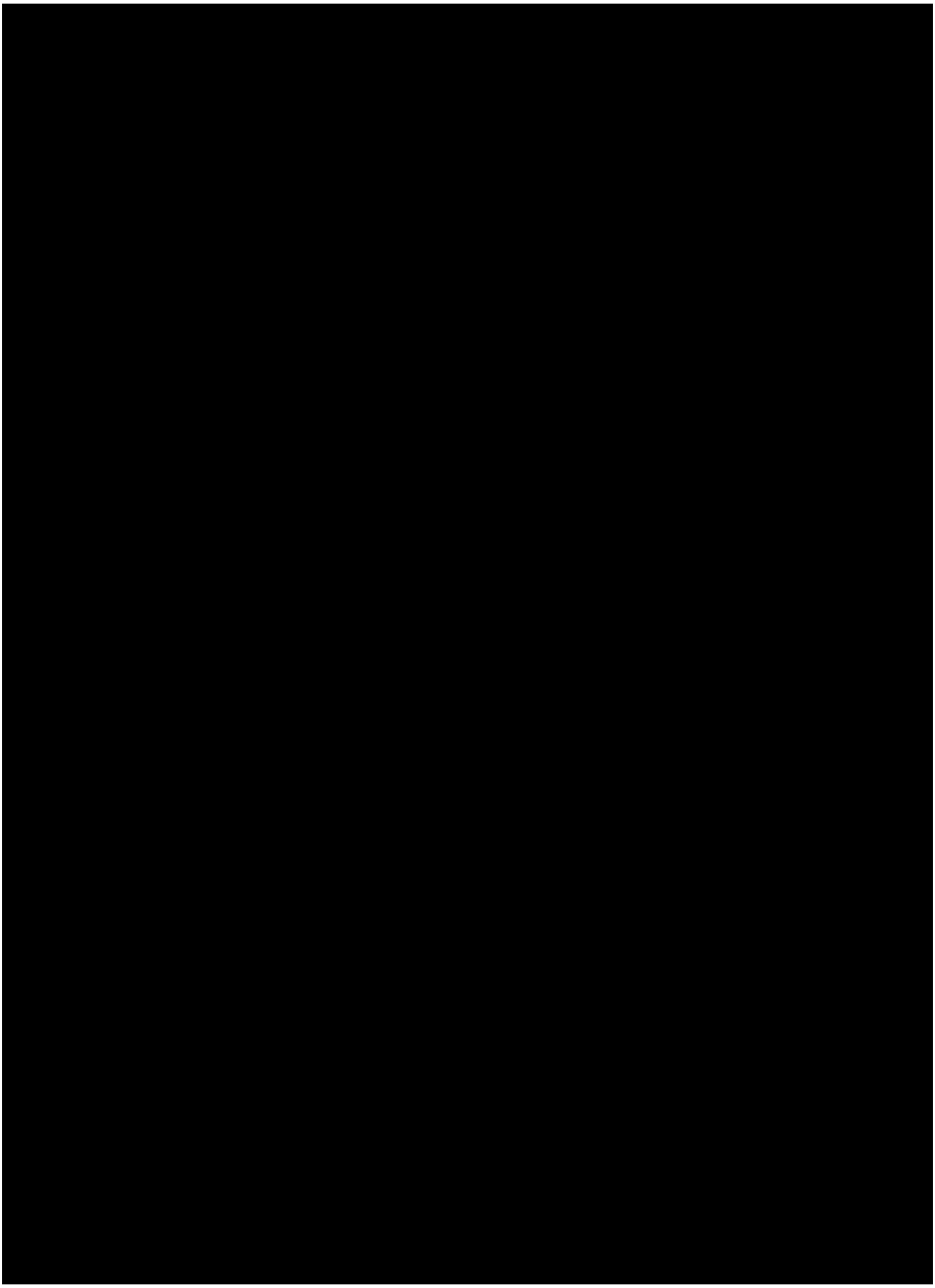
5.2.1 Key secondary endpoint(s)

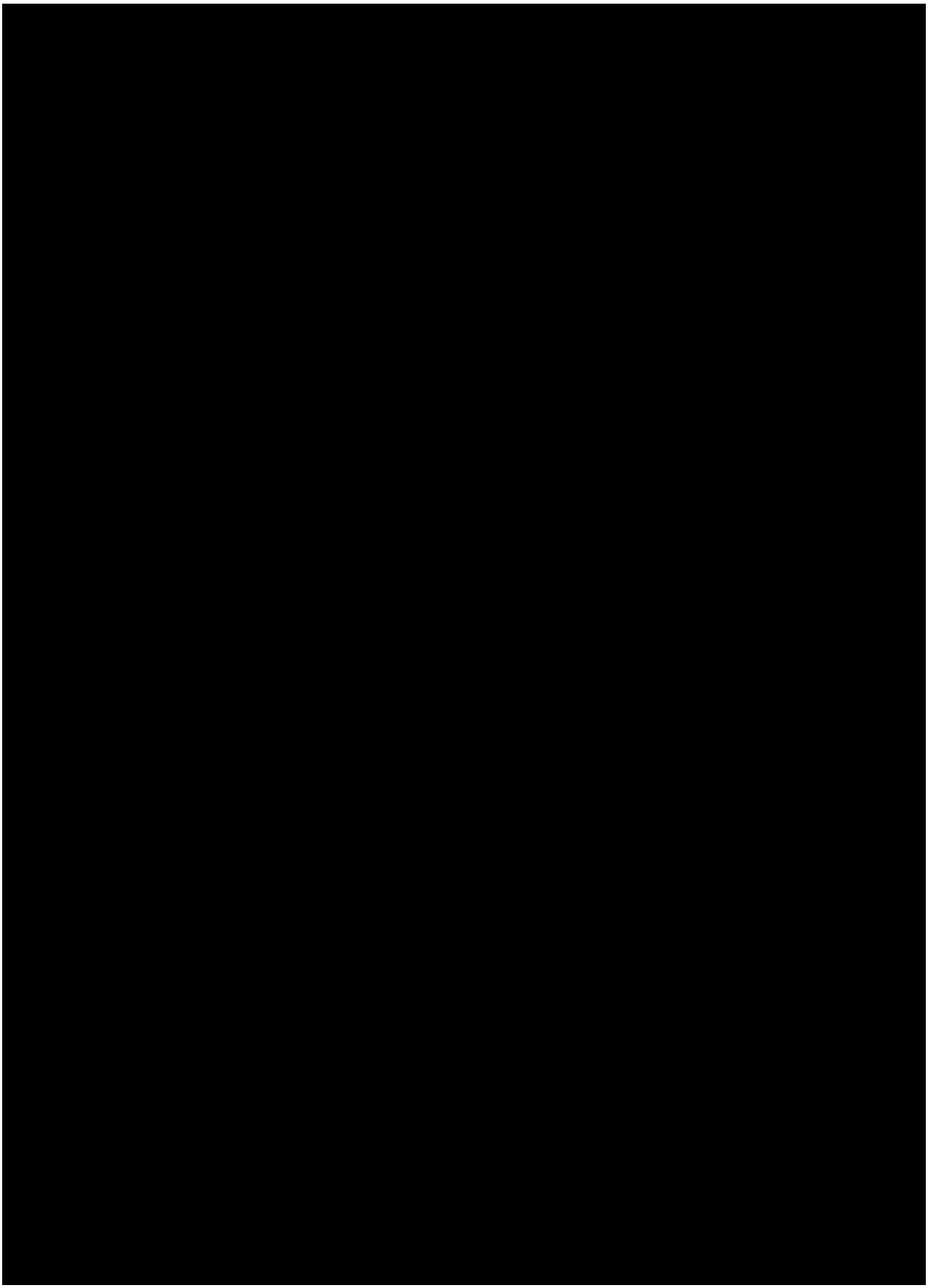
This section is not applicable as no key secondary endpoint has been specified in the protocol.

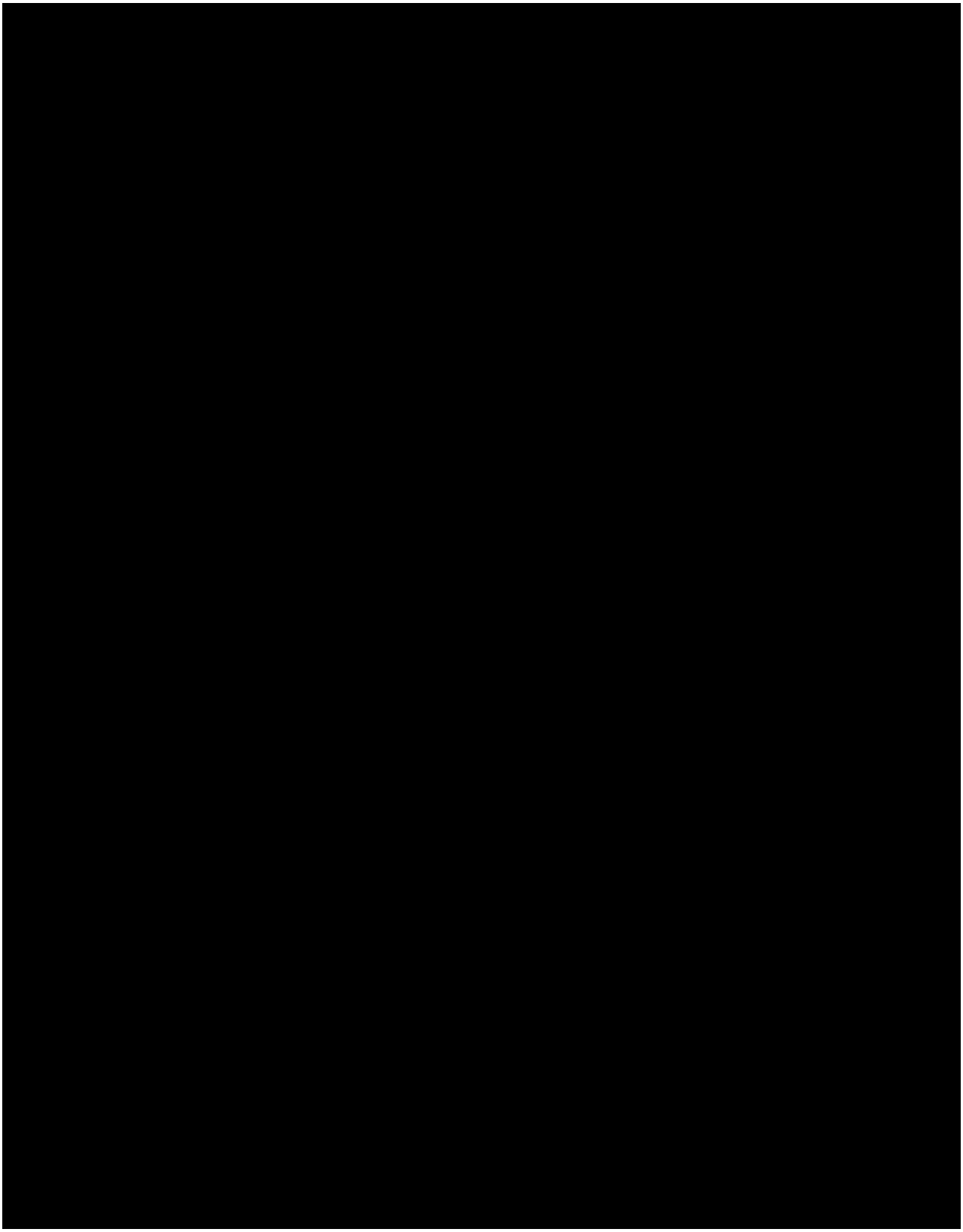
5.2.2 Secondary endpoint(s)

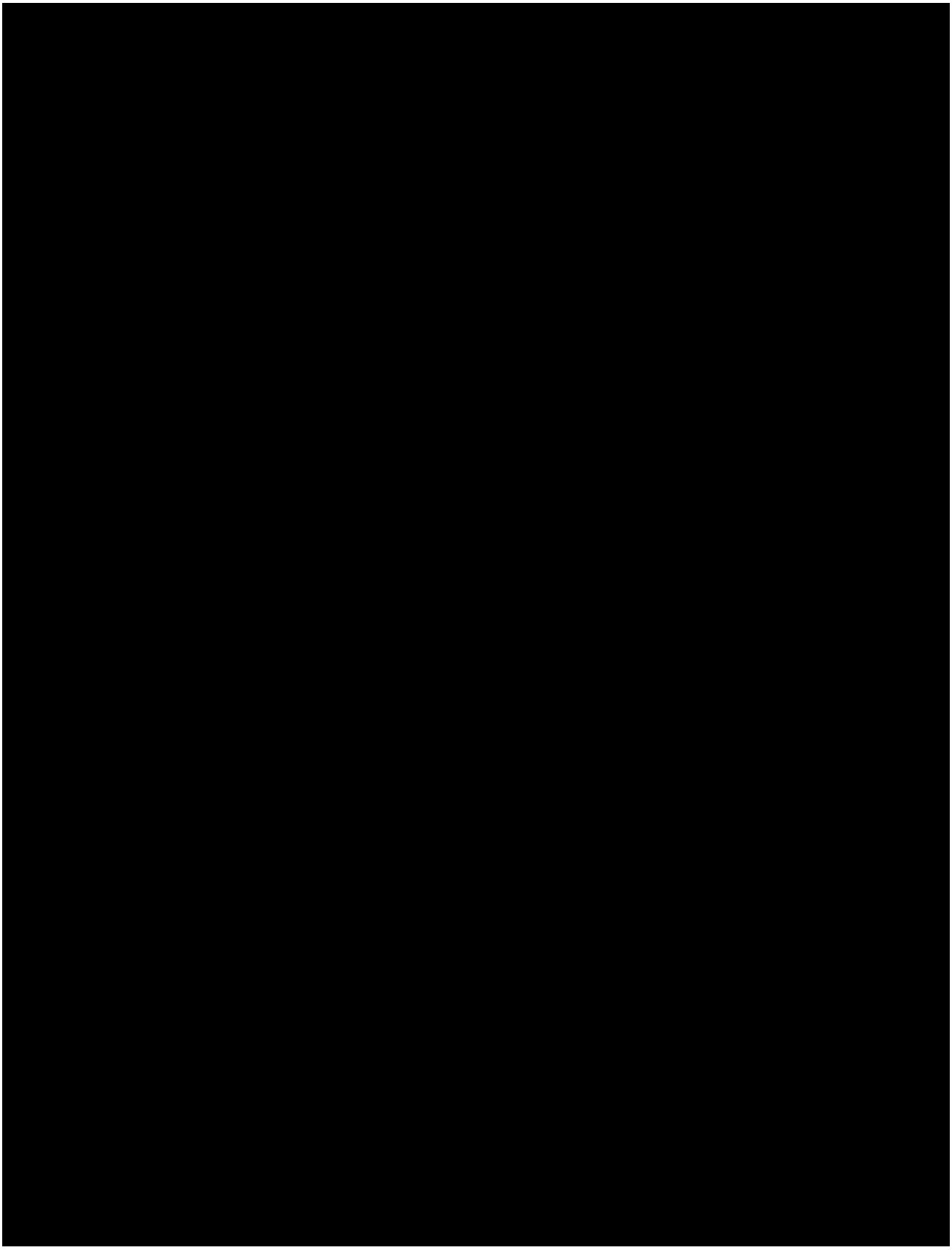
This section is not applicable as no secondary endpoint has been specified in the protocol.

