TRIAL STATISTICAL ANALYSIS PLAN c23026758-01

BI Trial No.:	1160.0284
Title:	Post-Marketing Surveillance on the Use of Prazaxa® Capsules in Japanese patients with nonvalvular atrial fibrillation after the availability of idarucizumab
Investigational Product(s):	Dabigatran etexilate
Responsible trial statistician(s):	[redacted] Phone: [redacted], Fax: [redacted]
Date of statistical analysis plan:	18 FEB 2021 SIGNED
Version:	"Final"

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LIST OF TABLES

2. LIST OF ABBREVIATIONS

Term	Definition / description
ACEI	Angiotensin-Converting Enzyme Inhibitor
ADS	Analysis Data Set
ADR	Adverse Drug Reaction
AE	Adverse Event
AF	Atrial Fibrillation
ARB	Angiotensin II Receptor Blocker
BI	Boehringer Ingelheim
BMI	Body Mass Index
DBP	Diastolic blood pressure
DOAC	Direct Oral Anti-Coagulants
eCRF	Electronic Case Report Form
eGRF	Estimated glomerular filtration rate
EMA	European Medicines Agency
GI	Gastrointestinal
ICH	Intracerebral Haemorrhage
INR	International Normalisation Ratio
LAA	Left atrial appendage
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
NIS	Non-Interventional Study
NSAID	Non-Steroidal Anti-Inflammatory drug
NVAF	Non-Valvular Atrial Fibrillation
PCI	Percutaneous Coronary Intervention
PMS	Post Marketing Surveillance
PPI	Proton Pump Inhibitor
PT	Preferred Term
PV	Protocol Violation
Q1	Lower Quartile
Q3	Upper Quartile
SAE	Serious Adverse Event

Term	Definition / description
SBP	Systolic blood pressure
SEE	Systemic Embolism
SMQ	Standardised MedDRA Query
SOC	System Organ Class
TIA	Transient Ischemic Attack
TSAP	Trial Statistical Analysis Plan

3. INTRODUCTION

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 post-marketing surveillance (PMS) data.

This Trial Statistical Analysis Plan (TSAP) assumes familiarity with the Non-Interventional Study (NIS) protocol, including protocol amendments. In particular, the TSAP is based on the planned analysis specification as written in the NIS protocol Section 9.7 “DATA ANALYSIS”. Therefore, TSAP readers may consult the NIS protocol 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.

SAS® Version 9.4 will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

There has been no change in the planned analysis from the statistical methods described in the NIS protocol.

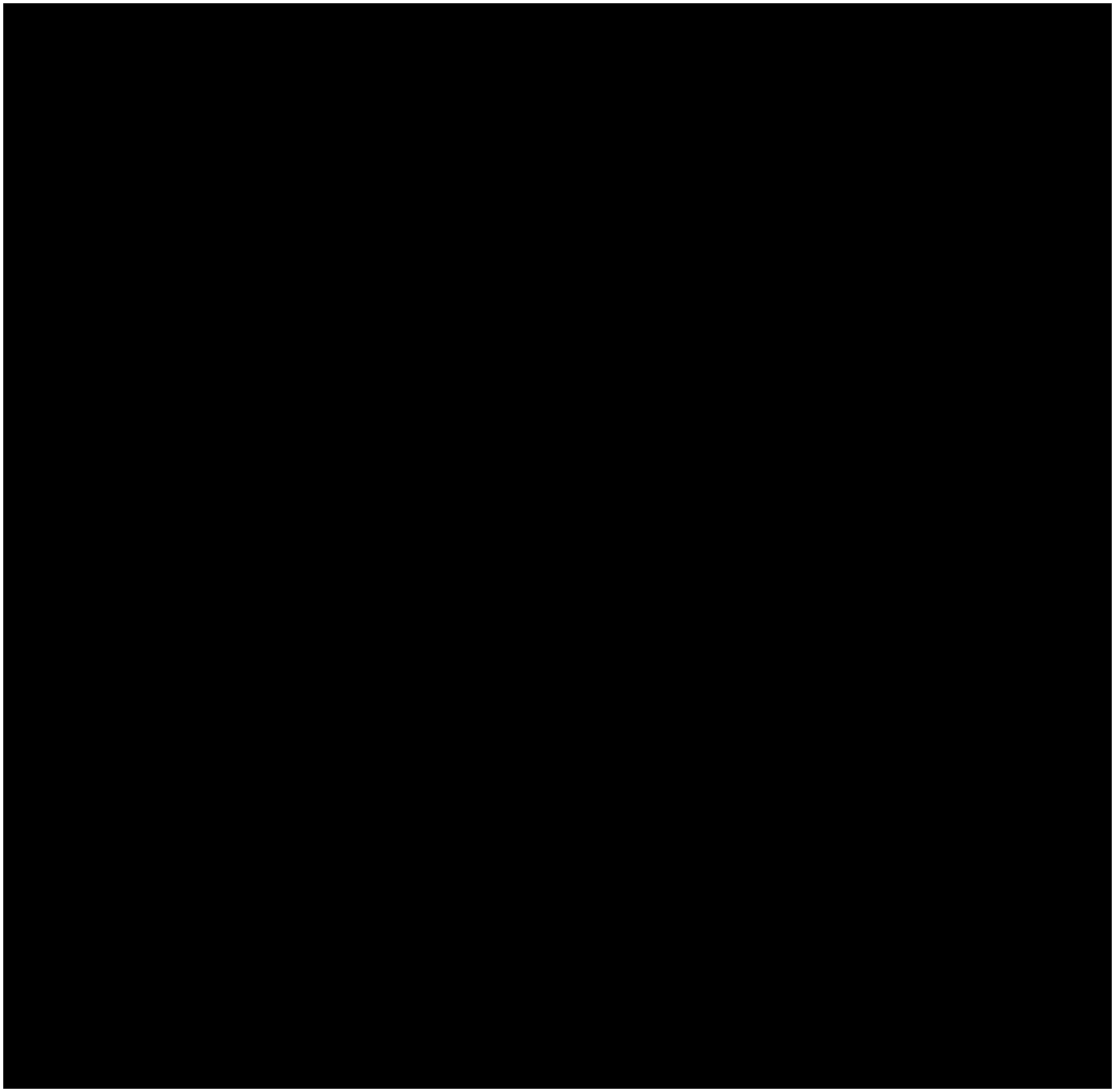
5. ENDPOINT(S)

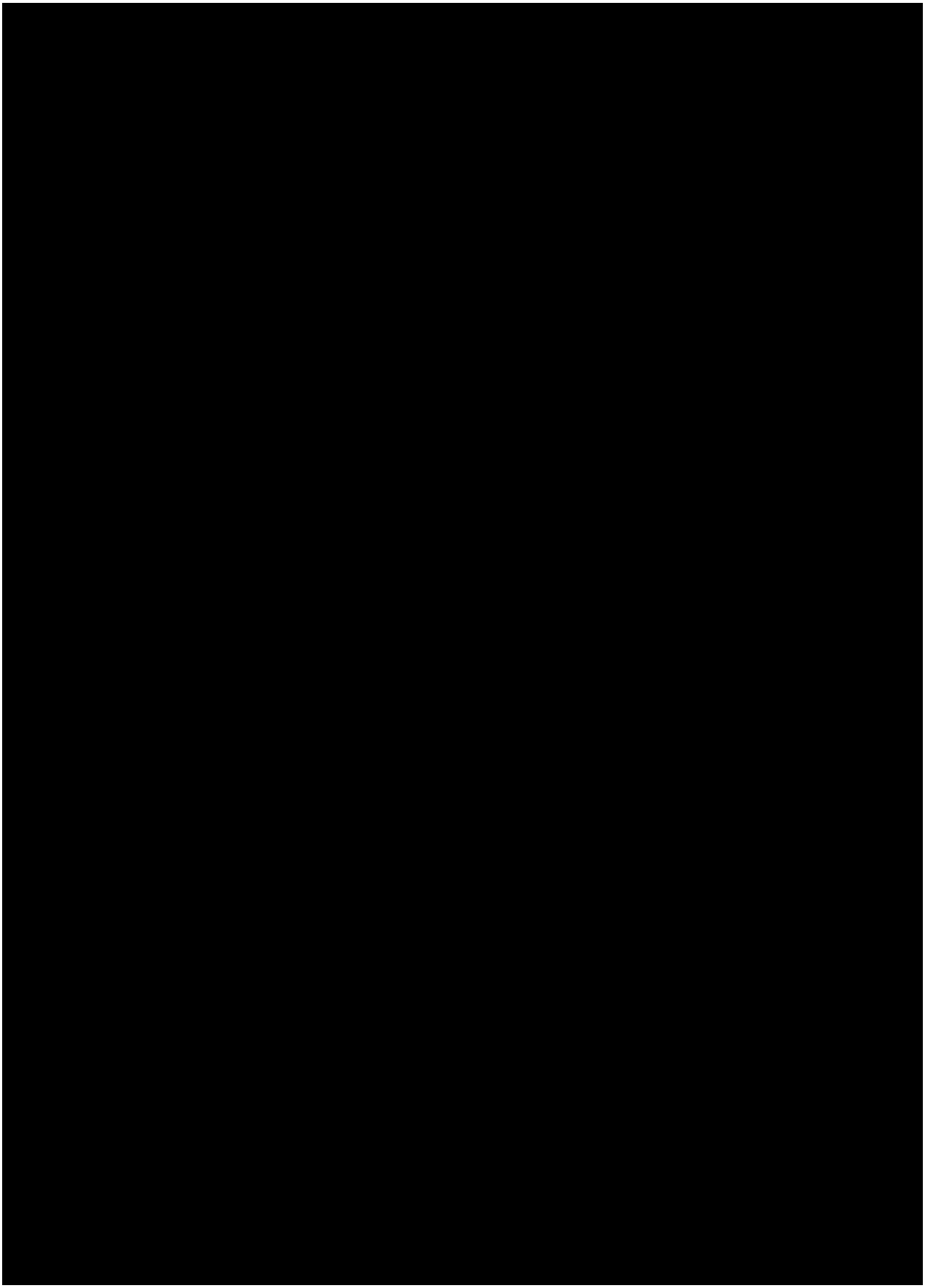
5.1 PRIMARY ENDPOINT(S)