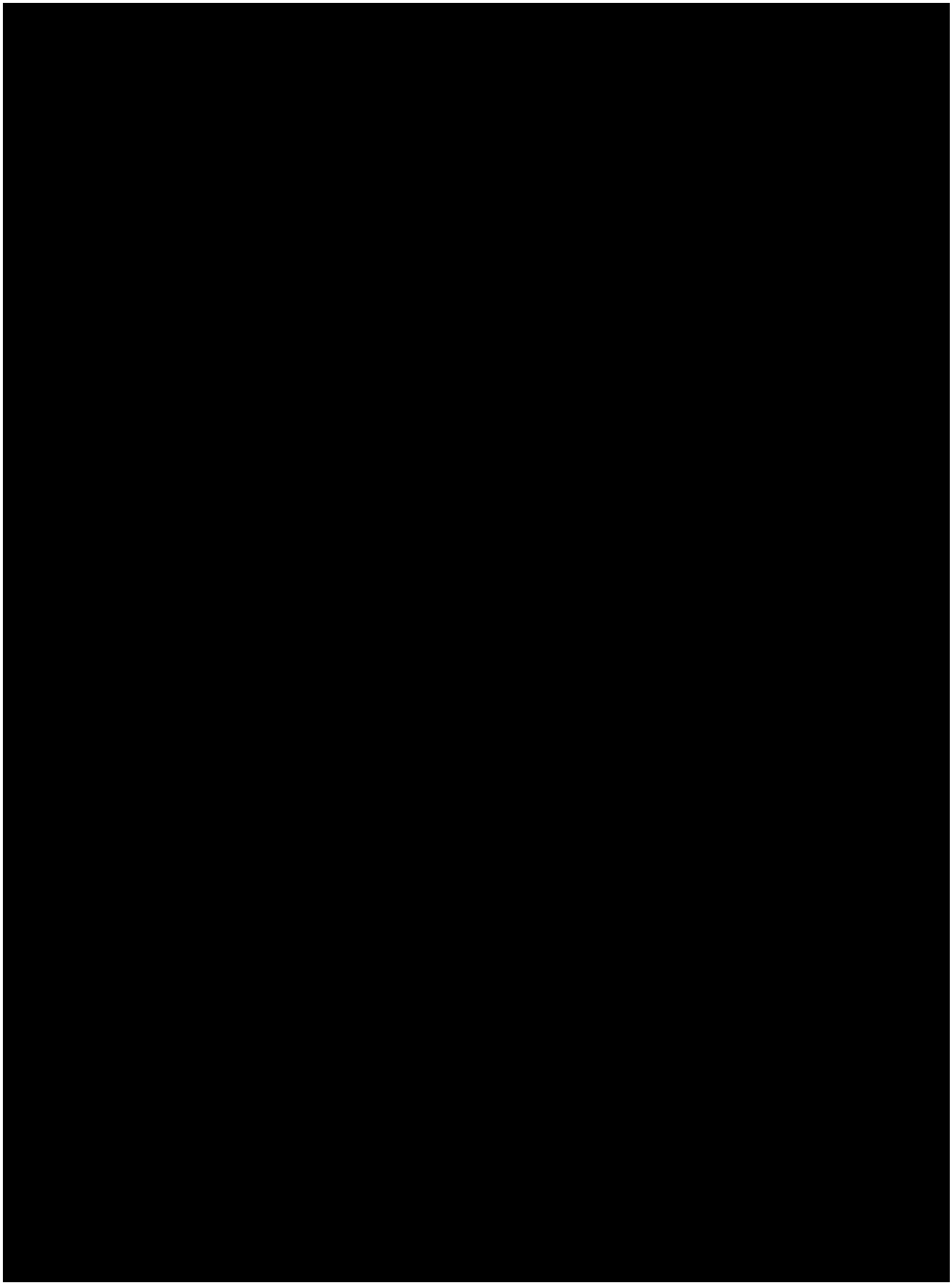


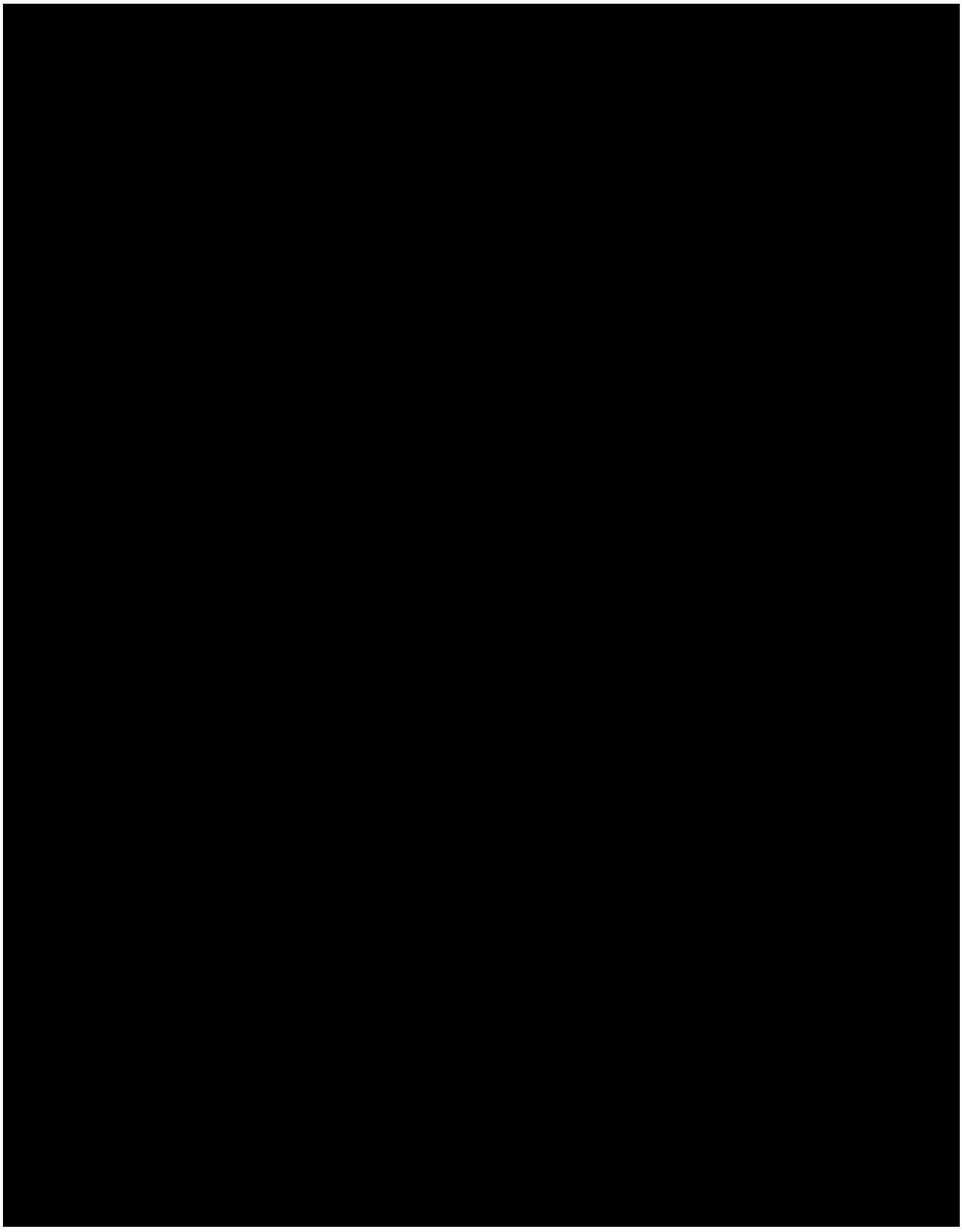


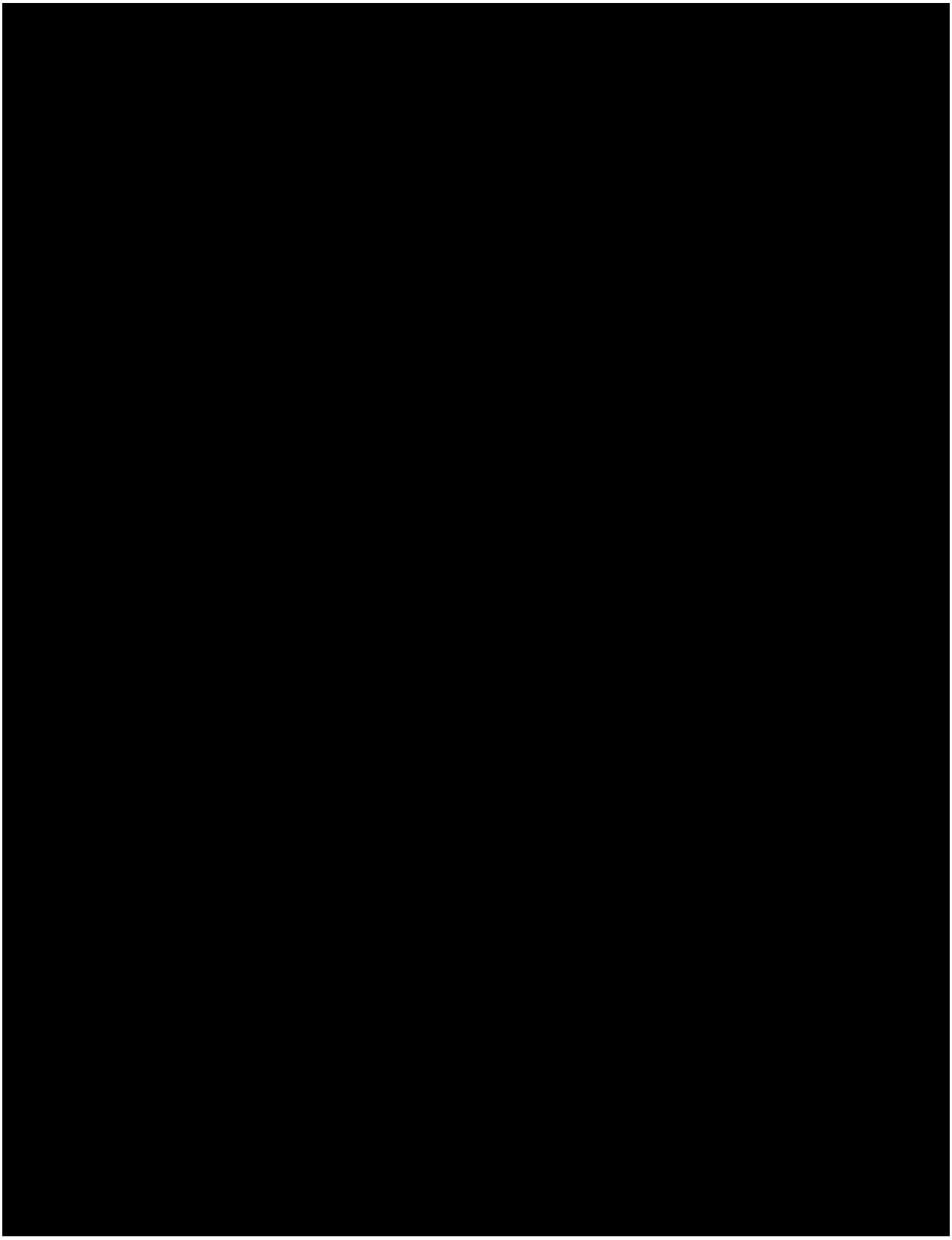


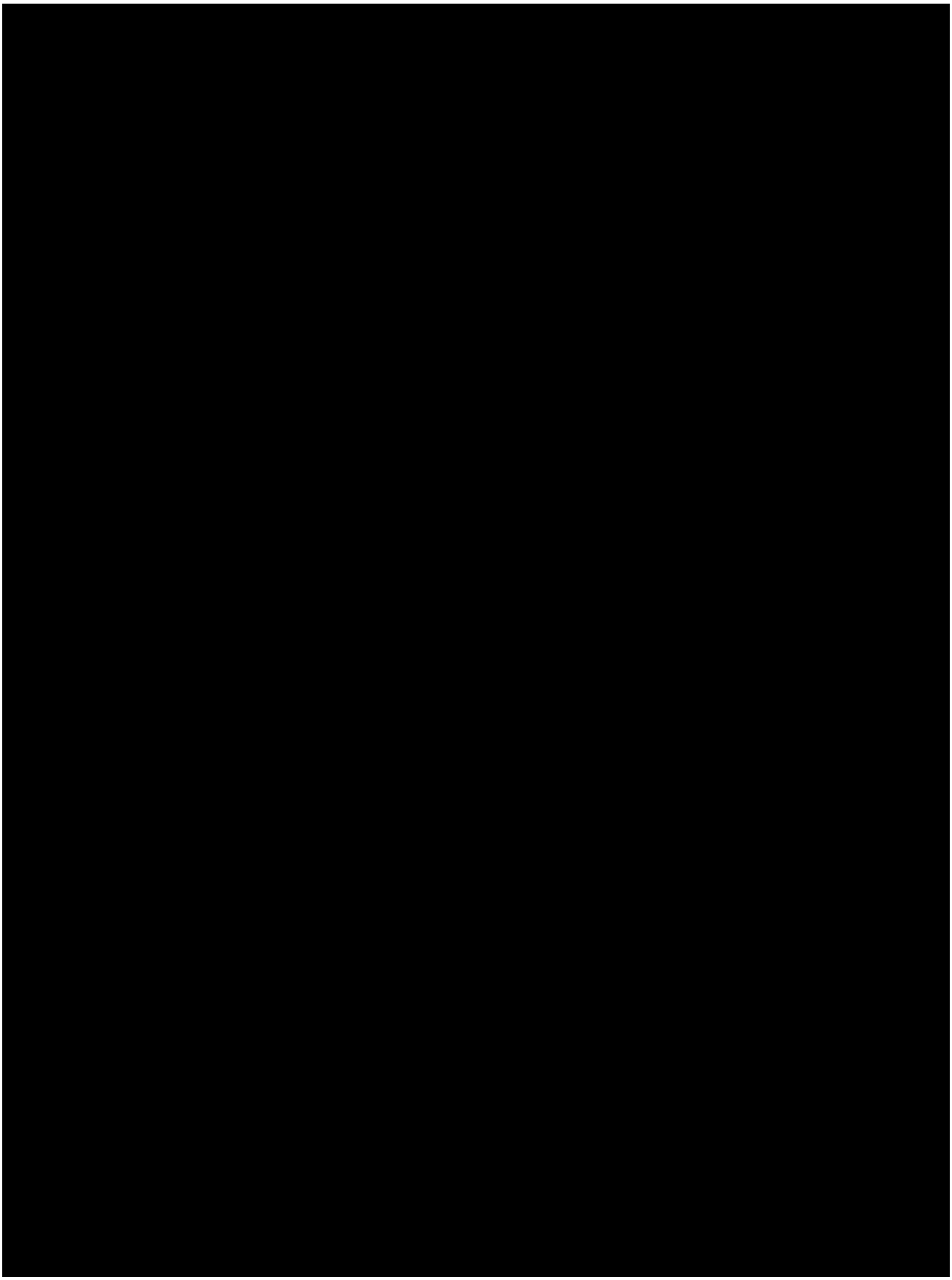












5.4 OTHER VARIABLE(S)

5.4.1 Demographics and baseline characteristics

5.4.1.1 Demographic data

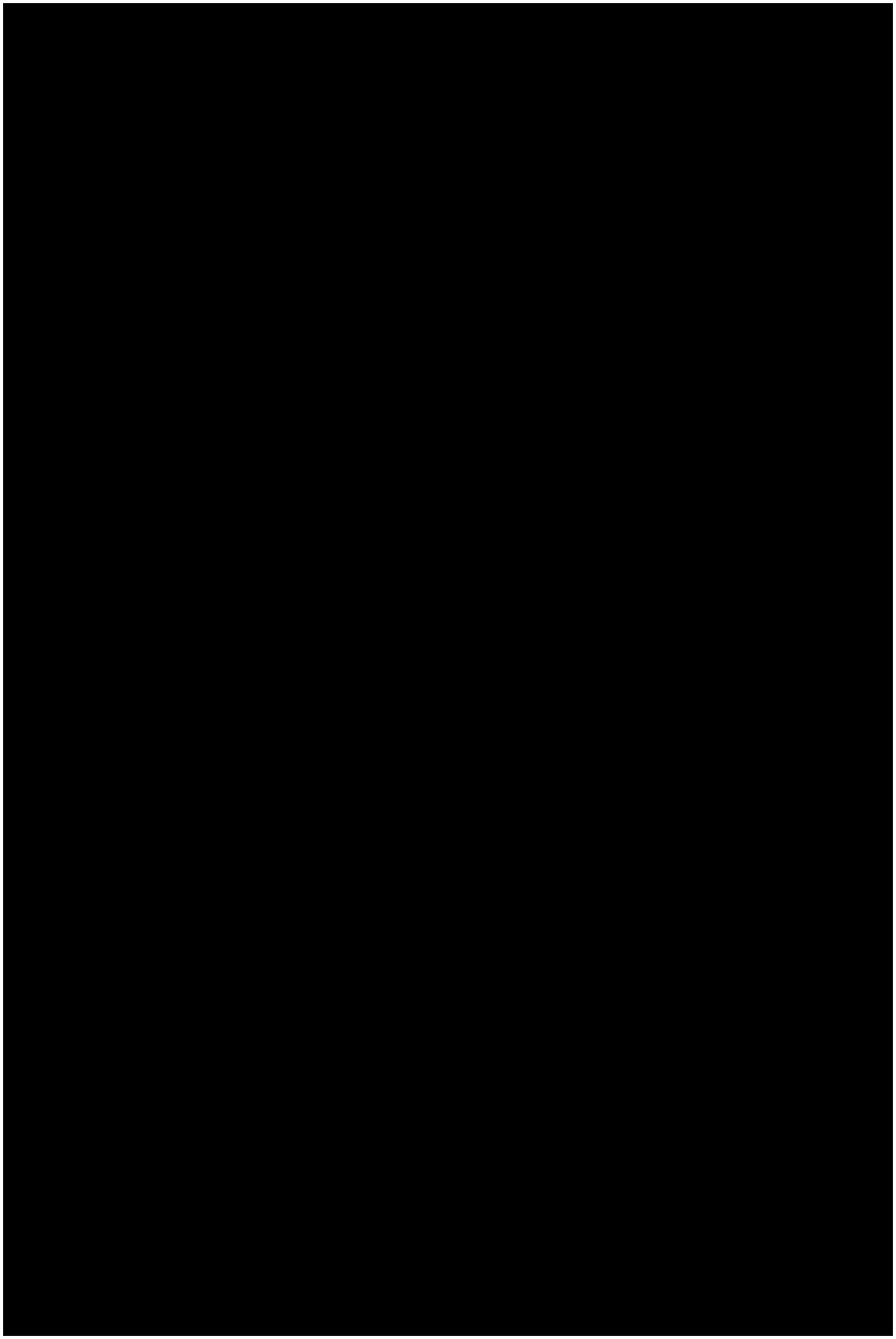
- Gender (Male; Female)
- Race: single race respondents, multiple race respondents (all combinations ticked), and all race categories regardless of how many race categories were ticked
- Ethnicity (Hispanic/Latino; Not Hispanic/Latino)
- Age [years] at time of informed consent (transferred by IRT) as continuous variable and in categories [years] (6 to <12; 12 to <18; >=18)[1]
- Weight [kg] at baseline as continuous variable and in categories [kg] (<13.5; 13.5 to <23.0; 23.0 to <33.5; 33.5 to <57.5; >=57.5)
- Height (standing) [cm] at baseline as continuous variable
- Body mass index [kg/m^2] at baseline, calculated as

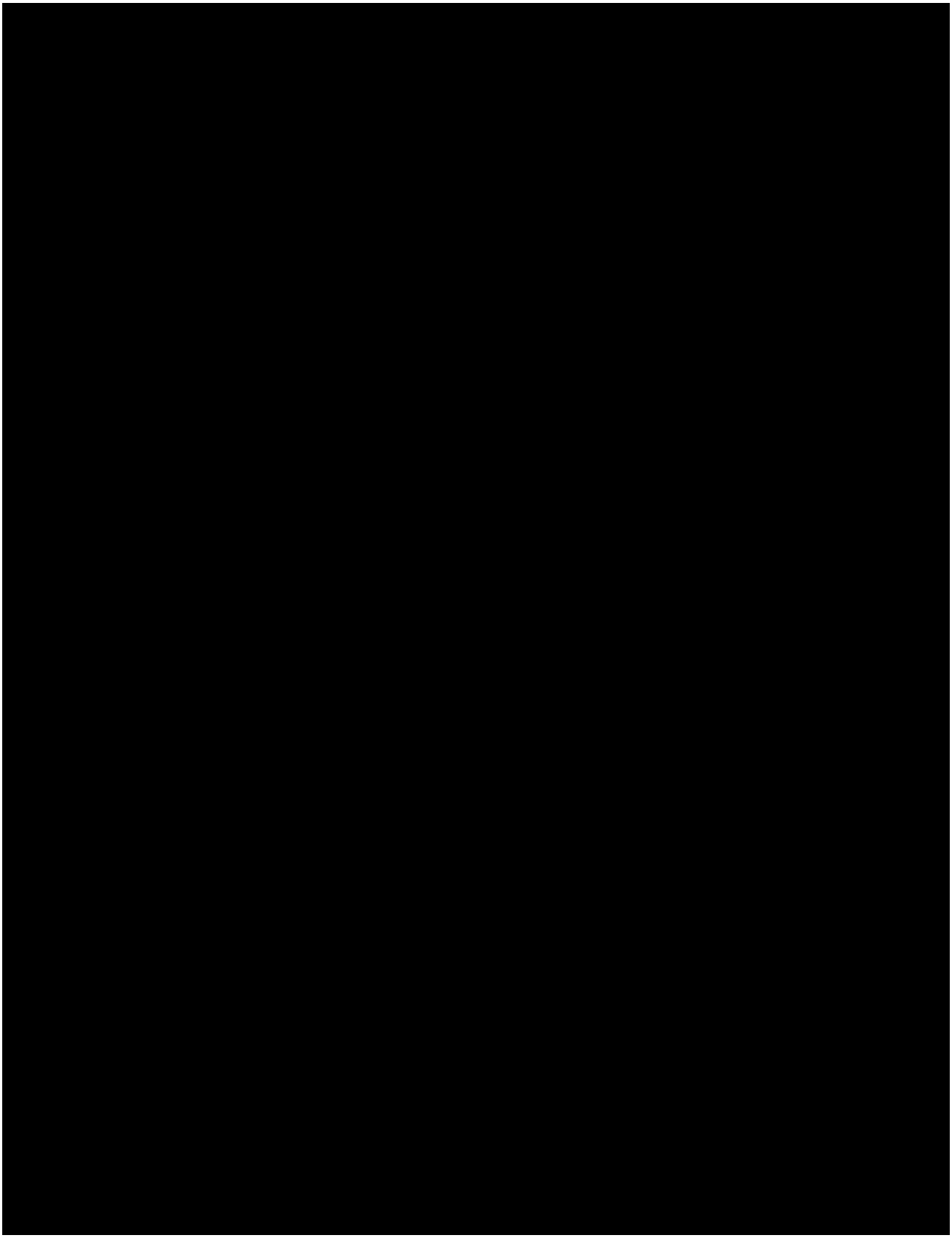
$$\frac{Weight\ [kg]}{Height\ [m] * Height\ [m]}$$

  as a continuous variable
- Smoking status (Never, Current, Former)
- Household/second-hand smoking (No; Yes)

[1] In France only patients >= 12 years were eligible for recruitment (local protocol amendment).

[redacted]





5.4.2 Compliance

Compliance [%] is assessed by the investigator per visit. For the analysis the reported values will be aggregated to an overall compliance per patient. If compliance is missing for at least one visit the overall compliance will be missing.

Overall compliance [%] will be summarised as continuous variable and in categories [%]:

- <50
- 50 to <80
- 80 to 120
- >120

5.4.3 Exposure

Duration of exposure [weeks] will be calculated as

$$\frac{\textit{Date of last trial drug intake} - \textit{Date of first trial drug intake}\ [\textit{days}] + 1\ \textit{day}}{7}$$

The day of first trial drug intake will only be counted as a half day if the intake time was 2:30 p.m. or later. The day of last nintedanib intake will only be counted as a half day, assuming that only the morning dose was administered.

Treatment interruptions will not be subtracted. Duration of exposure will be summarised as continuous variable and in categories [weeks]:

- <=2 (14 days)
- >2 to 6 (42 days)
- >6 to 12 (84 days)
- >12 to 24 (168 days)
- >24 to 36 (252 days)
- >36 to 52 (364 days)
- >52 to 64 (448 days)
- >64 to 76 (532 days)
- >76 to 88 (616 days)
- >88 to 104 (728 days)
- >104 to 116 (812 days)
- >116 to 128 (896 days)
- >128 to 140 (980 days)
- >140 to 156 (1092 days)
- >156

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

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

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

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

Calculating the duration of exposure on dose assigned according to weight range and on dose reduced due to AE, time periods with treatment interruptions as well as on dose reduced due to other reasons will be excluded. Both durations will be summarised as continuous variable and in categories [weeks] as defined for duration of exposure [weeks] above.

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 and treatment interruptions will be presented, containing

- Number of patients with at least one dose reduction
- Number of dose reductions per patient in categories (0; 1; 2; >2)
- Total number of dose reductions
- Reasons for dose reduction
- Number of patients with at least one dose increase
- Total number of dose increases
- Reasons for dose increase
- Number of patients with at least one interruption
- Number of interruptions per patient in categories (0; 1; 2; >2)
- Total number of interruptions
- Reasons for interruption
- Number of patients with at least one dose reduction or interruption

Duration of interruptions [days] will be calculated as

$$\textit{Sum of all treatment interruption durations } [\textit{days}]$$

Total dose [g] will be calculated as

$$\textit{Sum of durations of exposure on x g } [\textit{days}] \textit{ *2 * x g,}$$

with x in 0.025, 0.05, 0.075, 0.1, 0.15 and summarised as continuous variable.

Dose intensity [%] will be calculated as the amount of drug actually administered divided by the amount of drug that would have been administered, i.e. dose xx mg bid (depending on the body weight) during the planned treatment period (or until study discontinuation), multiplied by 100%. Dose intensity will be summarised 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][1]
- Time to first treatment interruption [days]
- Time to premature treatment discontinuation [days]

[1] Will only be calculated for patients who started the trial on full dose according to their weight bin at baseline.

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

Date of event/censoring – Date of first trial drug intake [*days*] *+ 1 day*

For the above mentioned time-to-event analyses patients with no such event occurred during the trial 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 and the date of the event is known	Event	Earliest date of event
2	Patient had a documented event 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 and already terminated trial drug (last intake on End of treatment eCRF page available)	Censored	Date of last trial drug intake
4	Patient neither had a documented event nor terminated trial drug permanently (only applicable for potential interim analyses)	Censored	Date of interim data snapshot

These times will also be summarised in categories [weeks] as defined for duration of exposure [weeks] above.

5.4.4 Liver enzyme and bilirubin elevations

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

- (ALT and/or AST >=3 fold ULN) and bilirubin >=2 fold ULN [1]
- ALT >=5 fold ULN and/or AST >=5 fold ULN
- ALT >=3 fold ULN and/or AST >=3 fold ULN

[1] within a time window of 30 days i.e. the elevation of bilirubin should appear within 30 days after the elevation of AST and/or ALT

The proportion of 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 10.5: 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
- >=1.5 fold ULN; >=2 fold ULN for alkaline phosphatase (ALK)
- >=3 fold ULN 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] is derived based on first trial drug intake as

Date of event/censoring – Date of first trial drug intake [*days*] *+ 1 day.*

Patients with no such event documented 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 (Event/Censored)	Date of event/censoring
1	Patient had a documented event before permanent trial drug discontinuation (or within the 28 days after permanent trial drug discontinuation)	Event	Earliest date of event
2	Patient had no documented event before permanent trial drug discontinuation (or within the 28 days after permanent trial drug discontinuation).	Censored	Earliest date of • last trial drug intake + 28 days, • derived date of last contact when patient was known to be alive, • date of death.
3	Patient neither had a documented event nor terminated trial drug permanently (only applicable for potential interim analyses)	Censored	Date of interim data snapshot

These times will also be summarised in categories [weeks] as defined for duration of exposure [weeks] in Section 5.4.3.

5.4.5 Vital signs

Weight minimum relative change from baseline will be summarised 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 different periods of interest, as per CTP flow chart are as described in Table 6.1: 1.

Table 6.1: 1 Periods of interest for the analysis

Period	**Start date**	**End date (excluded)**
Screening period	Informed consent	First trial drug intake
Treatment period	First trial drug intake (or re-start of treatment, if interruption)	Last trial drug intake (or day before start of interruption, if interruption) + 1 day
Off-treatment period (optional[a])	Start of interruption	Re-start of treatment
Residual effect period (REP)	Last trial drug intake + 1 day	Last trial drug intake + 28 days + 1 day
Follow-up period (optional[a])[b]	Last trial drug intake + 29 days	Start of post-study period
Post-study period (optional[a])	Latest of • Last trial drug intake + 29 days • End of study participation (from End of Study eCRF page) + 1 day	

[a] This period is optional insofar as it does not necessarily exist for all patients.
[b] This period is only created if last trial drug intake took place more than 28 days before trial completion (last contact date as collected on the end of study eCRF page), or for patients having prematurely discontinued the treatment and still continuing the trial.

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

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 INTERCURRENT EVENTS

The expected intercurrent event of interest in this trial is treatment discontinuation. The strategy for handling intercurrent events in this trial is While-on-Treatment. For more details see CTP Section 7.2.2.

Any intercurrent events that are not listed will be decided by review based on the general principle outlined.

6.4 SUBJECT SETS ANALYSED

- Screened set (SCS):
  This patient set includes all patients having signed informed consent.
- Treated set (TS):
  This patient set includes all patients who were dispensed study medication and were documented to have taken at least one dose of investigational treatment.
- Pharmacokinetic set (PKS):
  This patient set includes all patients from the Treated Set (TS) with at least one evaluable PK plasma concentration.

All evaluations for PK endpoints will be based on the PKS. All other analyses will be based on the TS, except for disposition which is based on the SCS.

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 or incomplete AE dates will be imputed according to BI standards (see “Handling of missing and incomplete AE dates”) (7).

[redacted]

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 or she will be censored as described in Section 5.3.2.

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 first trial drug intake (in case this AE is treatment-emergent), and on or after derived date of last contact as defined in Section 5.

For the time to first respiratory-related hospitalisation, 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

The same imputation rule will be applied for the time to first dose reduction in case of partially missing start date.

[redacted]

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.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

For roll-over patients Visit 1 and Visit 2 should be conducted on the same day and should, if possible, occur the same day as the EoT Visit of the parent trial to avoid any treatment interruption. In this case, assessments conducted as part of EoT of the parent trial are not repeated for the extension trial and results are only reported in the parent trial database. Therefore, the last available result in parent trial will be considered as baseline value for the extension trial if still meeting the baseline criteria as defined in this section.

As a general rule, the last assessment/measurement observed prior to first trial drug intake will be used as baseline. If the time of the assessment/measurement was not captured, and it was on the same day on which trial medication started, it will be assumed that it was taken prior to the intake of trial medication. Similarly, if no time is reported for start of trial medication it will be assumed that all trial procedures on that day happened before trial drug intake.

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

analysed using the re-assigned visits in the statistical tables. However, in the patient data listings, all visits performed will be displayed (even if outside time-window), along with the re-assigned visit.

If after windowing of visits at baseline, two or more values fall within the same baseline interval, then the last value prior to first trial 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 (e.g. vital signs, laboratory data), 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 [redacted] vital signs (syst. and diast. blood pressure, pulse rate, weight) and laboratory tests [redacted])

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**
-35	1	36	2	Baseline	1
2	50	49	3	2 weeks	15
51	127	77	4	12 weeks	85
128	211	84	5	24 weeks	169
212	309	98	6	36 weeks	253
310	407	98	7	52 weeks	365
408	491	84	8	64 weeks	449
492	575	84	9	76 weeks	533
576	673	98	10	88 weeks	617
674	771	98	11	104 weeks	729
772	855	84	12	116 weeks	813
856	939	84	13	128 weeks	897
940	1037	98	14	140 weeks	981
1038	1135	98	15	156 weeks	1093

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

[2] For analyses of LDH as biomarker, values are only considered up to + 7 days after last trial drug intake.

Table 6.7: 2 Time windowing rules for height and body mass index

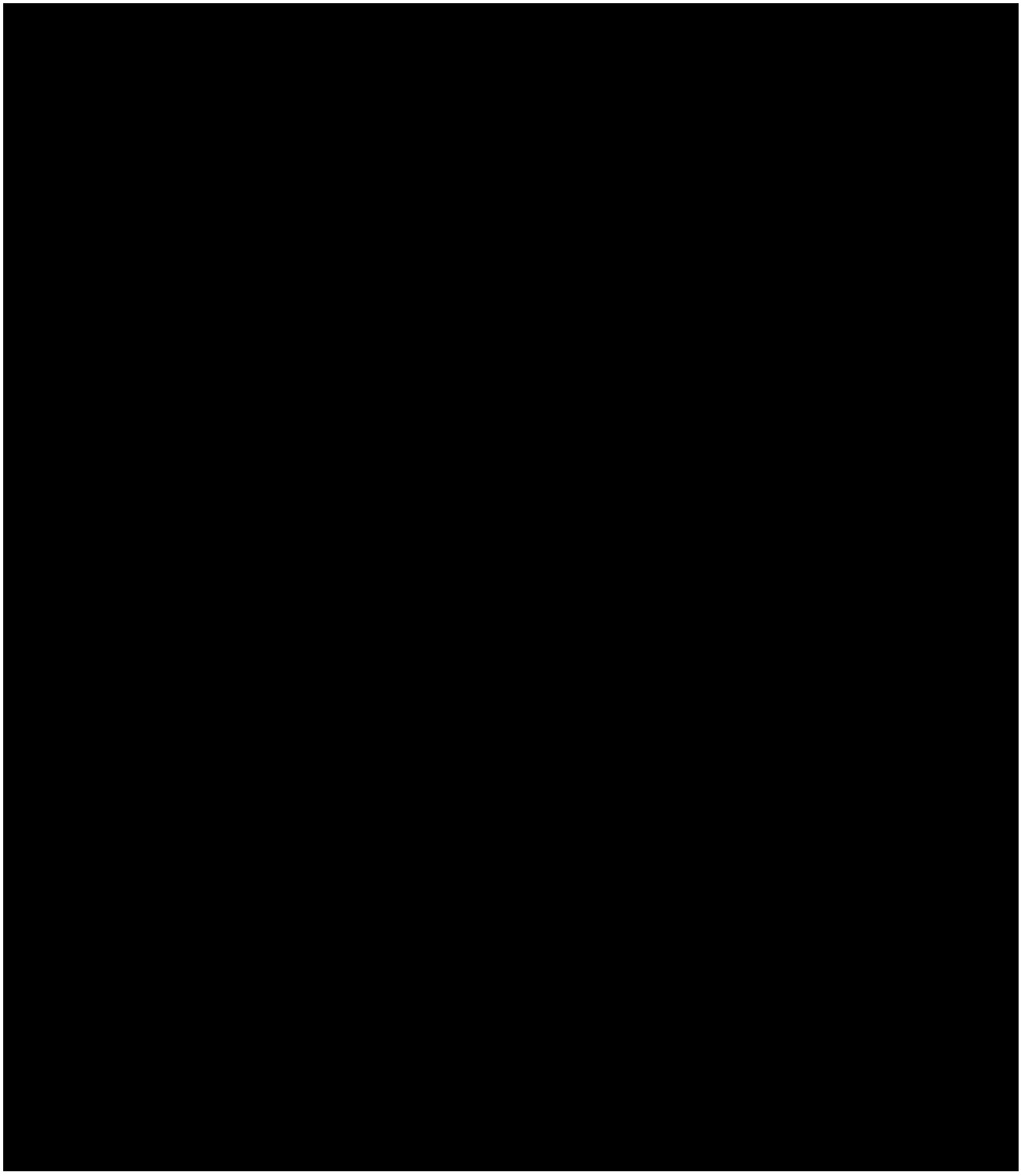
Time window of actual day[1]			**Allocated to**		
Start day	**End day (included)**	**Length of the time-window [days]**	**Visit number**	**Visit name**	**Planned day of the visit**
-35	1	36	2	Baseline	1
2	127	126	4	12 weeks	85
128	211	84	5	24 weeks	169
212	309	98	6	36 weeks	253
310	407	98	7	52 weeks	365
408	491	84	8	64 weeks	449
492	575	84	9	76 weeks	533
576	673	98	10	88 weeks	617
674	771	98	11	104 weeks	729
772	855	84	12	116 weeks	813
856	939	84	13	128 weeks	897
940	1037	98	14	140 weeks	981
1038	1135	98	15	156 weeks	1093