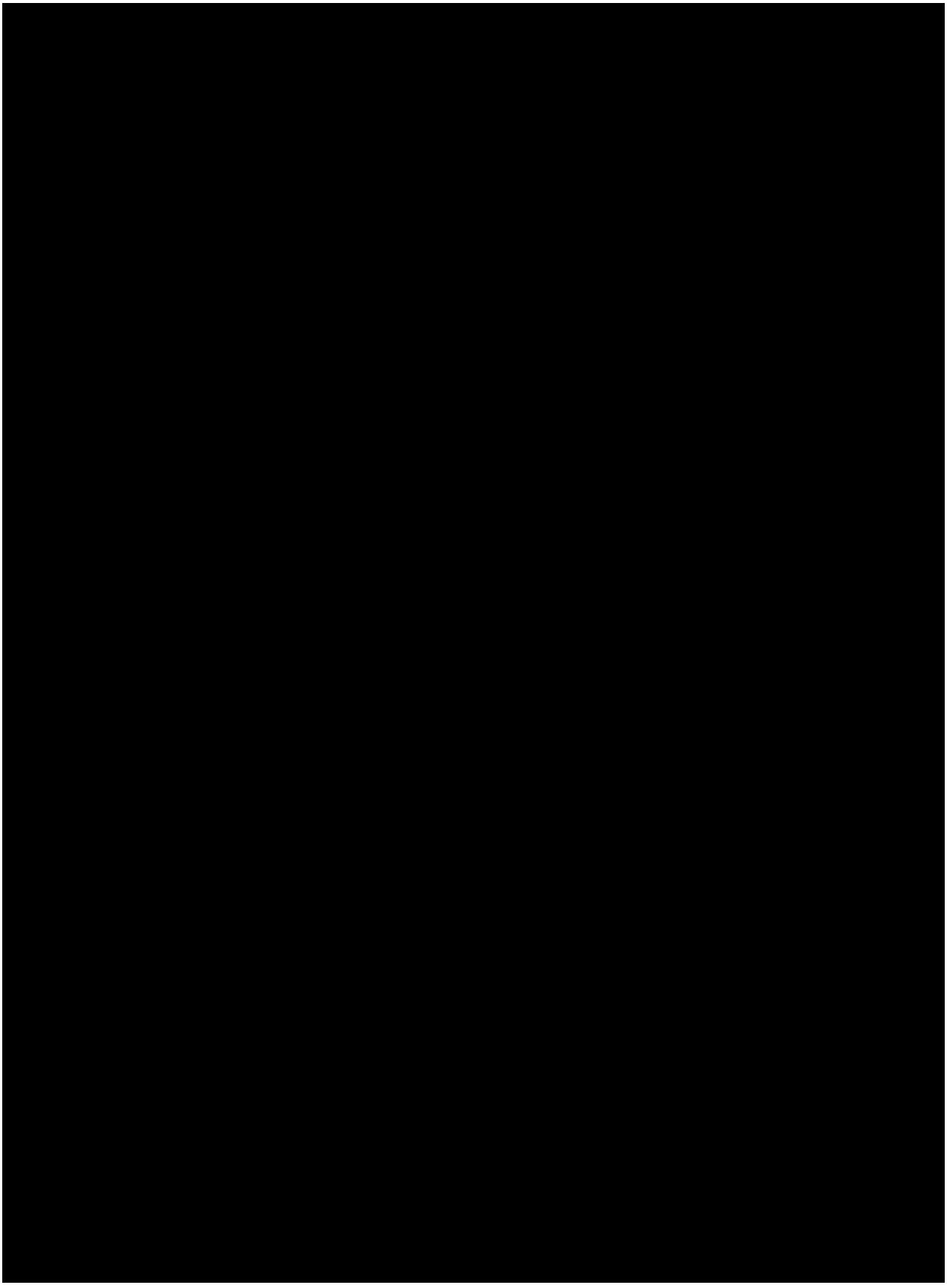
The primary endpoint of the PMS study is the frequency of patients with adverse drug reactions (ADRs).

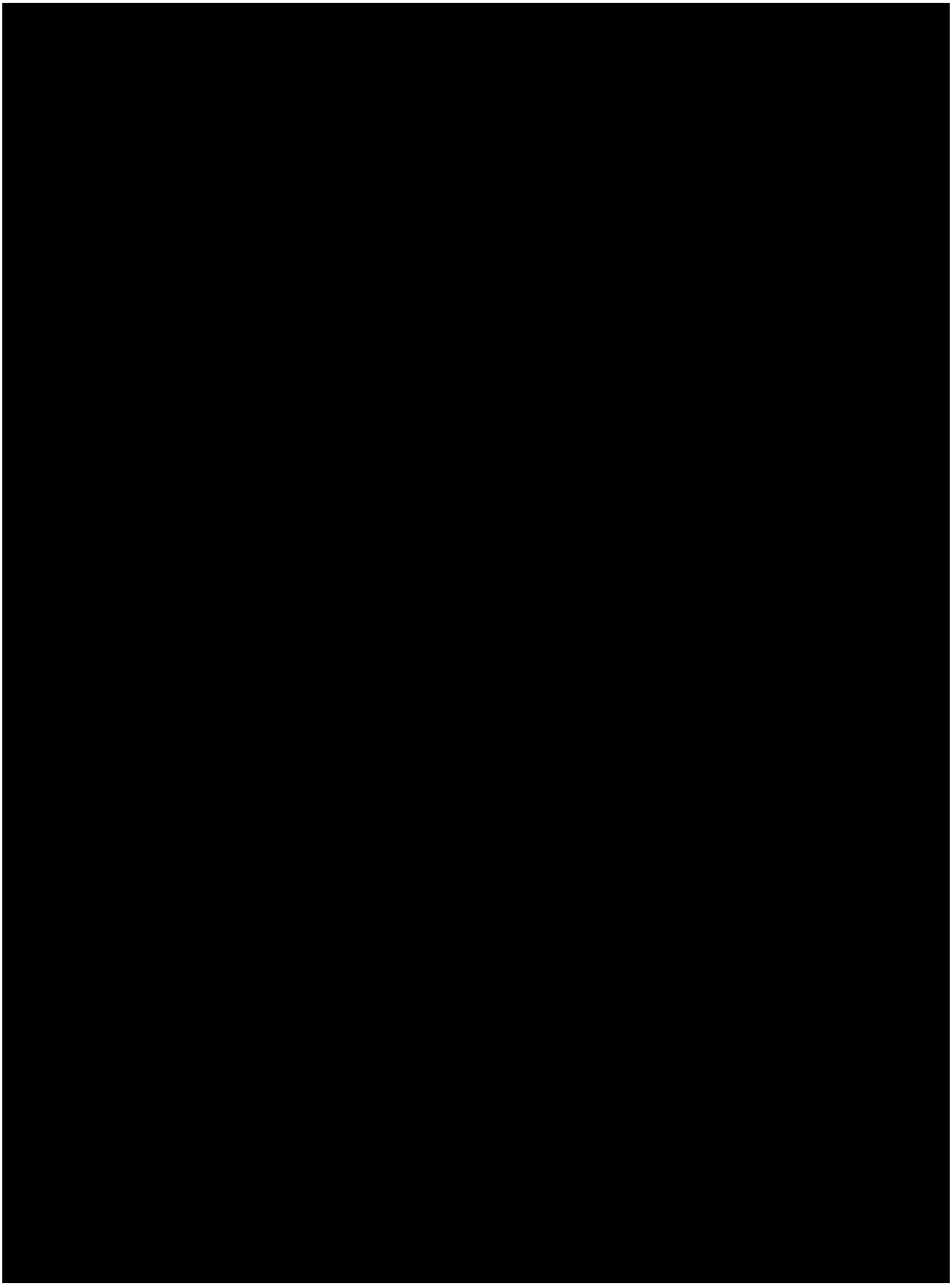
5.2 SECONDARY ENDPOINT(S)