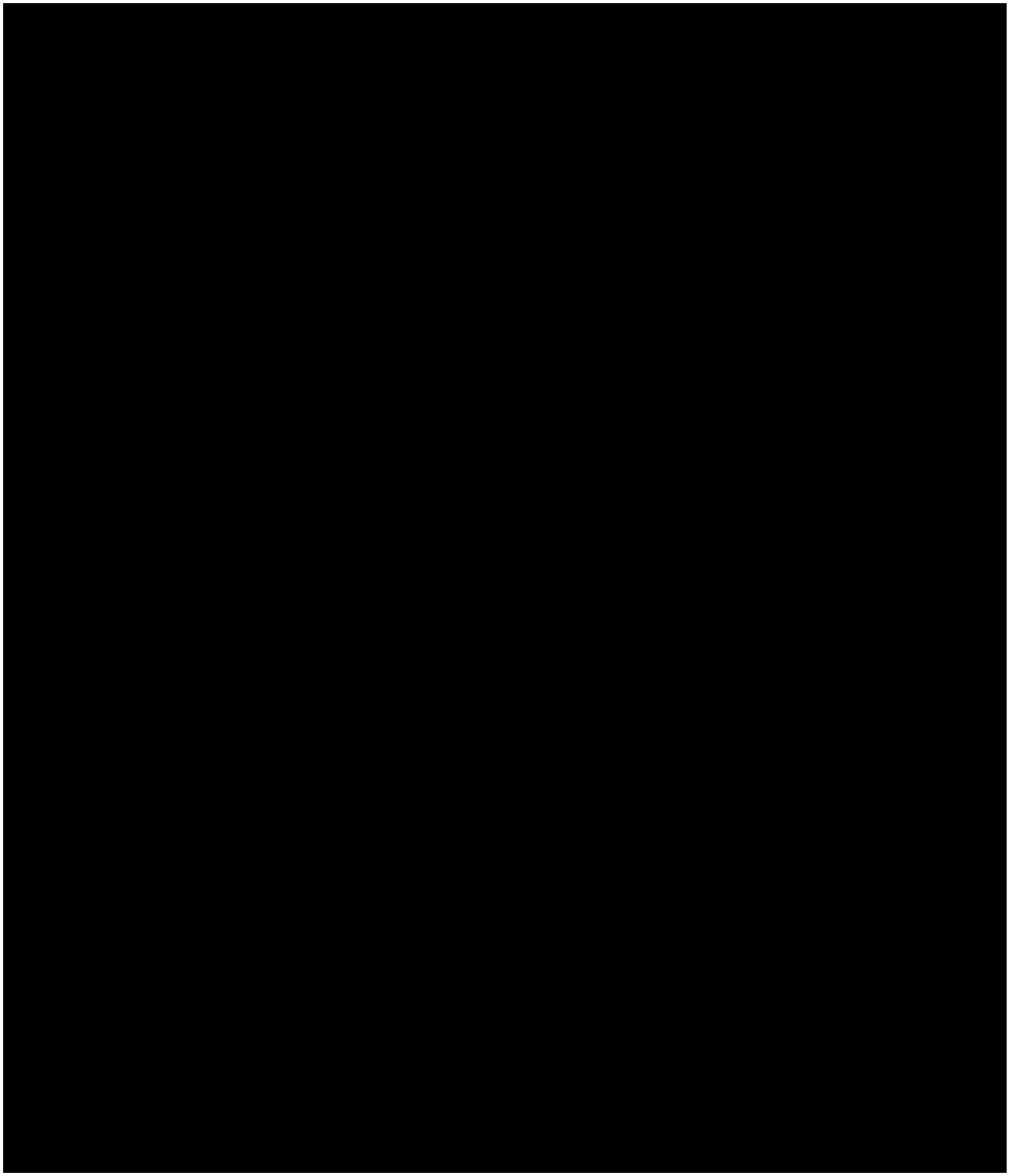
[1] First trial drug intake date is taken into account as reference to calculate time windows.

Table 6.7: 3 Time windowing rules for 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**
-35	1	36	2	Baseline	1
2	127	126	4	12 weeks	85
128	211	84	5	24 weeks	169
212	309	98	6	36 weeks	253
310	449	140	7	52 weeks	365
450	631	182	9	76 weeks	533
632	813	182	11	104 weeks	729
814	995	182	13	128 weeks	897
996	1177	182	15	156 weeks	1093

[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. All available data (i.e. data for all available timepoints, as defined in Section 6.7) will be presented in the summary tables, irrespective if the timepoint is specified in the endpoint definition in the CTP. For endpoints with time intervals, only data for the intervals specified in the endpoint definition will be presented.

The labelling and display format of statistical parameters will follow BI standards (9). For End-Of-Text tables, the set of summary statistics is: N / Mean / SD / Min / Median / Max.

In descriptive statistics tables, mean, SD and median will be rounded to one additional digit than the raw individual value. For tables that are provided for endpoints with some extreme data, median, quartiles and percentiles should be preferred to mean, standard deviation, minimum and maximum.

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 group (unless otherwise specified, all patients in the respective patient 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 patient group (initiated nintedanib or continued nintedanib) and overall (total):

- Group 1: Initiated nintedanib
  - New patients
  - Patients who prematurely discontinued treatment permanently in 1199-0337
  - Completed patients from 1199-0337 not able to roll over into the extension trial within 12 weeks following their End of Treatment visit in the parent trial (i.e. time period between last dose of trial drug in parent trial and first dose in extension trial is greater than 12 weeks)
  - Patients from 1199-0337 placebo arm Part A (i.e. from double-blind placebo arm who did not enter the open-label nintedanib period and only received placebo in the parent trial)

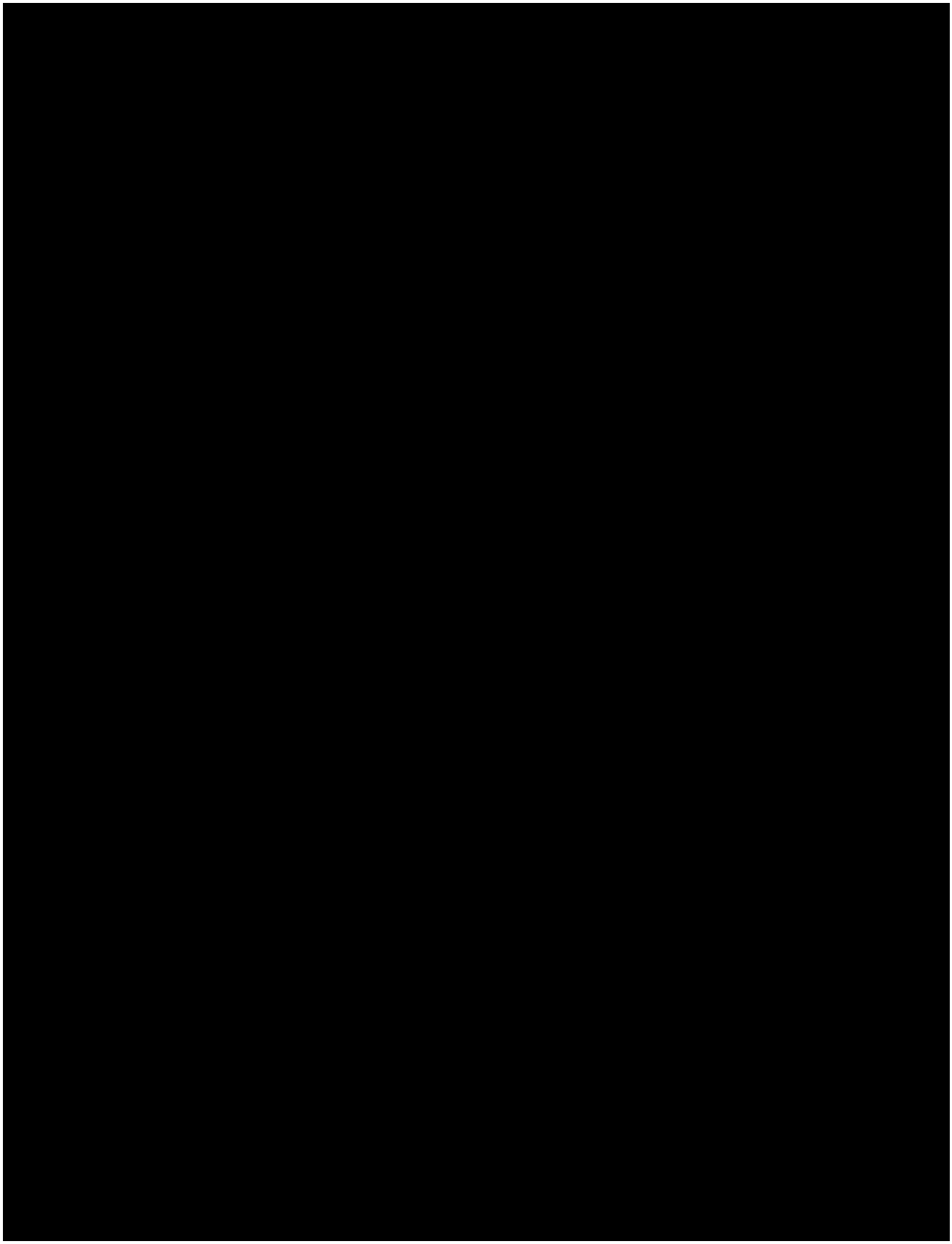
- Group 2: Continued nintedanib
  - Patients from 1199-0337 Part B (i.e. from open-label nintedanib period of the parent trial, time period between last dose of trial drug in parent trial and first dose in extension trial is less than or equal to 12 weeks)
  - Patients from 1199-0337 nintedanib arm Part A (i.e. from double-blind nintedanib arm of the parent trial, time period between last dose of trial drug in parent trial and first dose in extension trial is less than or equal to 12 weeks)

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, entered and treated. The number of patients prematurely discontinuing trial medication will be shown with the treatment discontinuation decisions as well as primary reasons for discontinuation. The number and percent of patients completing the planned treatment period and the number of patients with treatment ongoing (only applicable for potential interim analyses) will also be presented. Where percentages are shown, the denominator will be the number of patients treated in each patient 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 patient group.



[redacted]

7.4 PRIMARY OBJECTIVE ANALYSIS

The main objective is to assess the long-term safety and tolerability of nintedanib, on top of standard of care, in children and adolescents with clinically significant fibrosing Interstitial Lung Disease.

The primary endpoint is the incidence of treatment emergent adverse events over the whole trial. Only descriptive analyses will be performed. There will be no treatment comparison.

7.4.1 Main analysis

The number and frequency of patients with treatment-emergent adverse events by primary system organ class (SOC) and preferred term (PT), as described in Section 7.8.1, will be displayed. The primary analysis will implement the While-on-Treatment strategy of handing intercurrent event (ICE) defined in Section 6.3 and will be based on the treated set (TS).

[redacted]

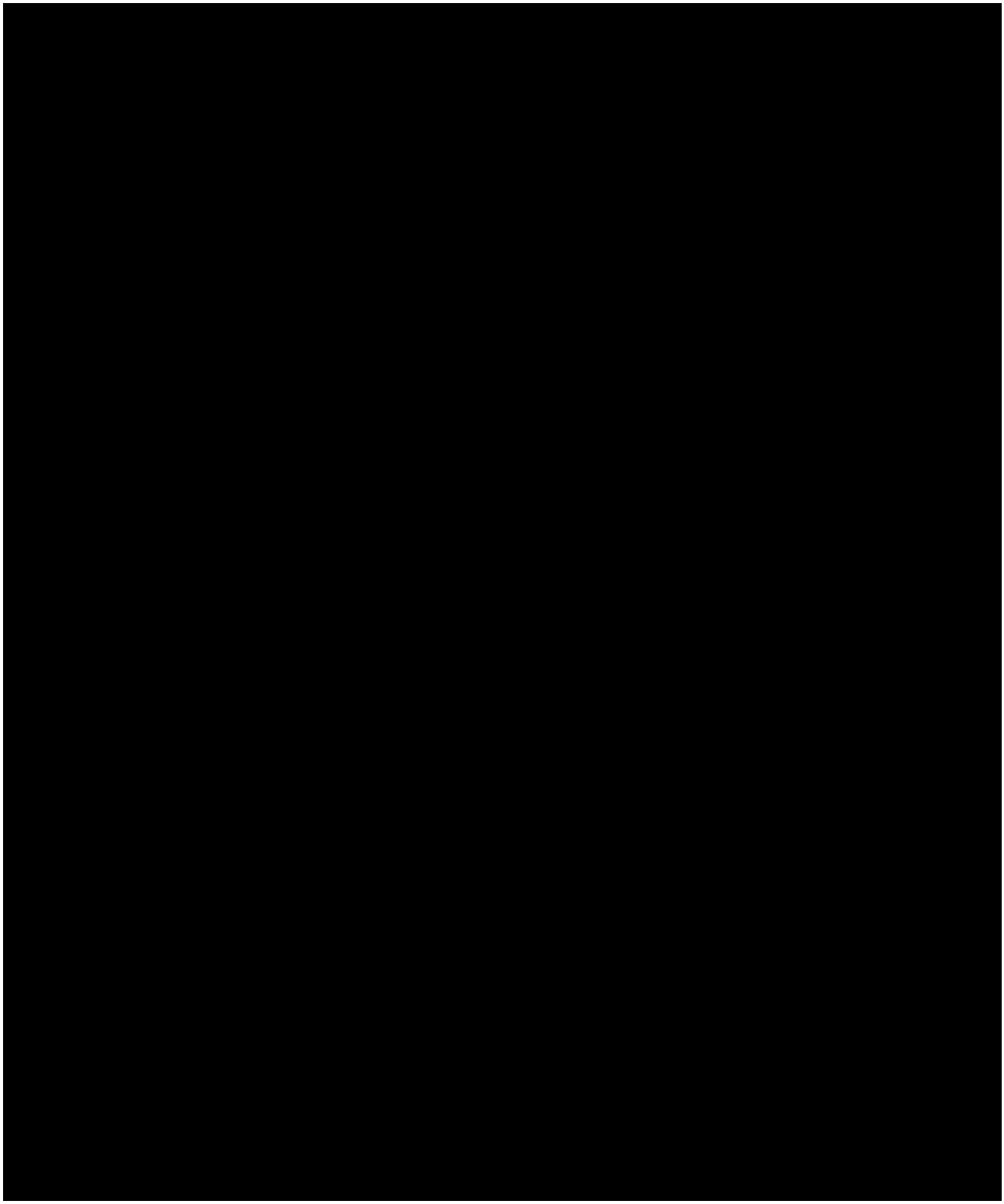
7.5 SECONDARY OBJECTIVE ANALYSIS

7.5.1 Key secondary objective analysis

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

7.5.2 Secondary objective analysis

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



7.6.3 Time-to-event endpoints

Separate Kaplan-Meier plots will be presented by patient group and overall (total group) for time–to-event in extension trial for endpoints defined in Section 5.3.2. Kaplan Meier estimates and confidence intervals (using Greenwood variance formula) for the cumulated time-to-event rate will be calculated over the whole trial. No statistical test will be performed.

7.7 EXTENT OF EXPOSURE

Extent of exposure data will be summarised and presented over the whole trial (refer to Section 5.4.3).

A summary table showing the duration on treatment in extension trial in weeks (both mean and frequency in categories, see Section 5.4.3) and dose intensity will be presented.

A summary of treatment interruptions will be performed including number of patients with at least one interruption, number and reason of interruptions, as well as time to first interruption (both mean and frequency in categories, see Section 5.4.3). A similar summary will be performed for dose changes.

Median, Q1 and Q3 percentiles are calculated from the Kaplan-Meier curve for time to premature treatment discontinuation, time to first dose reduction and for time to first treatment interruption. No statistical tests will be performed.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set.

The analysis of safety data will be based on the concept of treatment emergent AEs or measurements. That means that, for analyses over the whole trial, all AEs/laboratory or vital sign measurements occurring between first nintedanib intake till last nintedanib intake + 28 days will be assigned to the on-treatment period.

All analyses will be performed by patient group and overall.