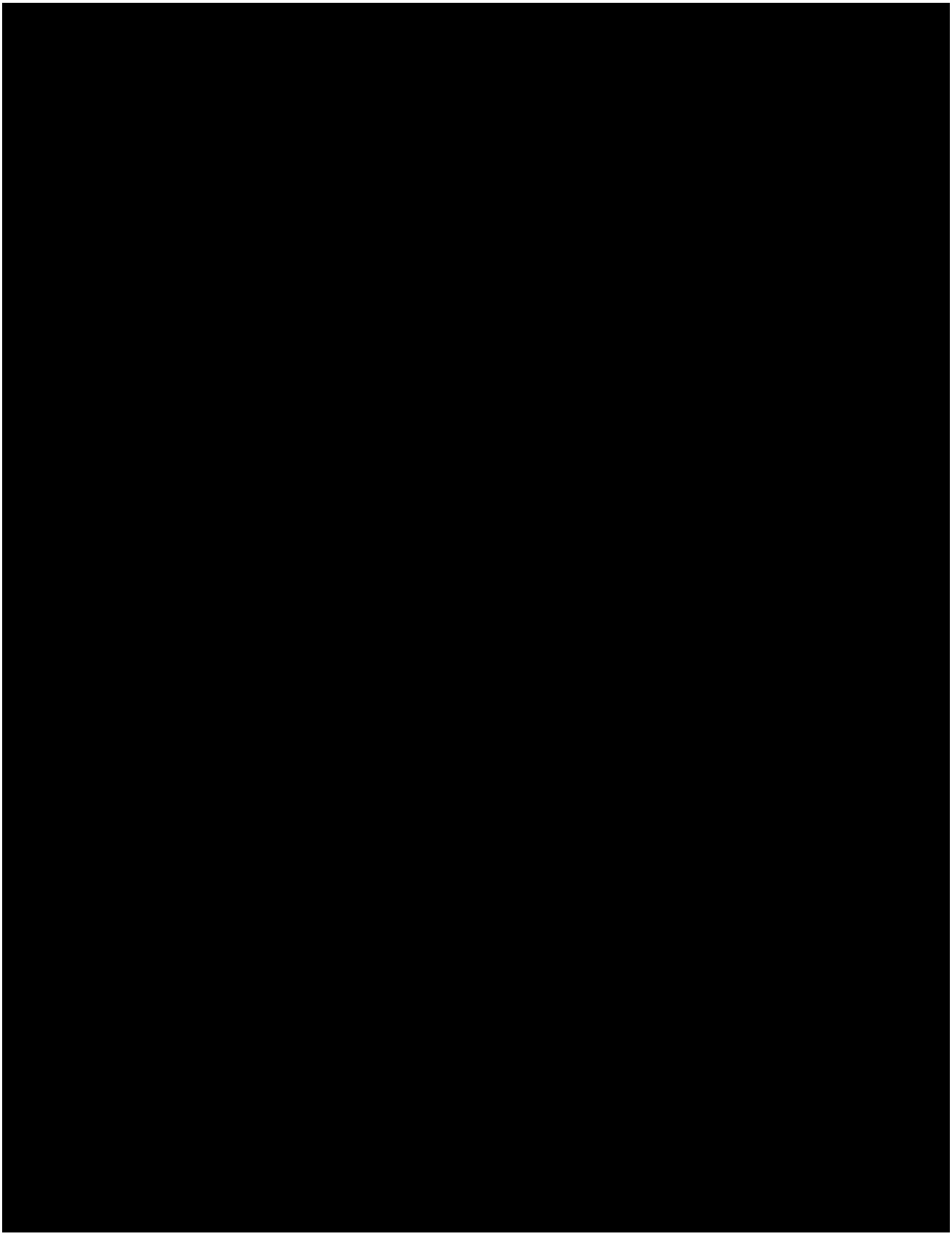
None











6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

For basic study information on treatments, please refer to NIS protocol Section 9.1. The technical specification for treatment set-up is described in the analysis data set (ADS) plan. Data collected up to 6 days (inclusive) after the last administration will be considered as on-treatment.

CAUTION

Usually in dabigatran studies, 6 days is used for washout if warfarin is the comparator and 3 days is used for washout in the case of single arm Prazaxa® study. We use 6 day for washout in 1160.284. Because the study settings are different between 1160.284 and randomized clinical trials, we need extremely cautious in the interpretation.

6.2 IMPORTANT PROTOCOL VIOLATIONS

The following table defines the different categories of important PVs. The right-most column describes which PVs will be used to exclude patients from the different patient analysis sets. The final decision about which patients will be excluded from analysis sets will be taken during the course of the study and at report planning meetings before database lock at the latest.

Table 6.2: 1 Important protocol violations

Category / Code		Description	Requirements	Excluded from
A		**Entrance criteria not met**		
	A1.1	Patient main diagnosis not met	Patient not mainly diagnosed as nonvalvular AF	Safety set 2*
	A1.2	Patient received Prazaxa® treatment before	Patient experienced with Prazaxa® treatment for the prevention of ischemic stroke and SEE	Safety set 1 Safety set 2*
	A3	Contraindication	Patient in contraindication received Prazaxa®	Safety set 2*
B		**Informed consent**		
C		**Study registration**		
	C2.1	Registration rule not followed	See NIS protocol section 9.2.3 Study visits	Safety set 1 Safety set 2*
	C2.2	Invalid registration	Patient registered outside the site contract period	Safety set 1 Safety set 2*

Category / Code		Description	Requirements	Excluded from
	C2.3	Contract Violation	Contract process is invalid. These contract violation cases are presented by TCM.	Registration set Safety set 1 Safety set 2*
	C3.1	Wrong dosage schedule	Prazaxa® taken once daily instead of bid and/or incorrect daily dose taken (more or less than two capsules) This also applies to patients to whom Prazaxa® 110 mg twice daily is recommended but 150 mg twice daily is actually given.	None
	C3.2	No actual visit	Patient made no visit after the entry	Safety set 1 Safety set 2*
D		**Concomitant medication**		
	D	Prohibited medication use	Itoraconasol (a P-glycoprotein inhibitor) taken during the observation period	Safety set 2*

*For definition of Safety 2, see Section 6.3.

6.3 SUBJECT SETS ANALYSED

The safety set 1 will be the basis of all demographic, baseline and safety analyses. The safety set 2 will be the basis for the assessment of effectiveness for events of stroke/SEE: frequency and incidence rate (including 95% confidence interval) of the stroke/SEE. The safety set 2 corresponds to the effectiveness set in 1160.130.

- Safety set 1
  This patient set includes all patients who were dispensed study medication and were documented to have taken at least one dose of investigational treatment.
  This patient set includes all patients who were documented to have taken at least one dose of Prazasa® except patients who had experienced with Prazaxa® treatment for the prevention of ischemic stroke and SEE, who had not followed registration rules, who had been registered outside the site contract period and/or who had made no visit after the entry (see Table 6.2: 1).
- Safety set 2
  This patient set includes all patients in the safety set except for patient not diagnosed as nonvalvular AF or in contraindication (see Table 6.2: 1).

Note: For interim safety updates, a set of patients who have completed the study (i.e., all CRF pages for Month 12 already collected) may be considered additionally. Based on this patient subpopulation, subsets of the safety set 1 and safety set 2 will also be defined for analyses.

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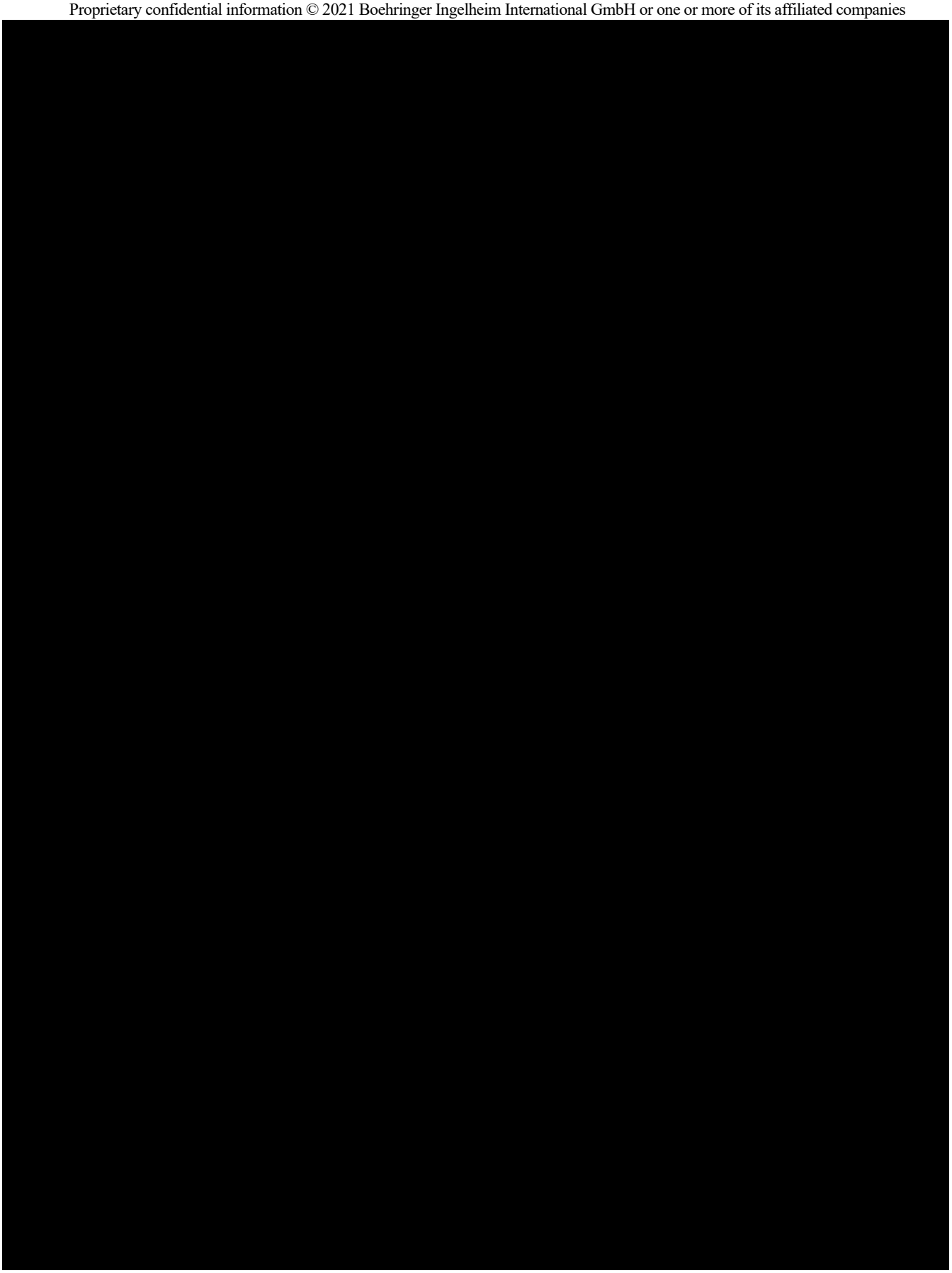

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6.5 POOLING OF CENTRES

This section is not applicable because no statistical model will be used for analyses.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

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Note: For the imputation of AE onset date for AEs reported between Months 3 and 12, use the BOOK 1 transmitted date as the date of last visit.

Incomplete dates except for AE dates are imputed as follows, if necessary:

- If both "day" and "month" are missing then impute the date as first dabi admin - 1 day, if the date must have taken place for the first dabi admin.
- If day is missing and the date must have taken place before the first dabi admin, then: if month coincides with the month of first dabi admin, use the day of first dabi admin -1day; else if the month differ, then set day to 15

In all other instances:

- If both ‘day’ and ‘month’ are missing, then impute the day and month as follows: Set ‘day’ as 1 and ‘month’ as 7 (i.e., July) .
- If only ‘day’ is missing, then impute the day and month as follows: Set ‘day’ as 1.

Note that no imputation is planned for missing/incomplete dates for concomitant therapies. That is to say, if we cannot judge the therapy as concomitant therapies from following 1) - 2), the therapies are judged as non-concomitant therapies.

1) The start date of therapy and/or end date of the therapy is missing, incomplete or unknown.

2) Both check boxes of “Before Prazaxa administration “ at start date of concomitant drug in CRF and “Continued“ at end date of concomitant drug in CRF are not ticked.

In addition, in general, when tabulating any variables reported as ‘unknown’, it will be treated as such; otherwise treated as missing data.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The following labels will be used for visits and planned times.

Table 6.7: 1 Baseline, time windows and calculated visits

Actual visit (week)	Planned day	Calculated visit	Actual day for calculated visit	Label
Week 0	0	Week 0	0	Baseline [a)]
4	28	4	1 to ≤42	Week 4
8	56	8	43 to ≤70	Week 8
12	84	12	71 to ≤133	Week 12
26	182	26	134 to ≤273	Week 26
52	364	52	≥274	Week 52

a) At entry or before Prazaxa® was initiated

7. PLANNED ANALYSIS

The detailed description of the planned analyses documented in the study protocol will be given in this section.

For End-of-Text tables, the set of summary statistics is: N / Mean / SD / Min / Q1 / Median / Q3 / Max.

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective treatment group (unless otherwise specified, all patients in the respective patient set whether they have non-missing values or not). Percentages will be rounded to two decimal places. The category missing will be displayed only if there are actually missing values.

Percentages will be based on all patients in the respective patient set whether they have non-missing values or not.

A summary will generally be provided per initial Prazaxa® dose group of interest (i.e., 110 mg bid, 150 mg bid) as well as for overall analysing patients unless otherwise specified (In the case of switching the Prazaxa® dose during the study, the initial Prazaxa® dose group of interest are determined by only the initial Prazaxa® dose but the full dabigatran treatment period will be analysed, e.g. in terms of AE analysis, including time periods after a potential dose switch of dabigatran.).

In addition, individual values on demographic and baseline characteristics, treatment compliance and exposure, and safety (AEs) will be presented in subject data listings.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

In addition to summarise overall patient characteristics, the following summary tables will be provided to assess if patient characteristics are comparable between the following subgroups: patients not treated with any anticoagulants or warfarin vs. those previously treated within 7 days before initiating Prazaxa® (i.e., treatment-naïve and switchers); patients satisfying low dose criteria vs. patients not satisfying them. Another summary will be provided base on a subset of patients who experienced any reduction of Prazaxa® dose.

Also, the demographic and other baseline characteristics for patients who have participated in the trial of 1160.0284 vs. patients who had participated in the trial of 1160.0130 will be tabulated.

7.2 CONCOMITANT DISEASES AND MEDICATION

Concomitant diseases will be coded with the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). Only descriptive statistics are planned for concomitant diseases.

Concomitant medication will not be coded or summarised unless otherwise used for defining patient subgroup to explore efficacy outcome or safety risks (for this, see Section 6.4).

7.3 TREATMENT COMPLIANCE

Frequency tabulation will be provided for reported treatment adherence at Months 3 and 12.

7.4 PRIMARY ENDPOINT(S)

The study defines no primary endpoint for effectiveness.

7.5 SECONDARY ENDPOINT(S)

None

7.5.1 Key secondary endpoint(s)

None

7.5.2 (Other) Secondary endpoint(s)

None

[redacted]

7.7 EXTENT OF EXPOSURE

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

Reasons for starting at the low dose (≤110 mg bid) and reasons for the dose reduction during the course of study will be listed.

For patients who were treated with Idarucizumab, information of demographic characteristics, AE (in the case of onset of AE), dosage of Prazaxa® at onset of AE and concomitant ablation treatment will be summarized in a listing.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the safety set 1.

7.8.1 Adverse events

Unless otherwise specified, the analyses of adverse events 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.

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

- The same MedDRA lowest level term was reported for the occurrences.
- Treatment did not change between the onsets of the occurrences.

For further details on summarisation of AE data, please refer to the guideline "Handling and summarization of AE data for clinical trial reports and integrated summaries" (2).

An overall summary of AEs will be presented.

In reporting AEs from the PMS study, frequency summaries are in general provided based on ADRs. An ADR is defined as an AE for which either the investigator or the sponsor (or both) assess the causal relationship to Prazaxa® Capsules as "Related".

The frequency of patients with ADRs will be tabulated by Prazaxa® dose at onset, system organ class (SOC) and preferred term (PT) according to the most recent MedDRA version (In this table, the definition of "off-treatment" is patient who was not treated with Dabigatran Etexilate when AE occurred at observation period.)

Separate tables will be provided for patients with serious adverse events (SAEs), serious ADRs and for patients with each of the following important AEs (termed 'AEs of special interest' in the study protocol, see Section 9.1.1 for the definitions): stroke, TIA, SEE, ischemic stroke, haemorrhage stroke, stroke of uncertain type, MI, vascular death, death of any cause, any bleeding events, major bleeding events, minor bleeding events, ICH, GI bleeding events, other bleeding events (i.e., non-ICH/non-GI bleeding), GI disorders, dyspepsia-like/gastritis-like symptoms, dyspepsia-like symptoms, and AEs leading hospitalisation. Note that among these important AEs, all variables associated with bleeding and GI events will be analysed as ADR.

In addition, all variables associated with stroke, TIA, SEE, ischemic stroke, haemorrhage stroke, stroke of uncertain type and ICH will be analysed by worst intensity.

For AEs and ADRs leading to discontinuation of Prazaxa® Capsules, a summary table will be created based on patients who discontinued the treatment due to AEs and ADRs.

Also, the frequency of patients with AEs and ADRs leading to death will be summarised by treatment, primary SOC and PT.

For the patients who were treated Idarucizmab, the frequency of patients with SAEs and ADRs will be tabulated by Prazaxa® dose at onset, SOC and PT.

SOCs will be sorted according to the standard sort order specified by European Medicines Agency (EMA). PTs will be sorted by frequency (within SOC).

To compare risks of overall ADR, SAE, serious ADR as well as each of the important AEs in different patient subgroups, frequency tabulation stratified by different patient subgroups will be provided with odds ratios and exact 95% confidence intervals whenever specified (see Section 6.4).

Separate ADR frequency tables will also be provided for patients with contraindication/any precaution drugs and patients satisfying the low dose criteria.

Patients with ADRs will also be examined in terms of the duration of Prazaxa® treatment.

In addition, for each important AE (see Section 9.1.1), incidence rate and exact 95% Poisson confidence limits will be calculated. Incidence rates will also be calculated together with these 95% confidence limits for various patient subgroups defined by demographics, baseline characteristics and concomitant drugs (see also Section 6.4). Time to the first occurrence of each important AE will be analysed using the Kaplan-Meier method. For this, the AE onset date will be used except for any case of 'death' for which the AE outcome date will be used. A Cox regression analysis will be performed to compare hazards of each important AE stratified by patient demographics, baseline characteristics and concomitant drugs (see Section 6.4) If no event was reported for a patient, the patient is assumed to have been event-free until the treatment end date (see Section 5.4) the date will be used for censoring.

These analyses will be repeated for those assessed as serious and related (serious important ADRs).

For AEs reported in patients with initial Prazaxa® doses other than 110 mg bid and 150 mg bid (i.e., doses not approved in Japan), a listing will be provided per initial Prazaxa® doses.

7.8.2 Laboratory data

Only clinically relevant findings reported as AE will be analysed as a part of AE analyses.

7.8.3 Vital signs

Only clinically relevant findings reported as AE will be analysed as a part of AE analyses.