7.8.1 Adverse Events

Adverse events will be coded using the current Medical Dictionary for Regulatory Activities (MedDRA) version in use at BI at the time of database lock. 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.

All AEs occurring before first drug intake in extension trial will be assigned to ‘Screening period’ and all AEs occurring after the residual effect period will be assigned to ‘Follow-up period’(for patient data listings only).

For further details on summarisation of AE data, please refer to (7, 10).

According to ICH E3 (11), 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 or interrupted). An overall summary of adverse events will be presented.

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) (see CTP Section 5.2.7.1.4), and are ticked as such in the eCRF.

The frequency of patients with AEs will be summarised by patient group and overall, primary system organ class and PT (mention MedDRA levels to be displayed in the tables). Time at risk and exposure-adjusted incidence rates per 100 patient years of AEs by patient group and overall will be presented in addition. Please refer to Section 7.8.1.2 for further details on the derivation of time at risk and exposure-adjusted incidence rates.

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

Separate tables will be provided for patients with

- serious AEs (SAEs)
- severe AEs
- other significant AEs
- 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 eCRF AE page)
- Investigator defined drug-related SAEs

Adverse event groupings by safety topic have been defined outside the trial protocol, which will be continuously updated at project level (12). 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 summarised 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).

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 categorised 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 summarised by treatment, adjudicated cause of death (Cardiovascular, Respiratory or Other), and PT.

The frequency of patients with AEs categorised as MACE (that is all AEs categorised as MACE and therefore sent for adjudication) will be summarised by patient group and outcome

of adjudication (adjudicated as MACE or adjudicated as not MACE). The frequency of patients with AEs adjudicated as MACE will also be summarised by patient group and PT.

7.8.1.2 Exposure adjusted analysis of adverse events

Time at risk and incidence rates per 100 patient-years will be calculated based on the first onset of an AE in the trial.

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

$$\frac{\textit{Sum of time at risk across all contributing patients } [\textit{days}]}{365.25}$$

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

- *Date of first onset of the AE – date of first study drug intake* [*days*] *+1 day*
  for patients with the specific AE,
- *End of time at risk – date of first study drug intake* [*days*] *+ 1 day*
  for patients without the specific AE.

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

- date last trial drug intake + 28 days
- derived date of last contact (for definition see Section 5)
- date of death
- date of (interim) database lock.

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

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

7.8.1.3 Adverse events with additional information collection

Diarrhoea, bleeding and ILD are AEs with additional AE-specific information collected on the eCRF. These are investigator reported on the eCRF and will be identified using this information for this analysis. That is if the diarrhoea information has been completed for an adverse event then the adverse event will be considered as diarrhoea for this analysis regardless of subsequent MedDRA coding of the verbatim term. Likewise, if the bleeding information has been completed for an adverse event then the adverse event will be considered as bleeding for this analysis regardless of subsequent MedDRA coding of the verbatim term. The same applies to ILD.

The frequency of patients with AEs with additional information collection will be summarised by patient group and overall, primary SOC and PT and separately for diarrhoea, bleeding and ILD. The additional information collected will also be summarised at the AE level (occurrence level) rather than at the patient level separately for diarrhoea, bleeding and ILD.

For the time to first onset of diarrhoea, bleeding or ILD, respectively, Kaplan-Meier plots by treatment will be created taking into account the respective data over the whole trial. The same censoring rules as for time to first liver enzyme elevation 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 patient data 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 (13). The variables to be recorded are listed in Section 5.2.3 of the CTP.

Analyses of laboratory variables will be displayed by patient group and overall, over the whole trial. Please refer to Table 6.7: 1 for time windowing definition.

For data received from the 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 patients, and the reference range for INR depends on whether a patient 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 patients not taking anticoagulants and which is more conservative than the range for patients taking anticoagulants (LLN=2, ULN=3).

The estimated Glomerular Filtration Rate (eGFR) is calculated based on serum creatinine according to Schwartz formula in children and adolescent (2-17 years old) and according to CKD/EPI formula in adults (see CTP Sections 5.2.3 and 10.3). As the parameter (eGFR) evaluated is the same and just the formula are chosen appropriately as recommended per age, for the analyses these two methods of calculation are considered to result in the same parameter.

7.8.2.2 Liver enzyme and bilirubin elevations

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

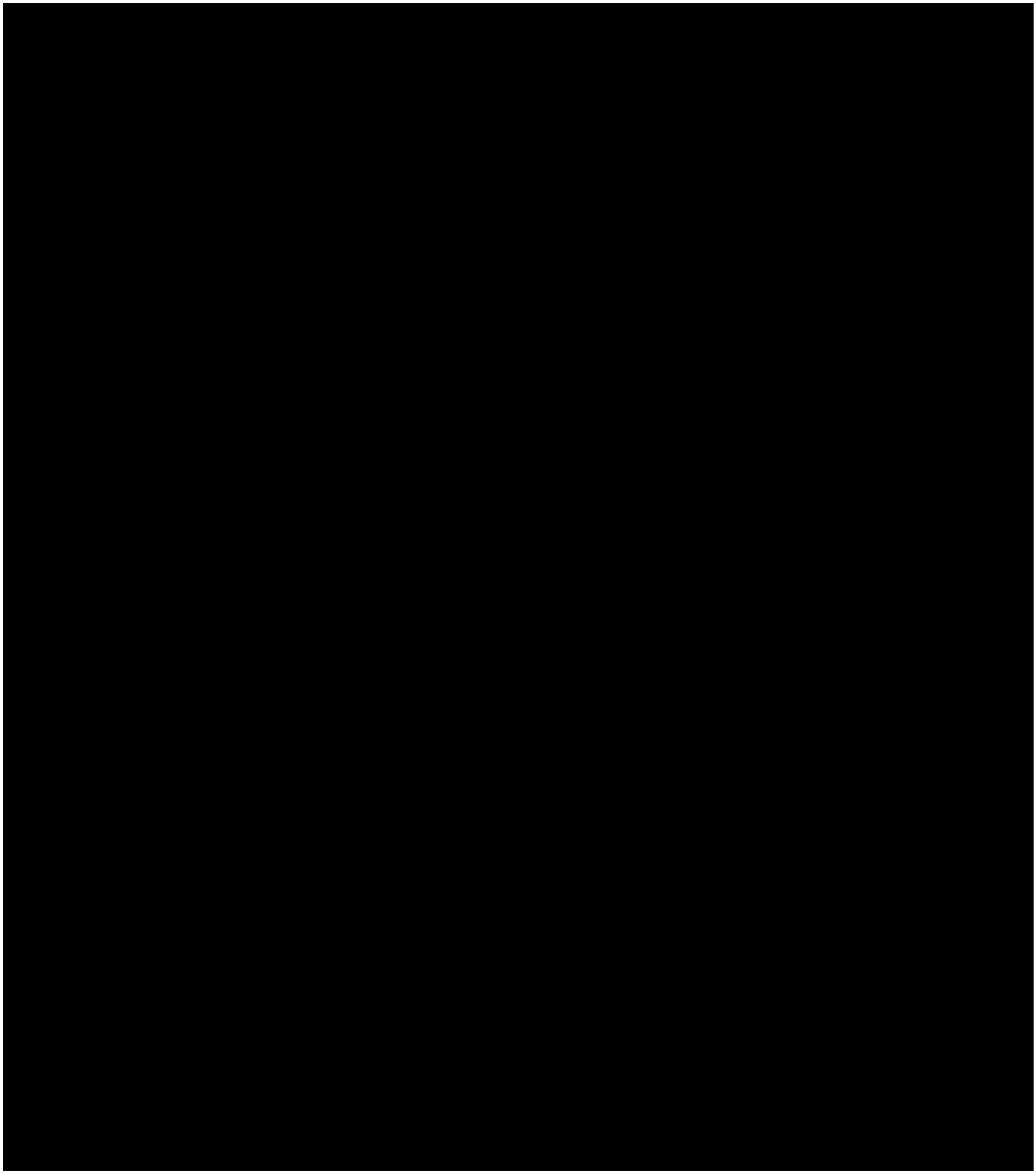
- Summary table of liver enzyme elevation
- Summary of signs of hepatic injury (see Section 5.4.4)
- Summary table of individual maximum liver enzyme and bilirubin elevations
- Time to first onset and number of patients with liver enzyme elevation. The time to onset of first liver enzyme and bilirubin elevation [days] will be summarised 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 patient group and overall.
- Single time course profiles of liver enzymes and other laboratory parameters (ALT, AST, alkaline phosphatase, total bilirubin, 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. Due to inconsistent method of measurement impacting comparability of data, sitting height and leg length will not be summarised across patients but only presented in patient data listings.

7.8.4 ECG

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



8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

The treatment information will be loaded into the trial database at trial initiation.

9. 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.	*VV-TMF-96326:* Note to file on sitting height measurement for 1199-0378 from 2022-08-02, TMF
3.	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]
4.	*Website:* https://www.who.int/tools/growth-reference-data-for-5to19-years/indicators (WHO 2007) (last access date: 02 June 2023).
5.	Cole TJ, Green PJ. Smoothing reference centile curves: The LMS method and penalized likelihood. Statistics in Medicine. 1192. 1992;11:1305-1319 [R21-0301]
6.	Philip H. Quanjer, Multi-ethnic reference values for spirometry for the 3–95 year age range: The global lung function 2012 equations. [R15-0845]
7.	*KMED-BDS-HTG-0035:* “Handling of Missing and Incomplete AE Dates”, current version; KMED.
8.	*BI-VQD-12161_30-476*: “TMCP Data Analysis”, current version; KMED.
9.	*BI-KMED-BDS-HTG-0045*: “Reporting of clinical trials and project summaries”, current version; KMED.
10.	*BI-KMED-BDS-HTG-0066*: “Analysis and Presentation of Adverse Event Data from Clinical Trials”, current version; KMED.
11.	*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.
12.	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.
13.	*BI-KMED-BDS-HTG-0042*: “Handling, Display and Analysis of Laboratory Data”, current version; KMED.
14.	Varni JW, Scaling and scoring of the Pediatric Quality of Life Inventory PedsQL. Mapi Research Trust. http://www.pedsql.org/PedsQL-Scoring.pdf (Version 21.3: March 2023) [R21-1786]

10. ADDITIONAL SECTIONS

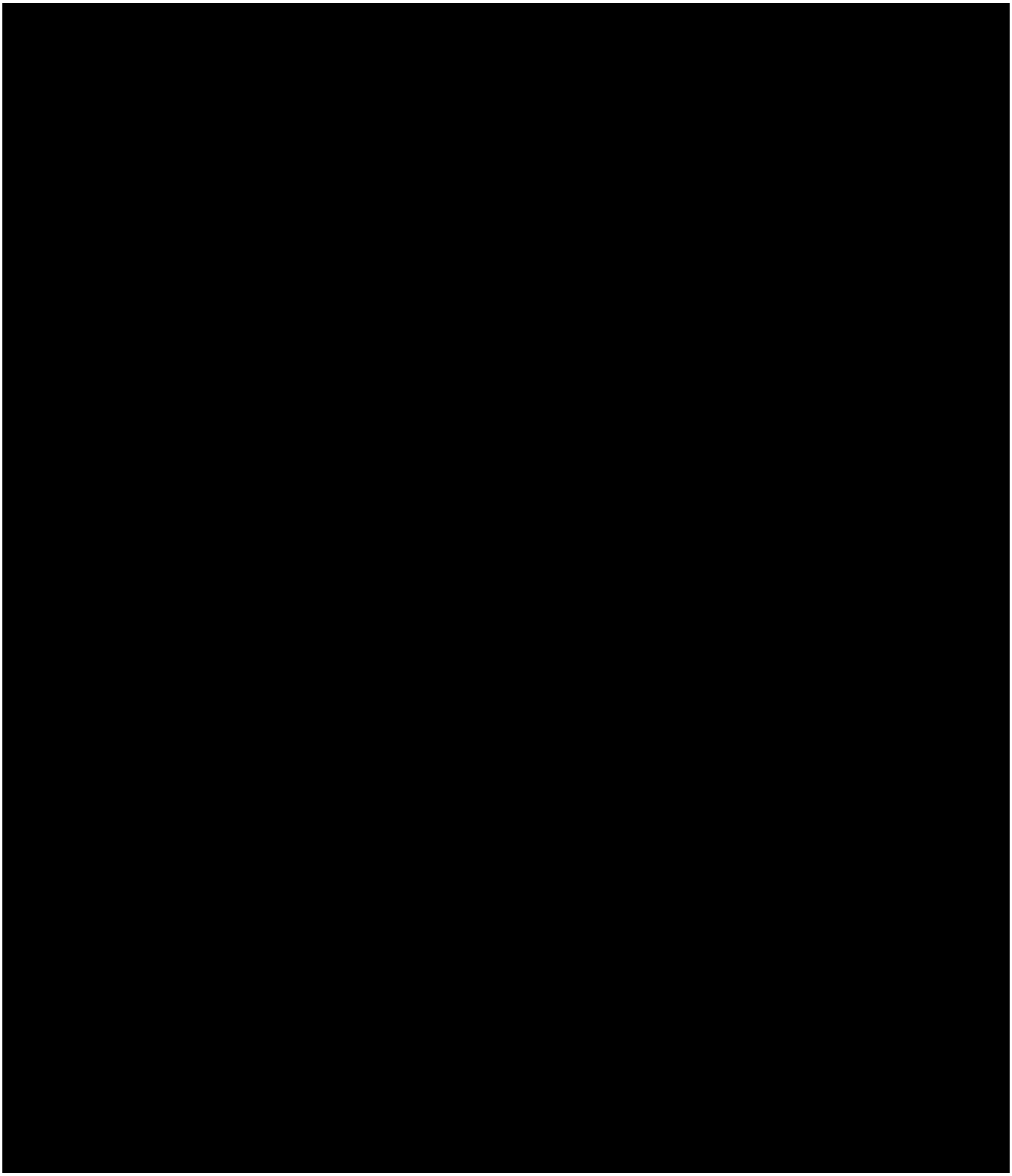
10.1 INTERIM ANALYSES

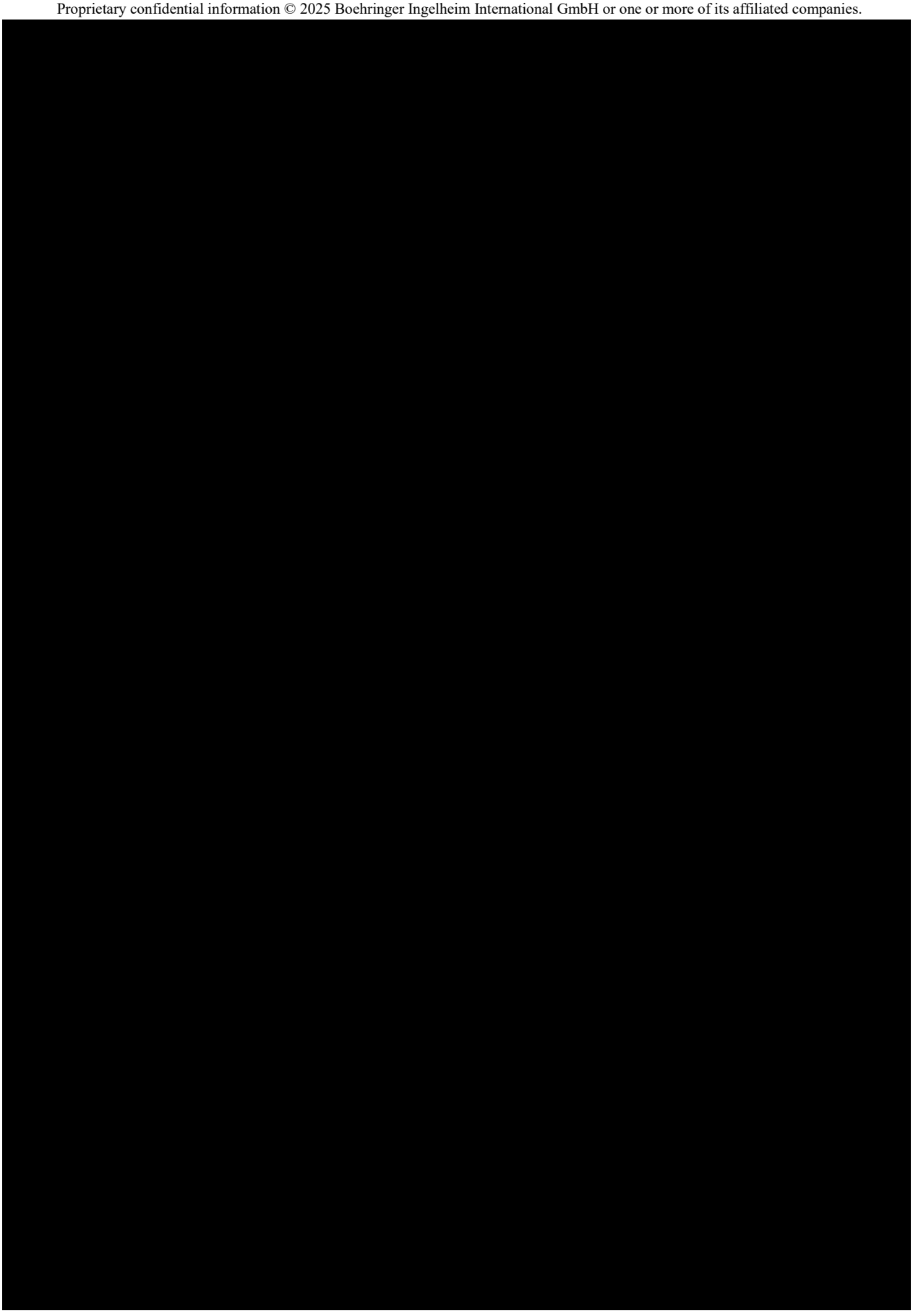
Interim analyses might be required for regional submissions and safety updates.