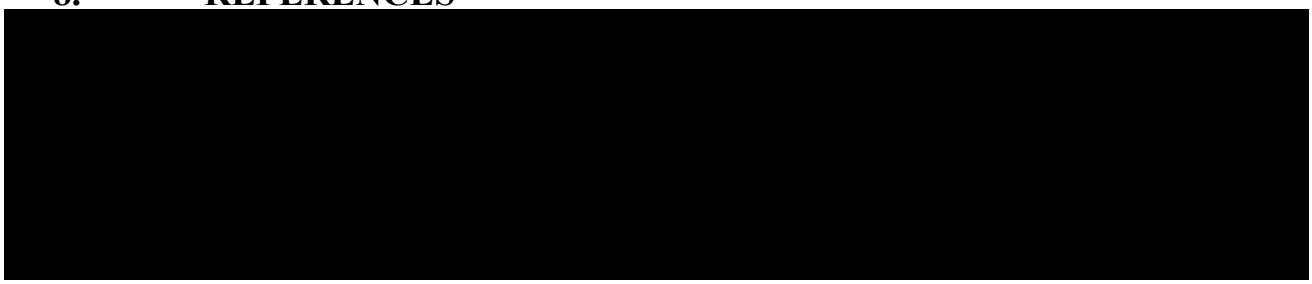
7.8.4 ECG

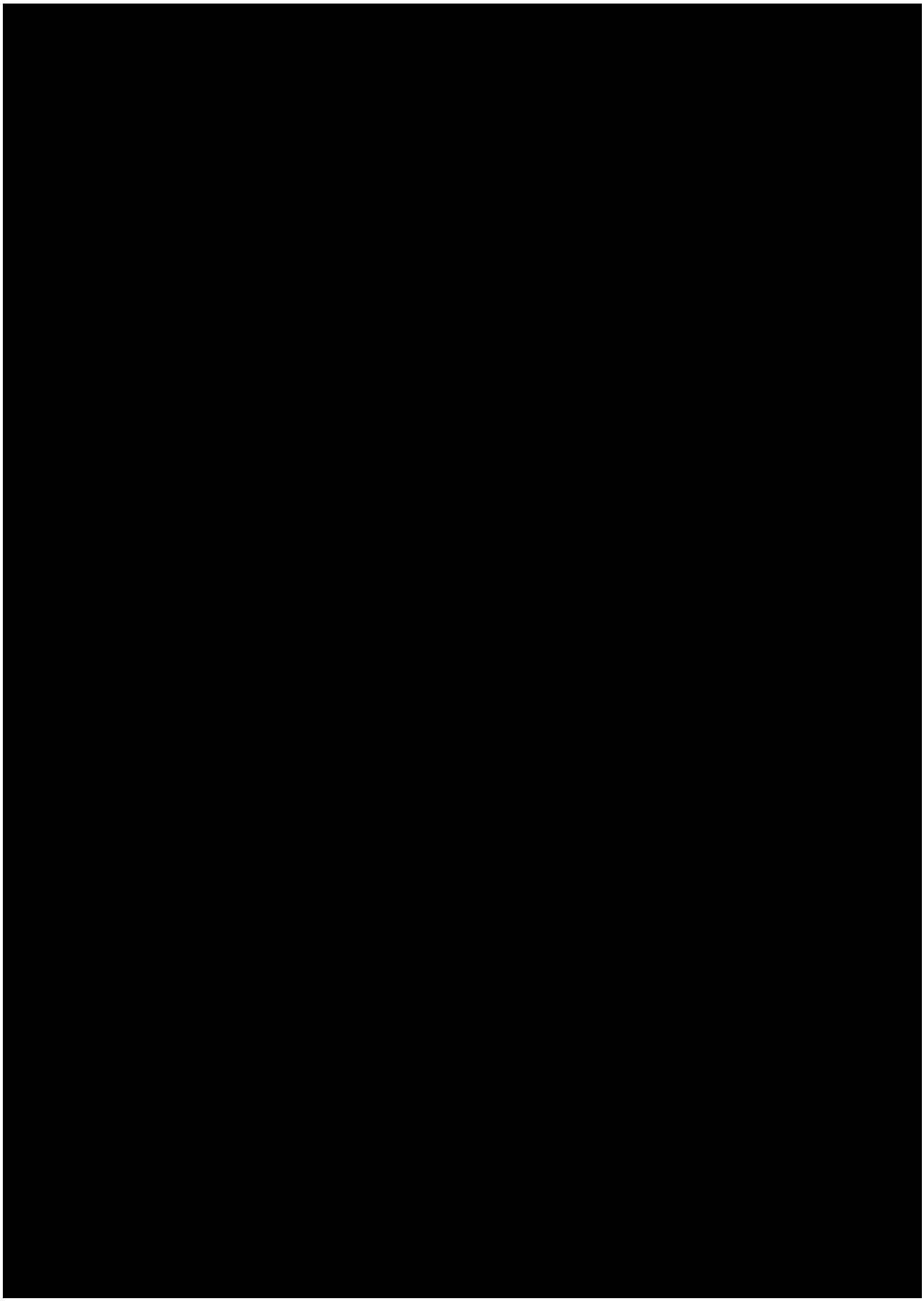
Only clinically relevant findings reported as AE will be analysed as a part of AE analyses.

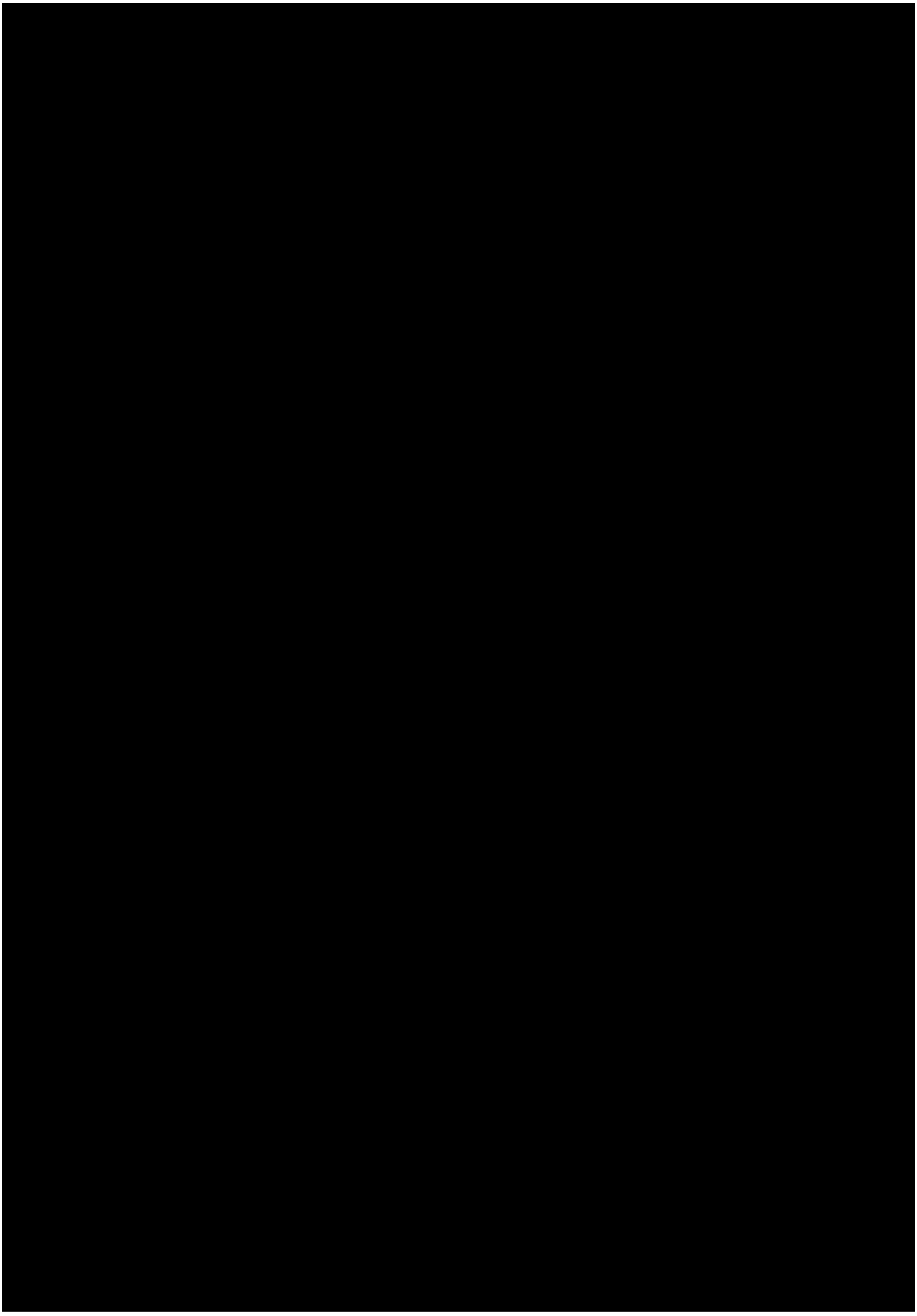
7.8.5 Others

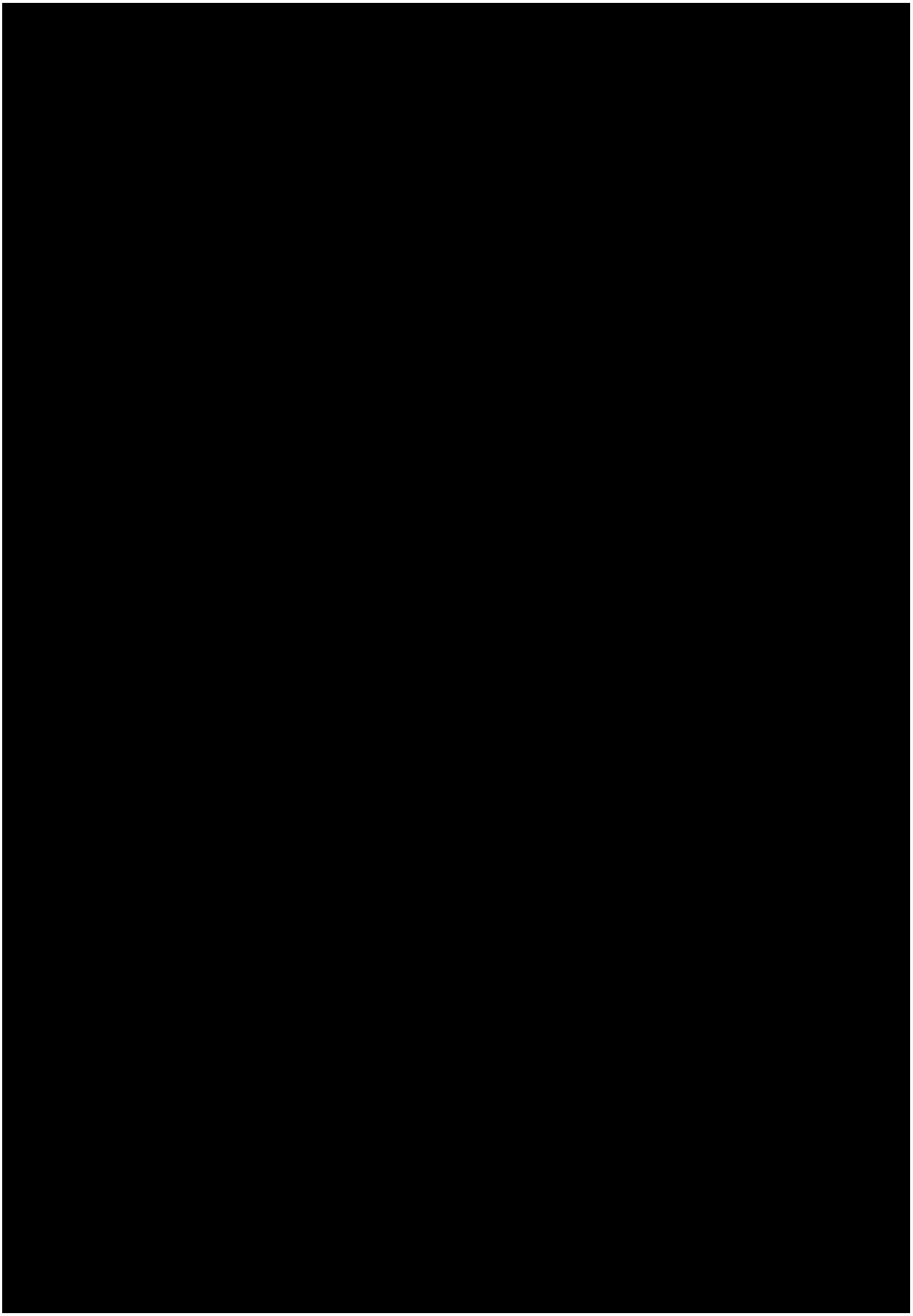
Frequencies of alternative antithrombotic medication after discontinuation of Prazaxa® doses will be summarised.

8. REFERENCES









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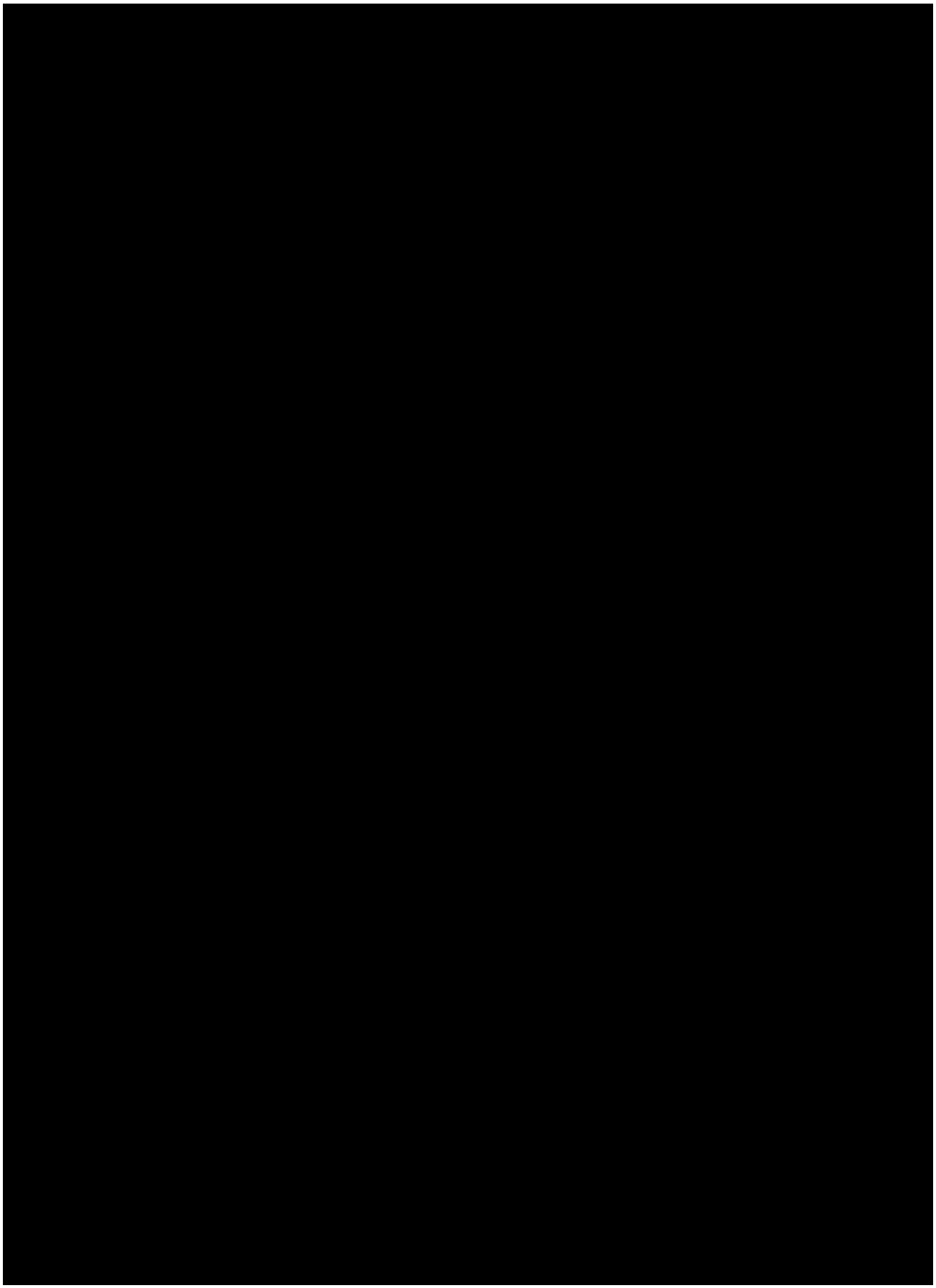