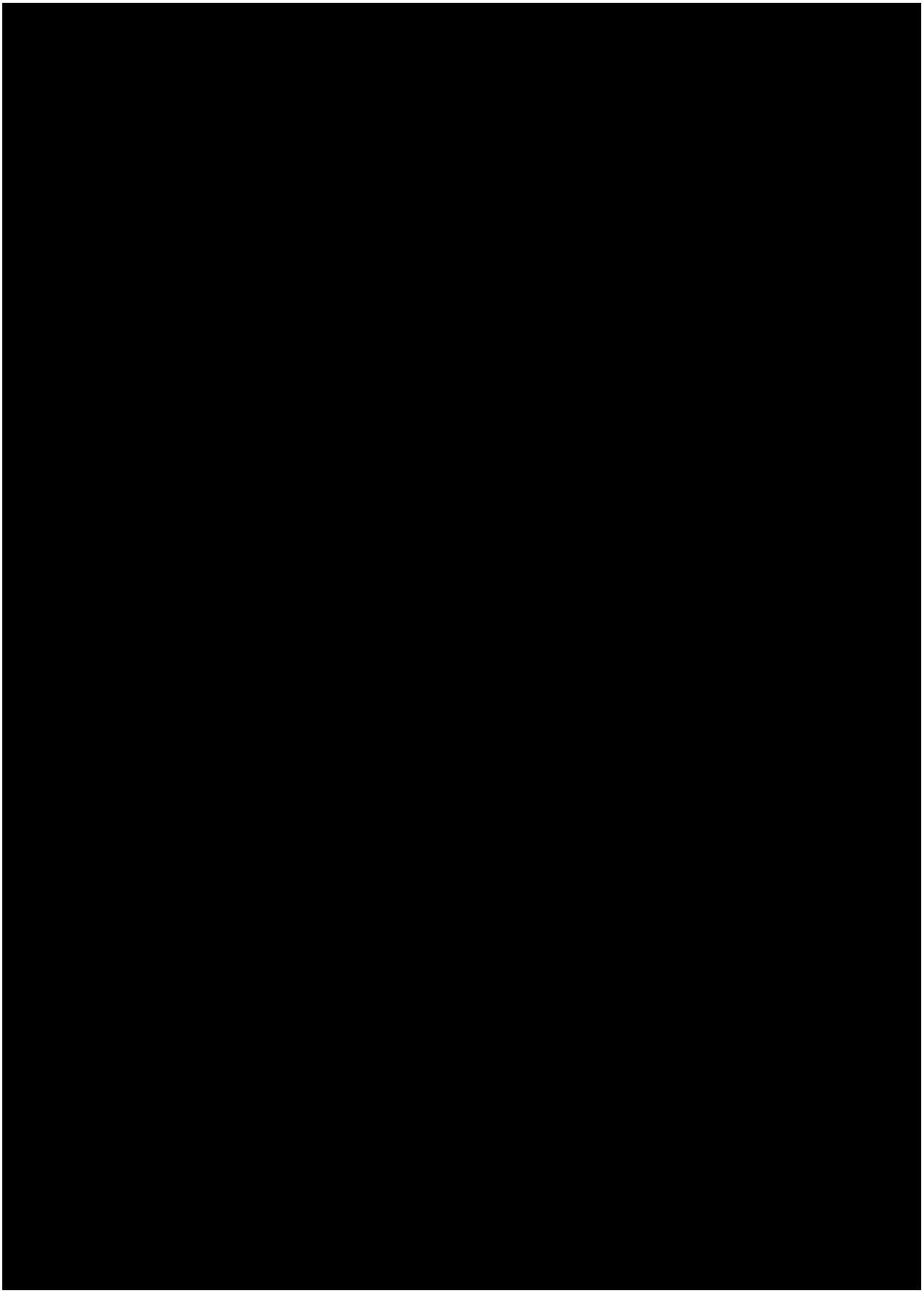
For any interim analysis all data collected up to the corresponding interim data snapshot will be analysed, using the same methodology as defined in TSAP Section 7 for the final analysis.

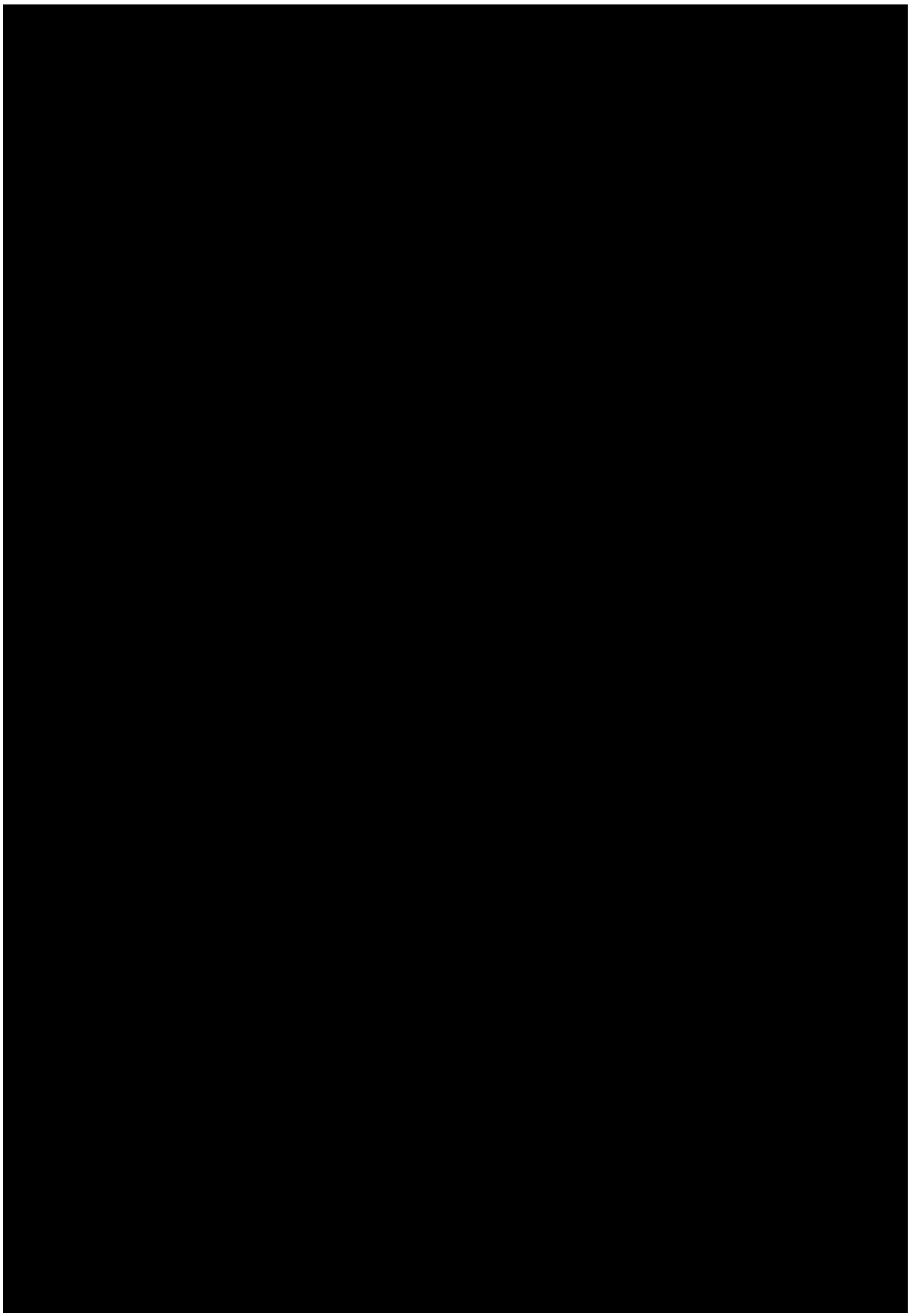
An interim analysis is planned after all patients who rolled over into from parent trial within 12 weeks following their End of Treatment visit in the parent completed their 52 weeks visit.

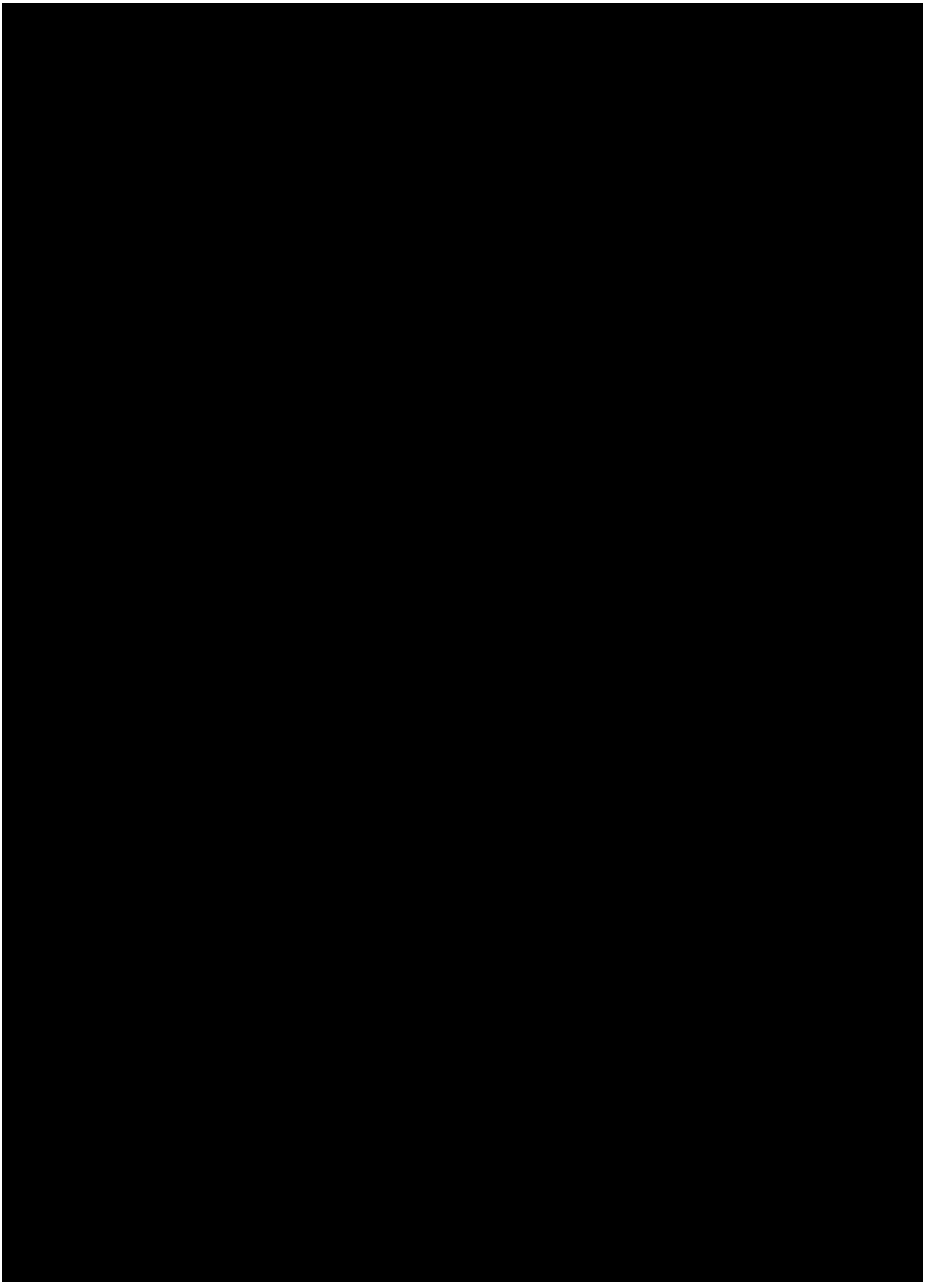
The interim analyses will be based on partly unclean and maybe even incomplete data.