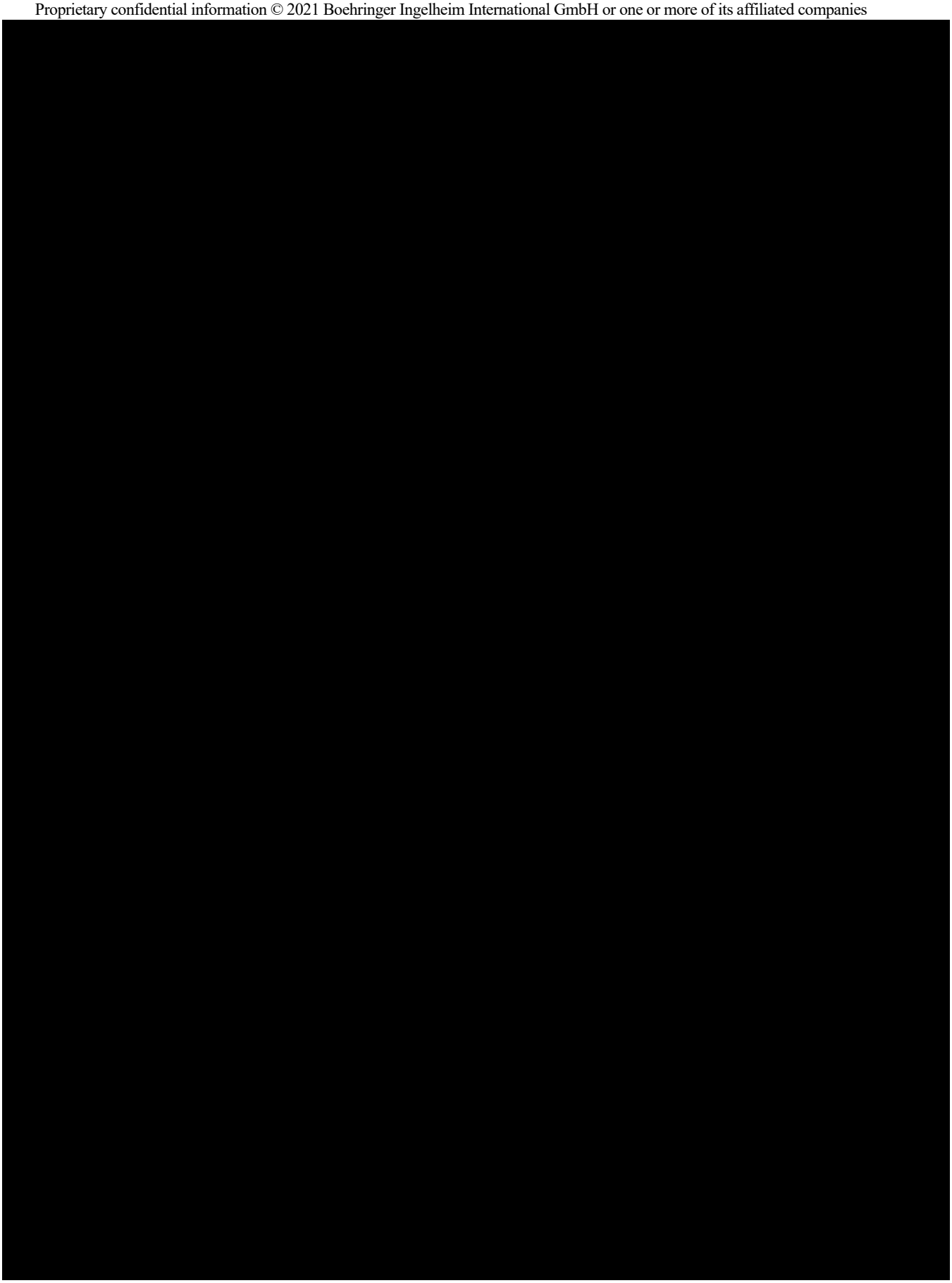

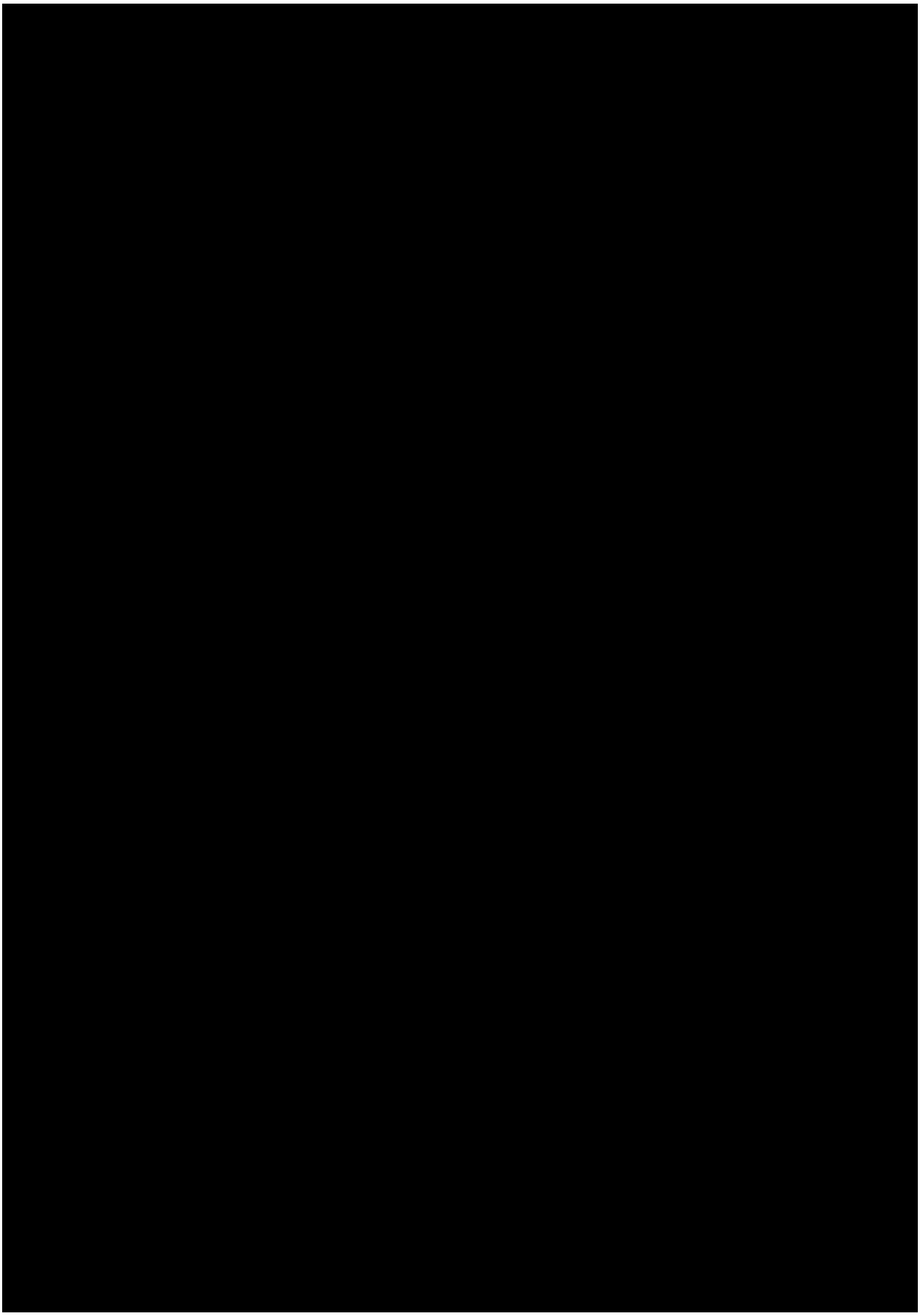

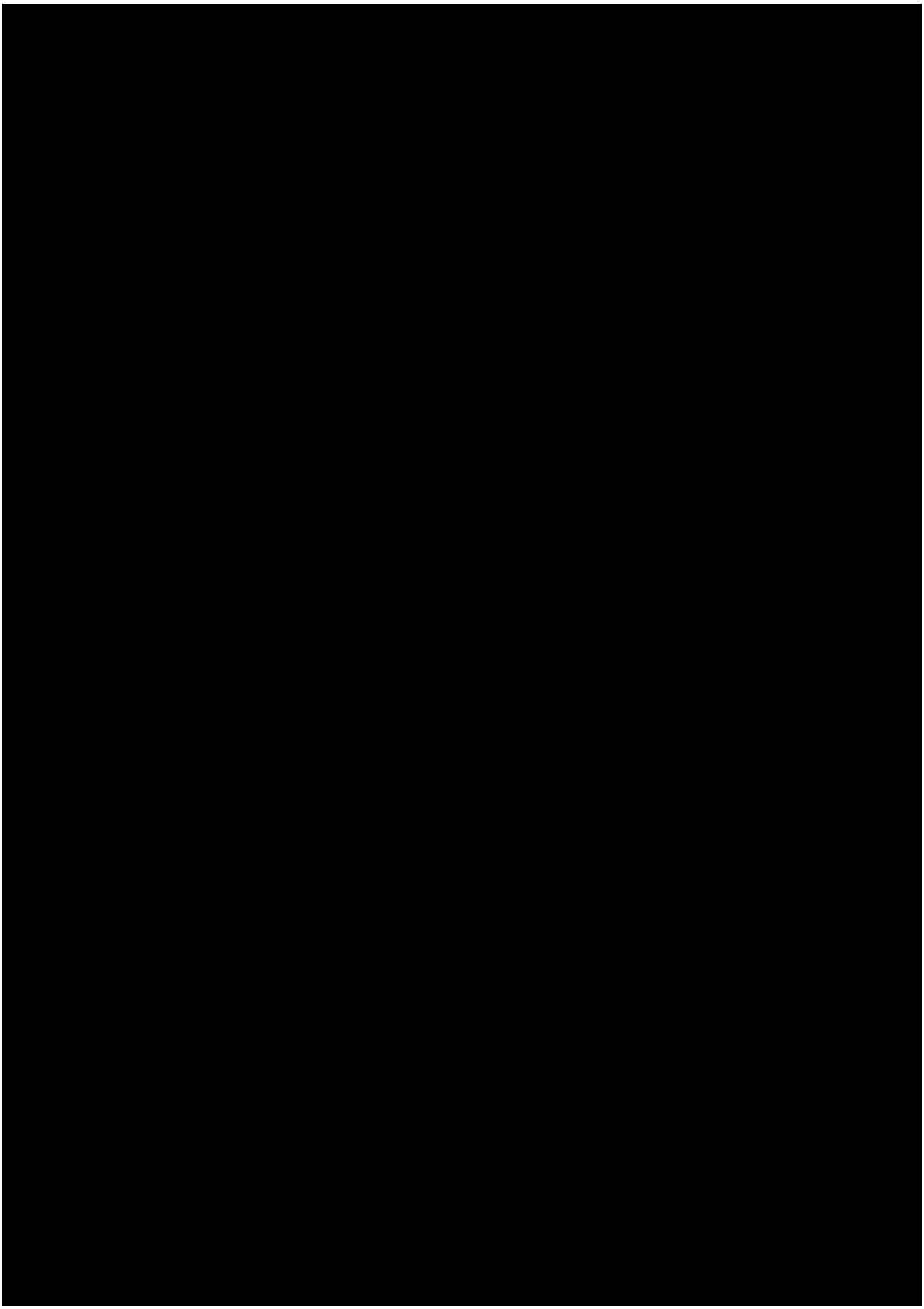