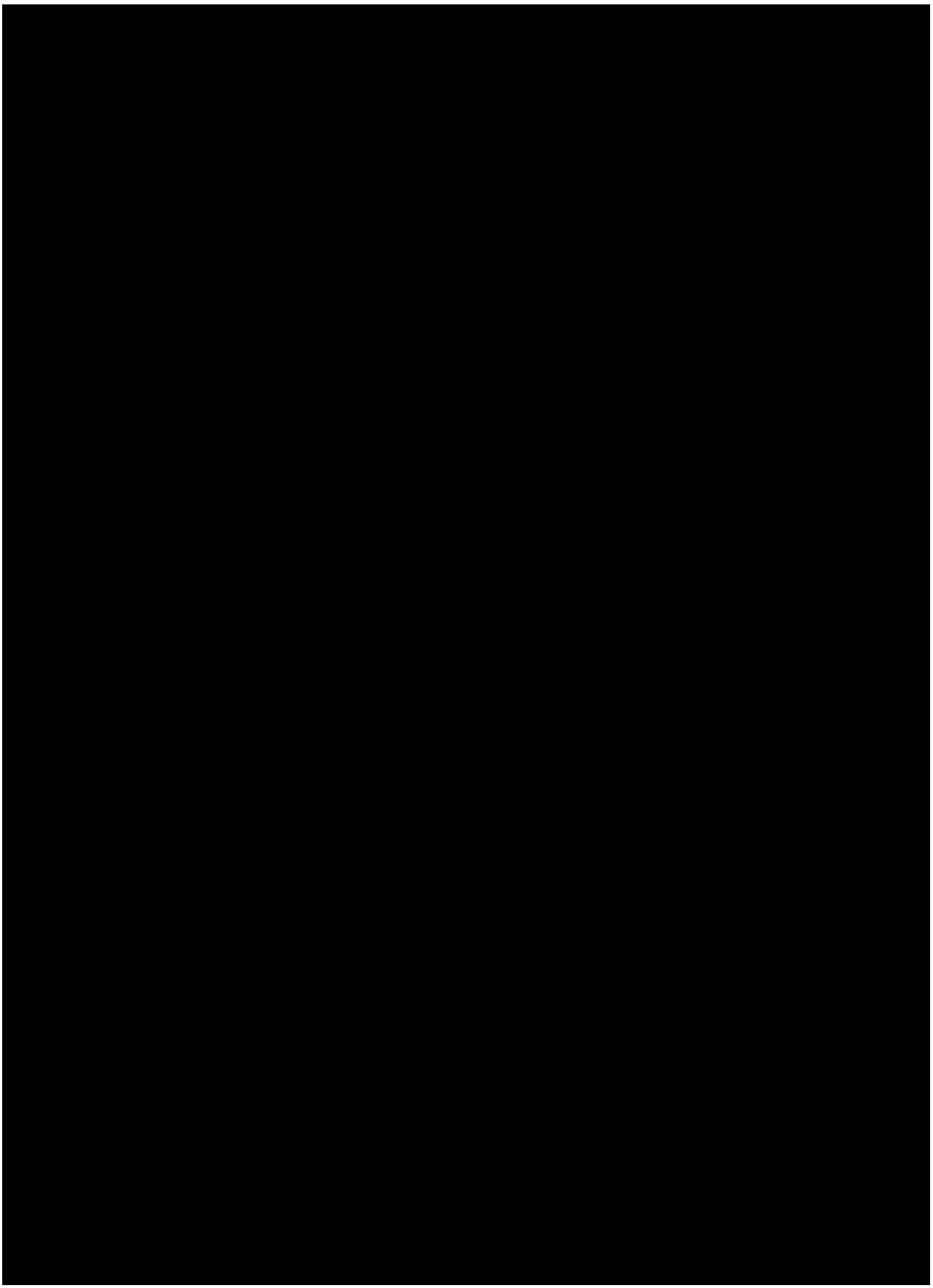


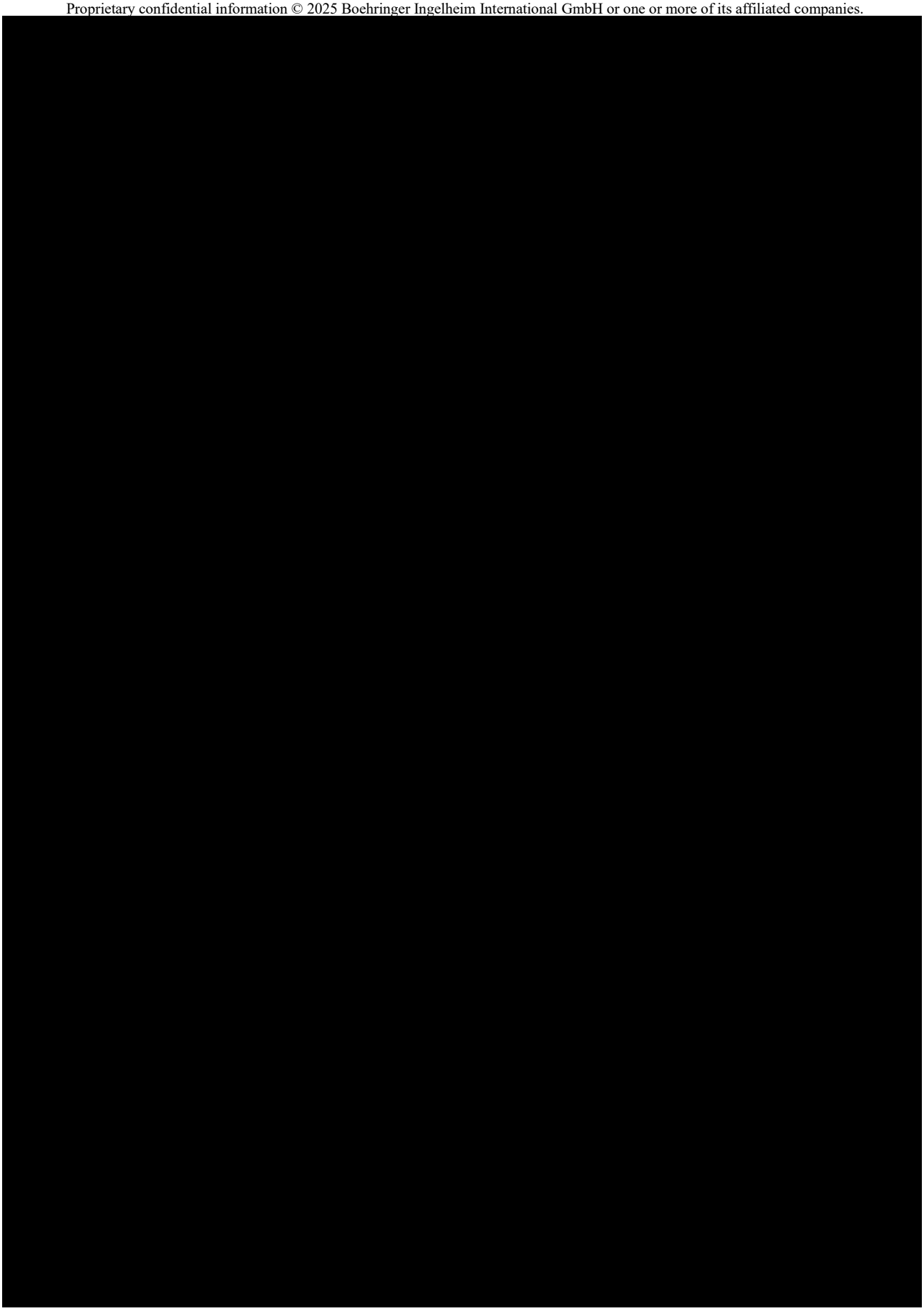


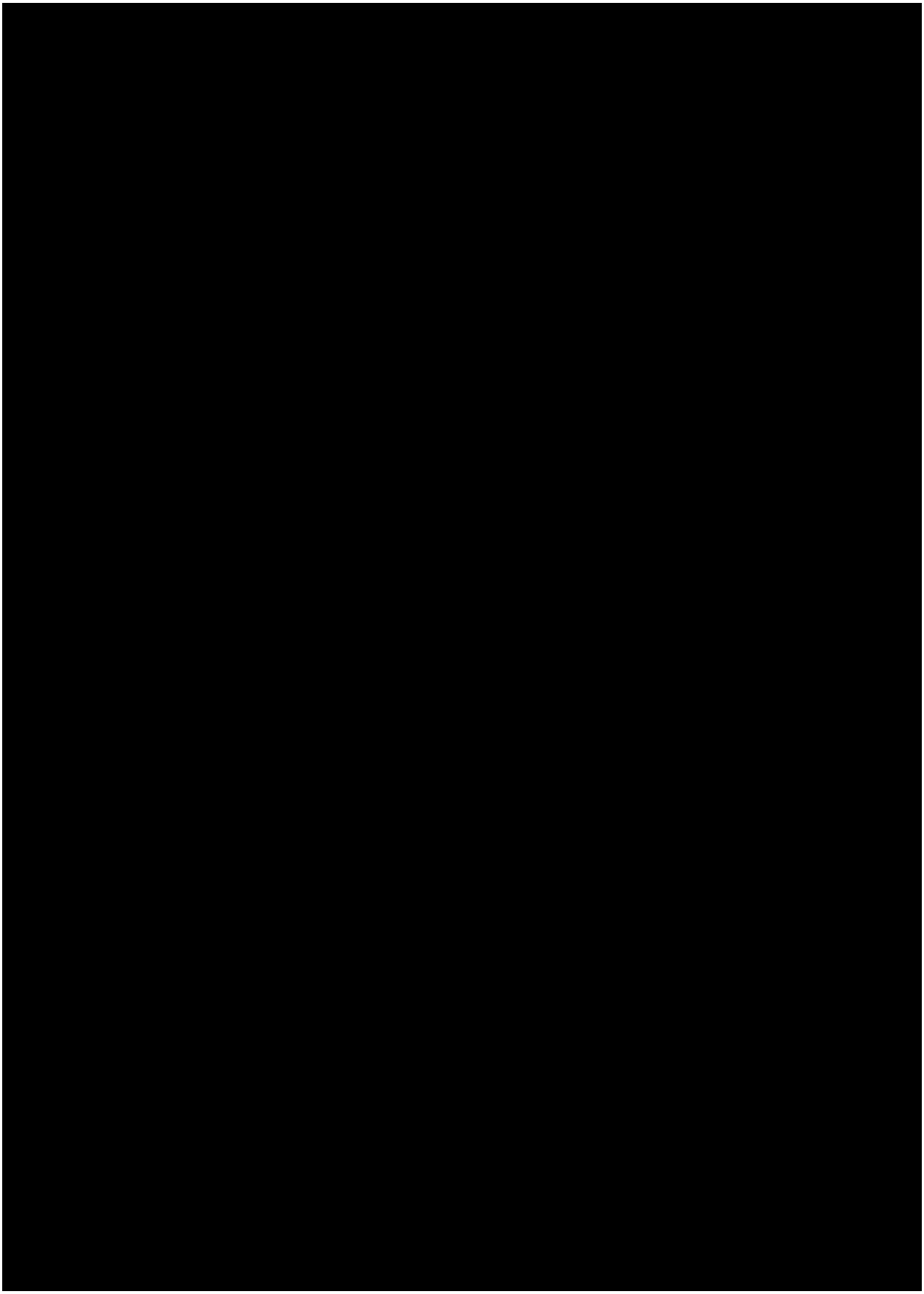


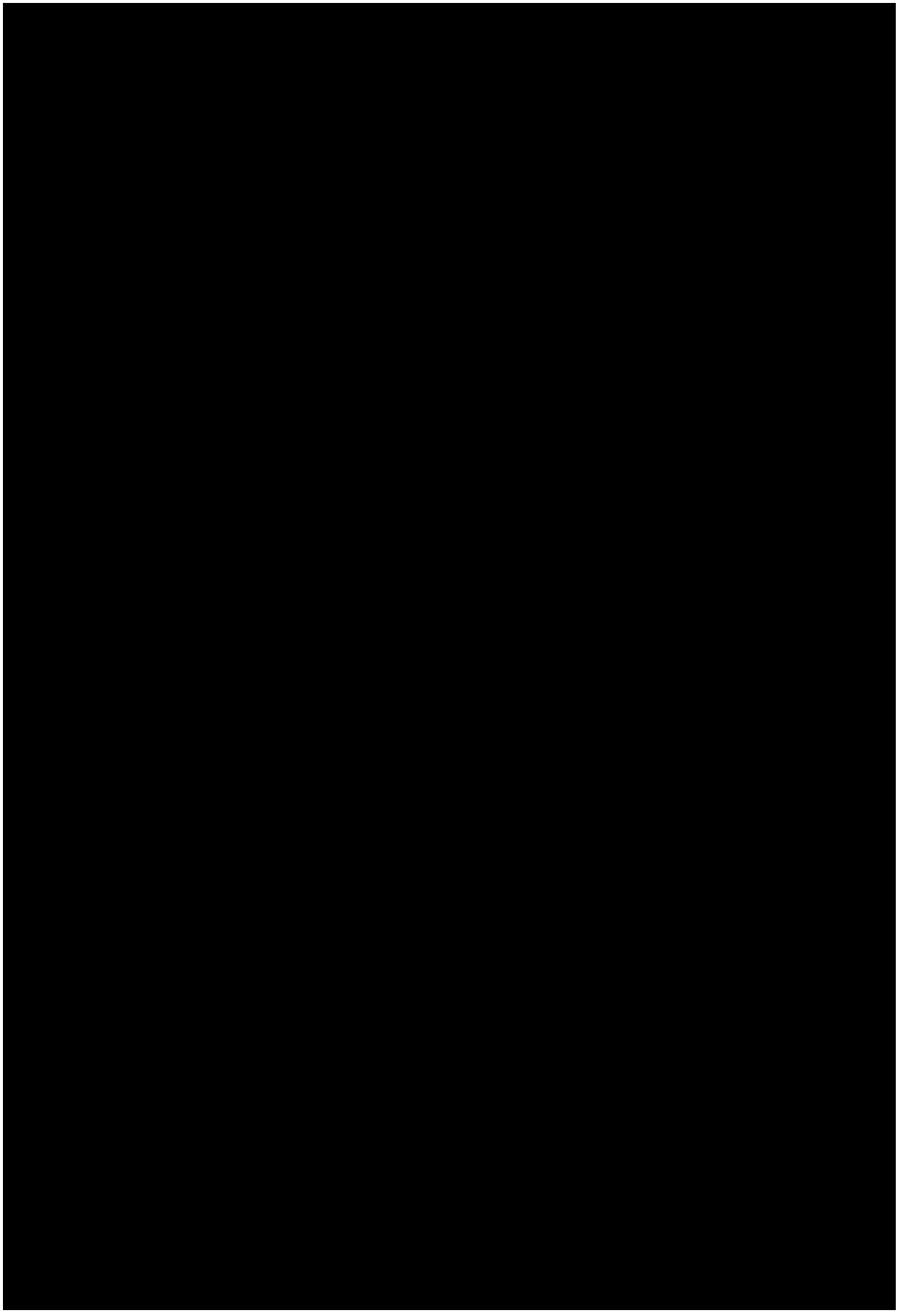


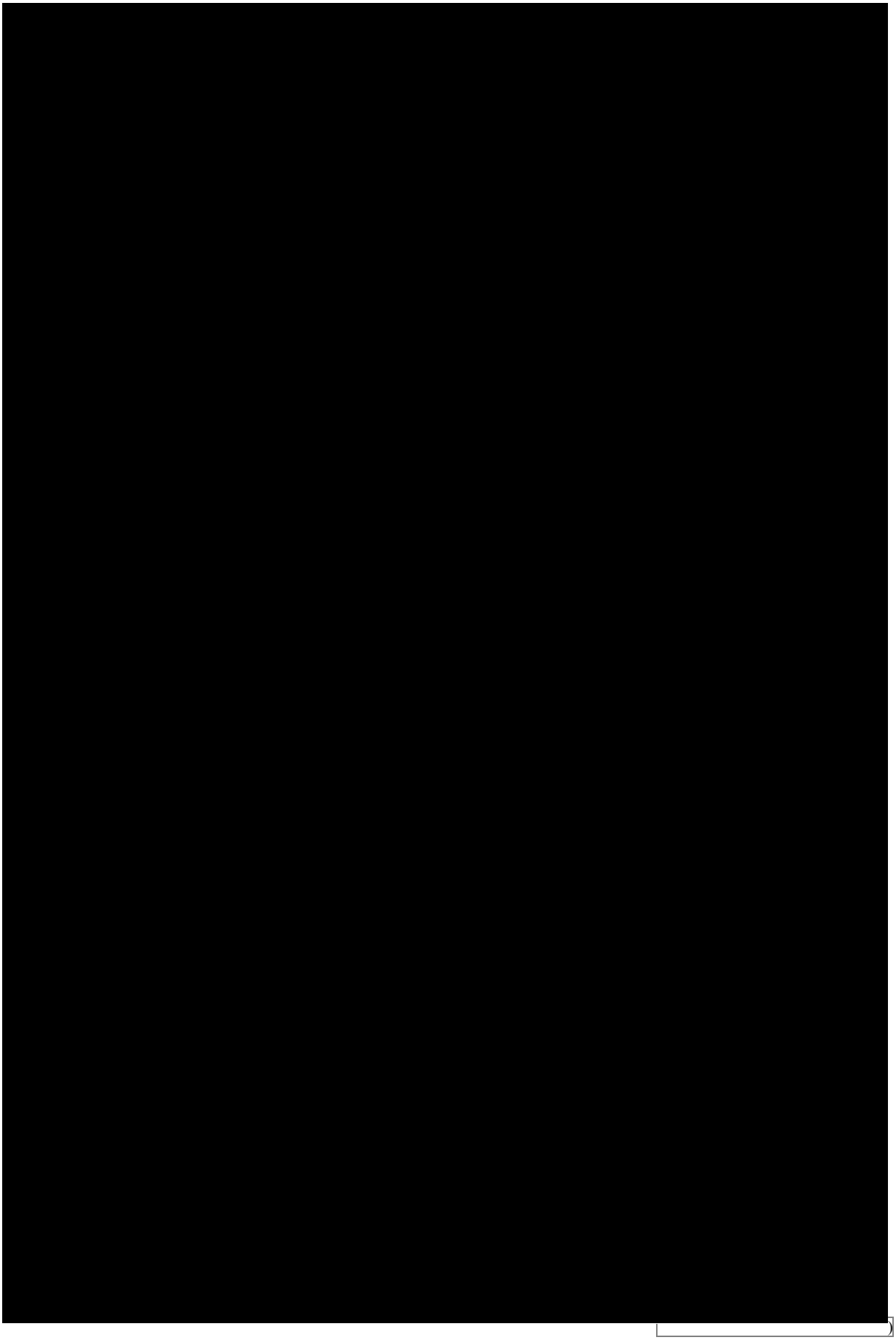


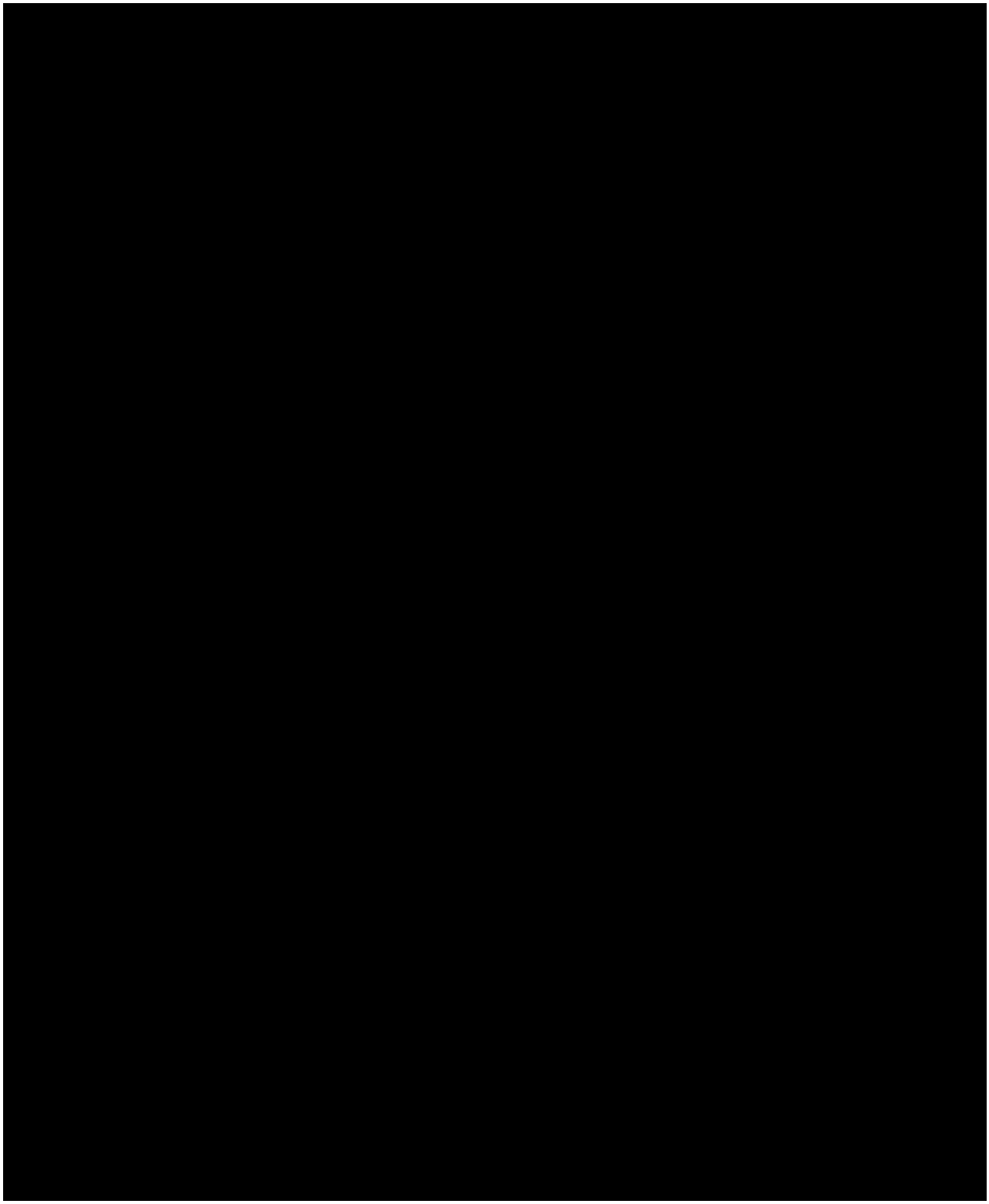


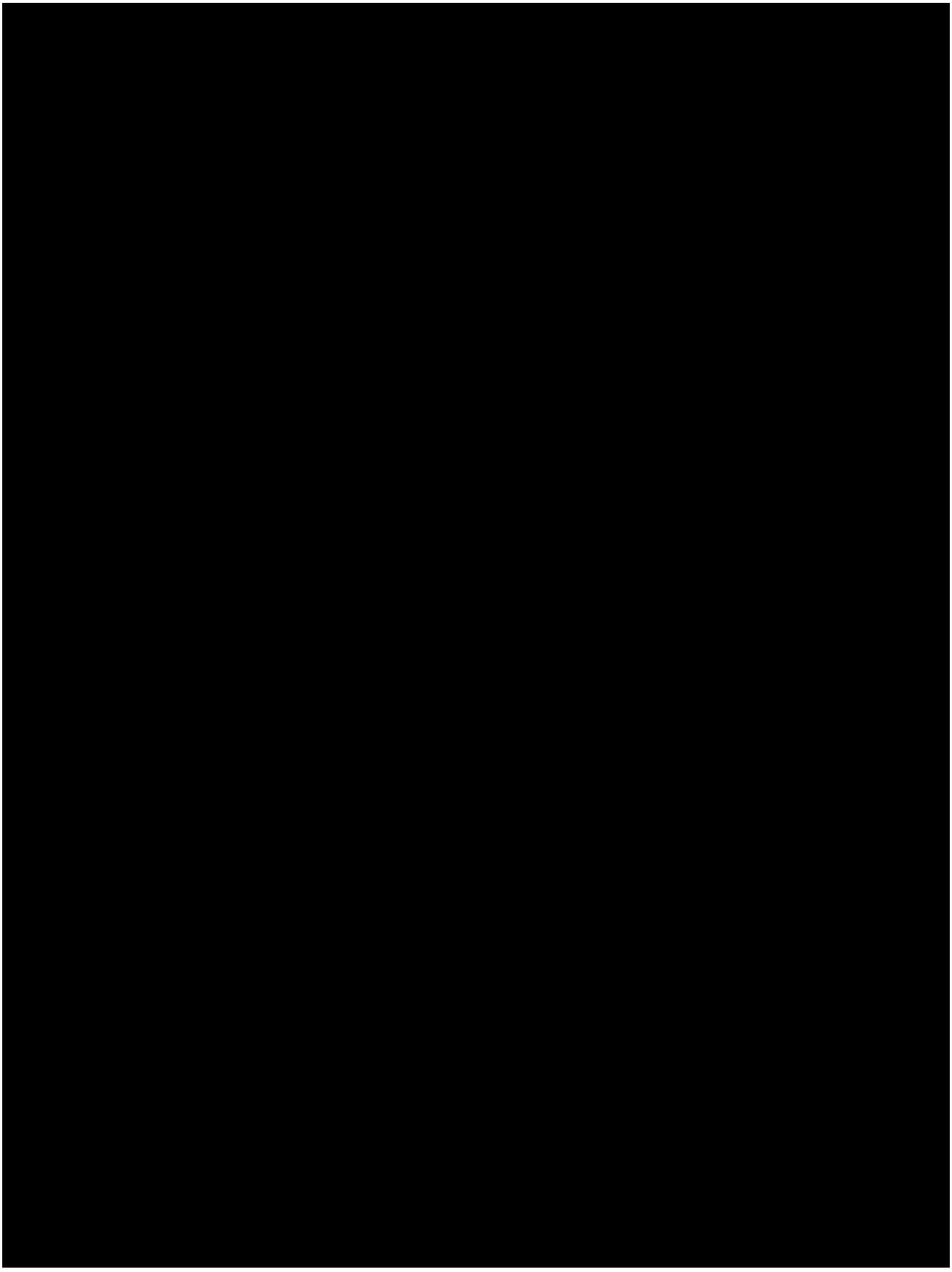


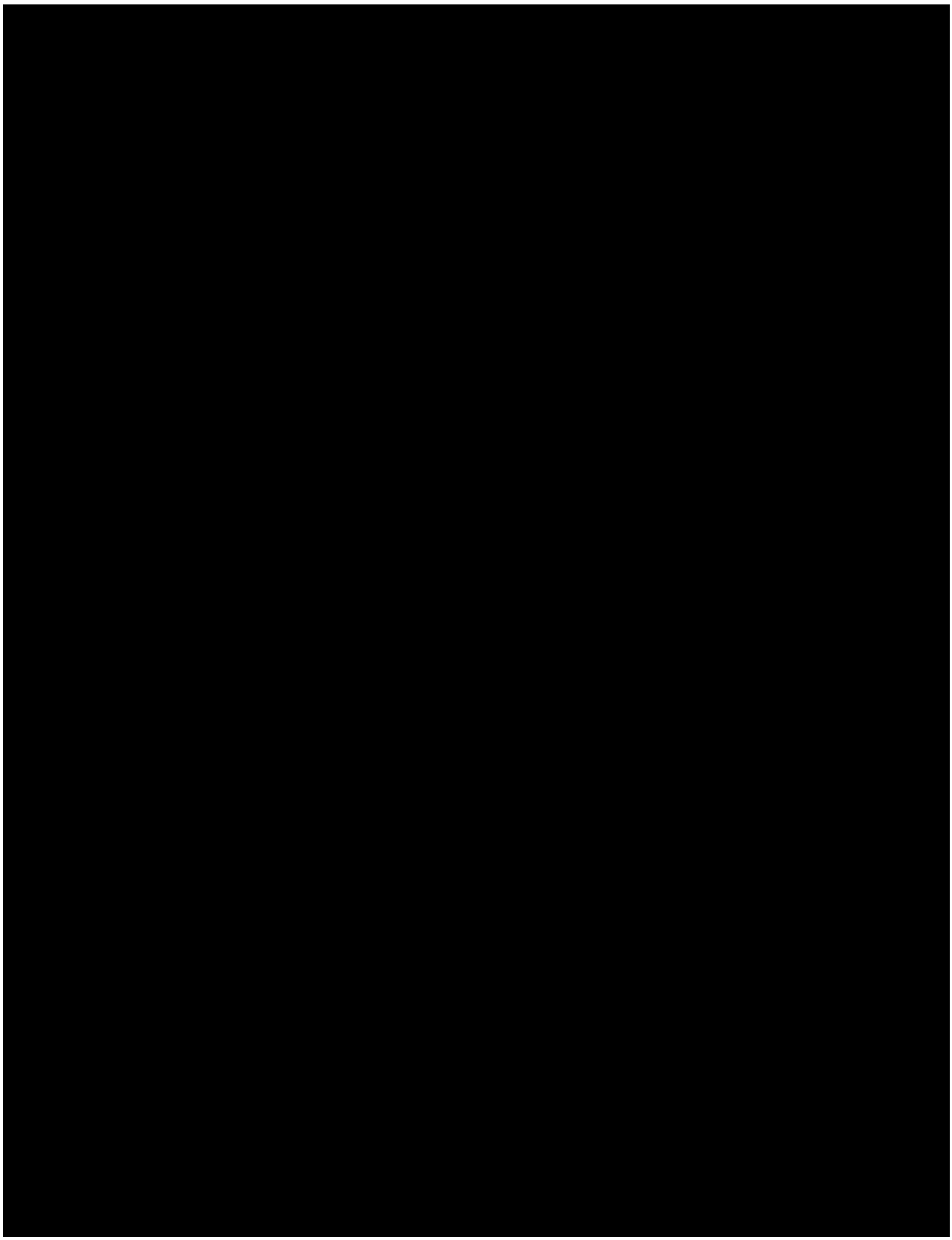












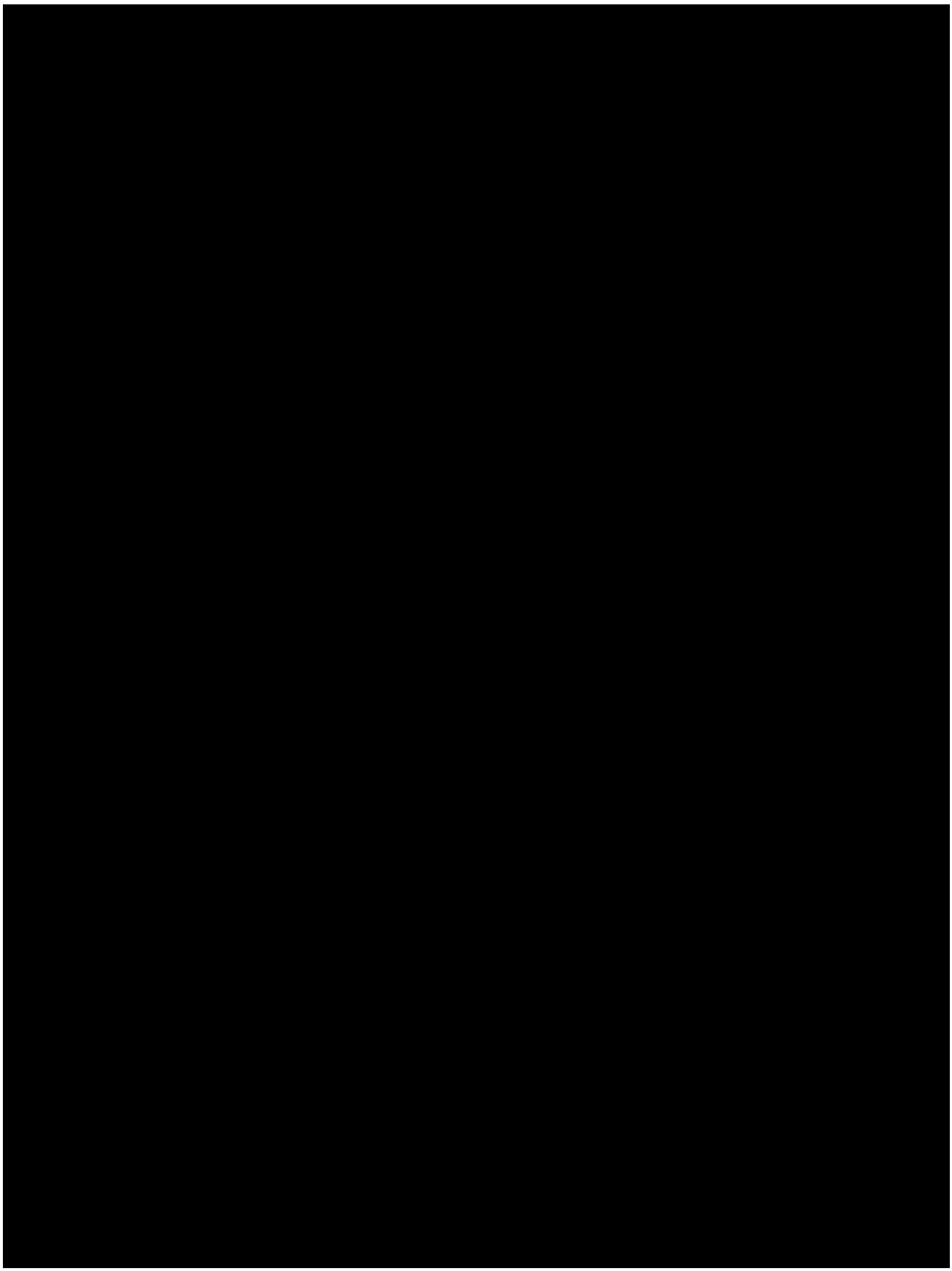
[redacted]

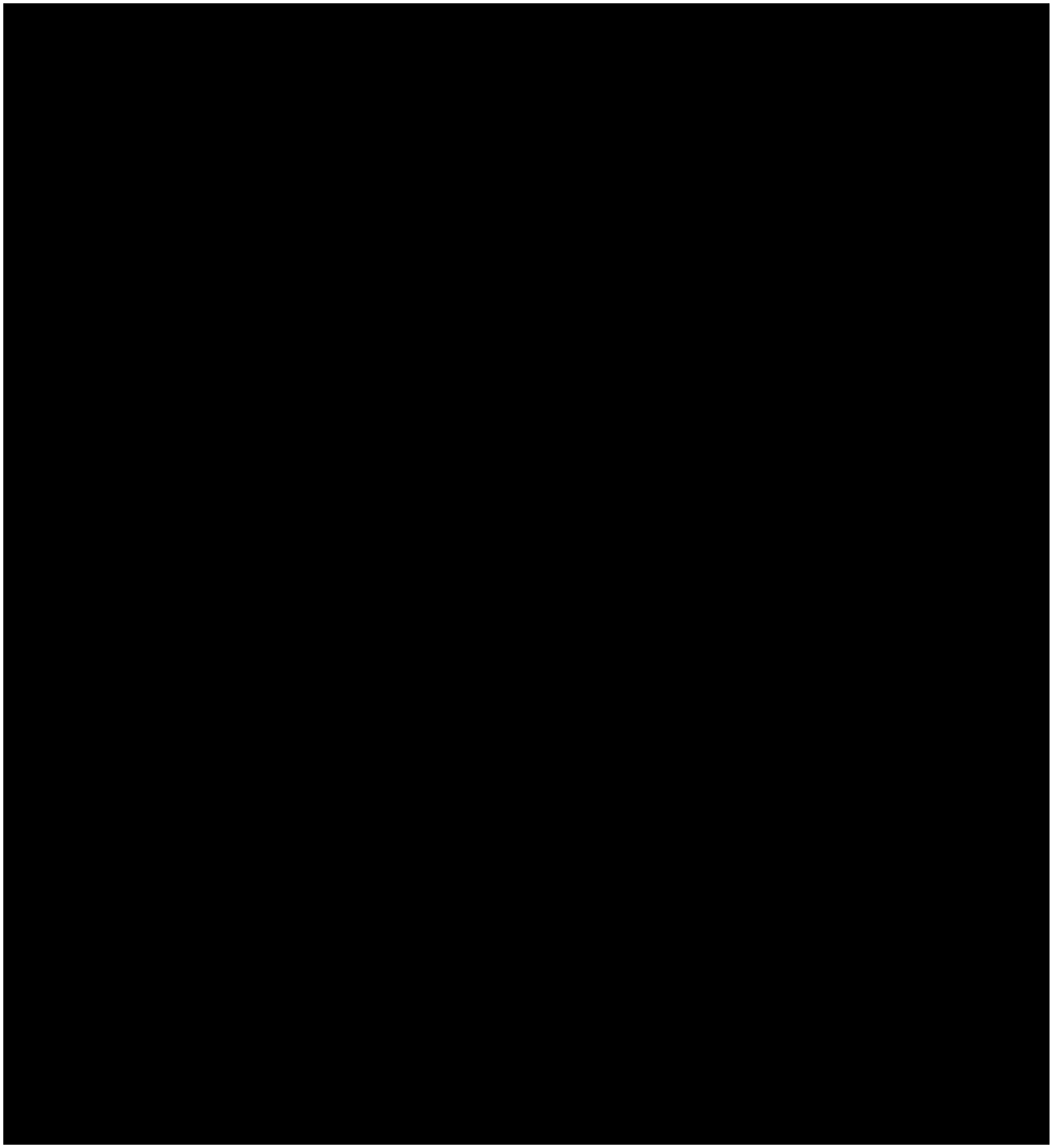
10.5 LIST OF POTENTIAL TERMS FOR HEPATIC INJURY DERIVATION

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

Table 10.5: 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)	30000087





11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1.0	**13-JUN-23**	[redacted]	None	This is the final TSAP.
2.0	**14-MAY-25**		4	Exclusion of post lung transplant data added. Already applied for interim CTR. [redacted]
			5	Specification details added for clarification to derivation of last contact date when the patient was known to be alive. Already applied for interim CTR.
			[redacted]	
			5.4.3	Calculation rule extended for duration of exposure and unit changed to days for duration of interruptions. Already applied for interim CTR. Categories for duration of exposure extended to account for trial prolongation.

Table 11.1 History table (continued)

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
2.0 (cont.)	**14-MAY-25**	[redacted]	[redacted]	
			7	Clarified that for parameters summarised at specific timepoints data of all available timepoints will be presented even if not all are specified in the CTP endpoint definition. Already applied for interim CTR.
			[redacted]	
			10.6	Table 10.6: 1 extended with 3 further specifications for other childhood ILD now available in the data. First one already applied for interim CTR.
			10.7	Section removed as impact of COVID-19 on the trial is not to be reported anymore.