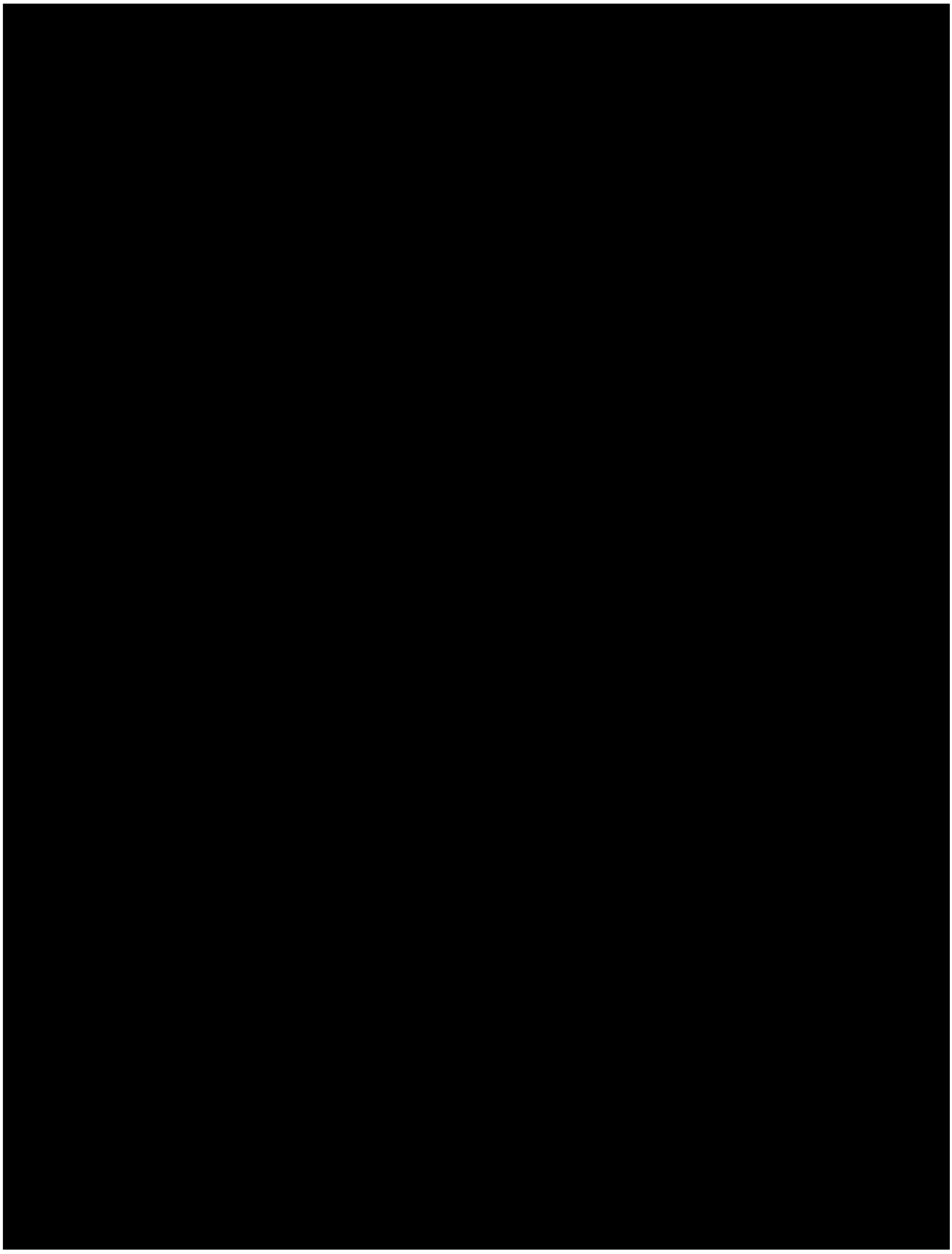

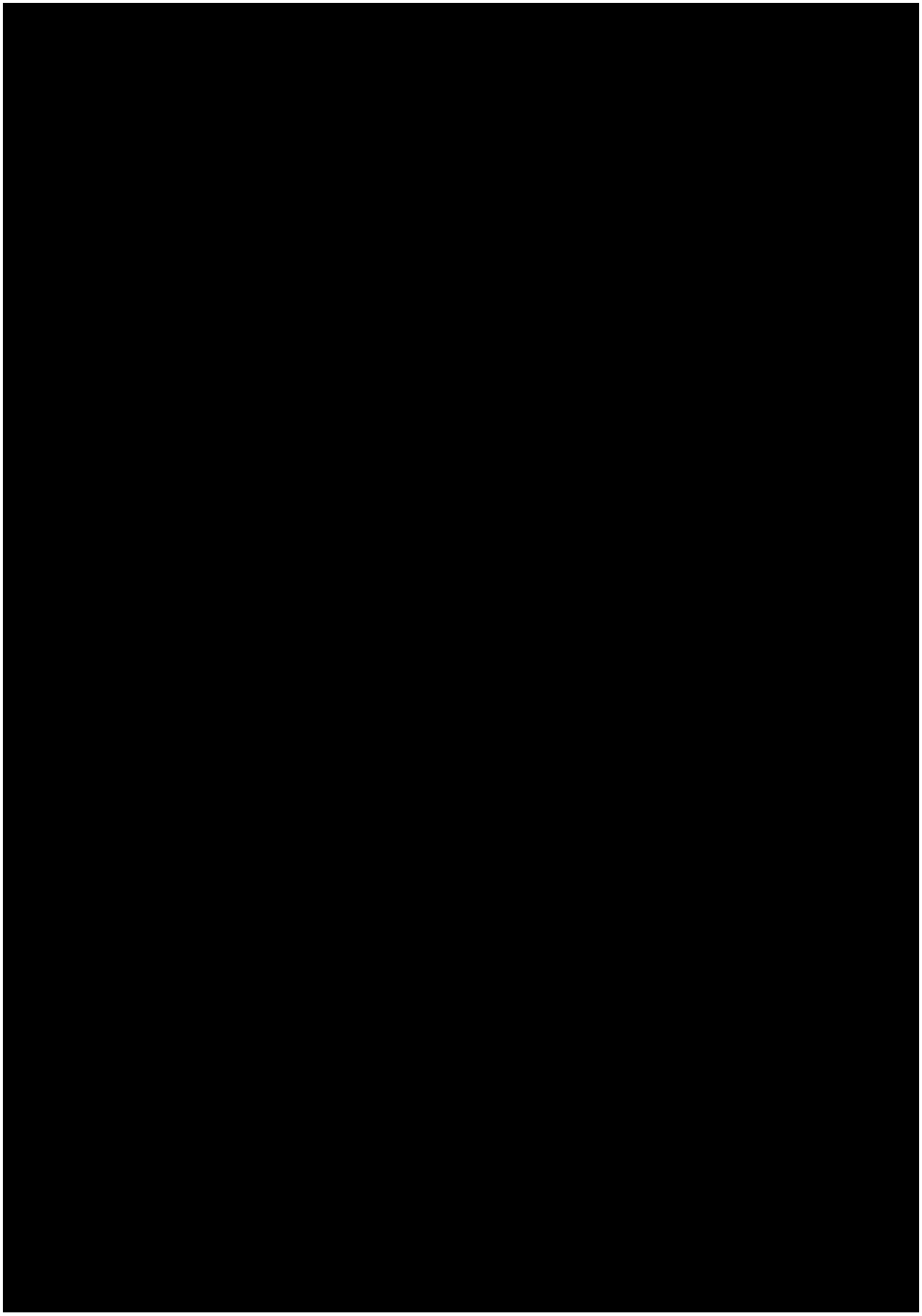

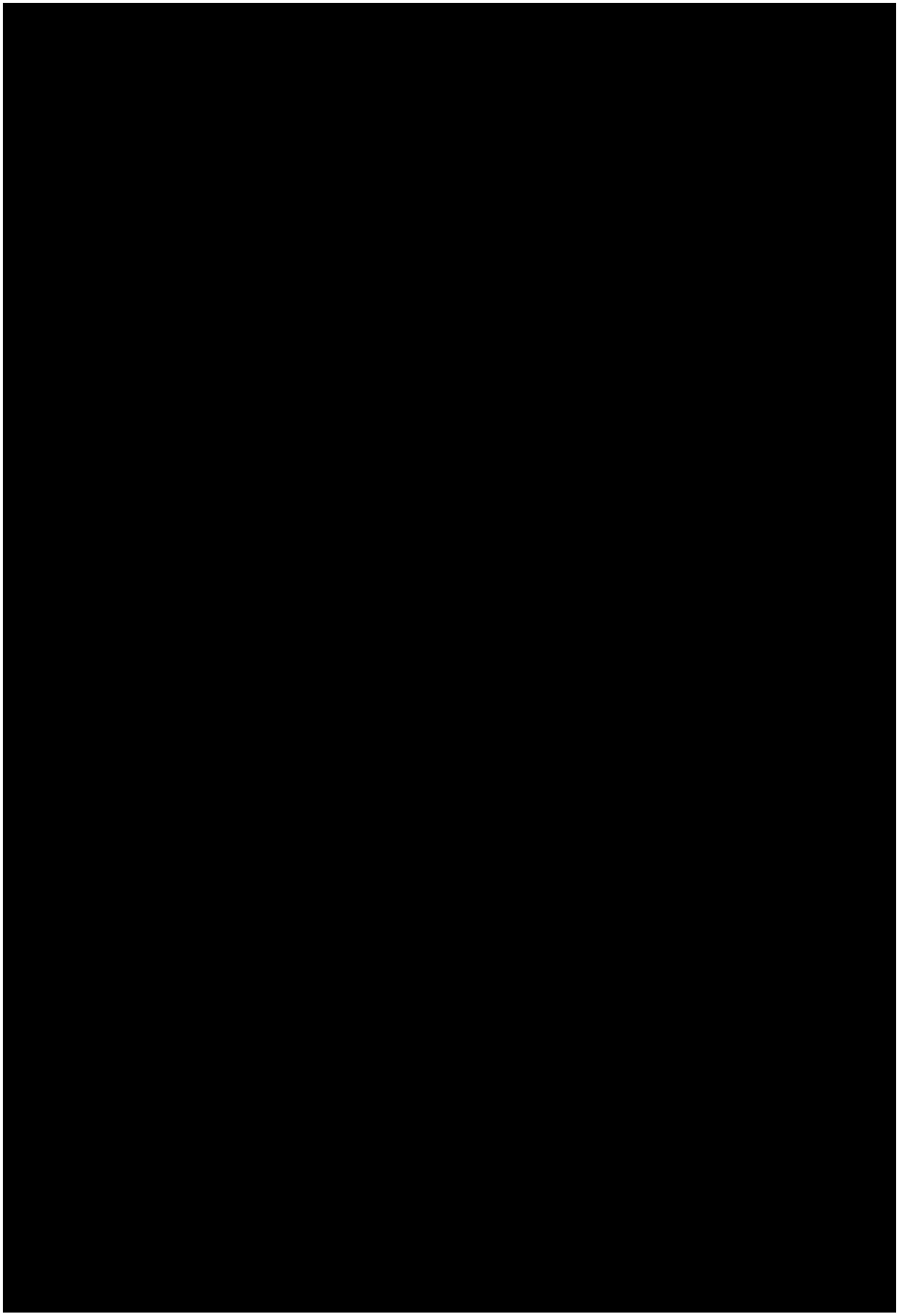

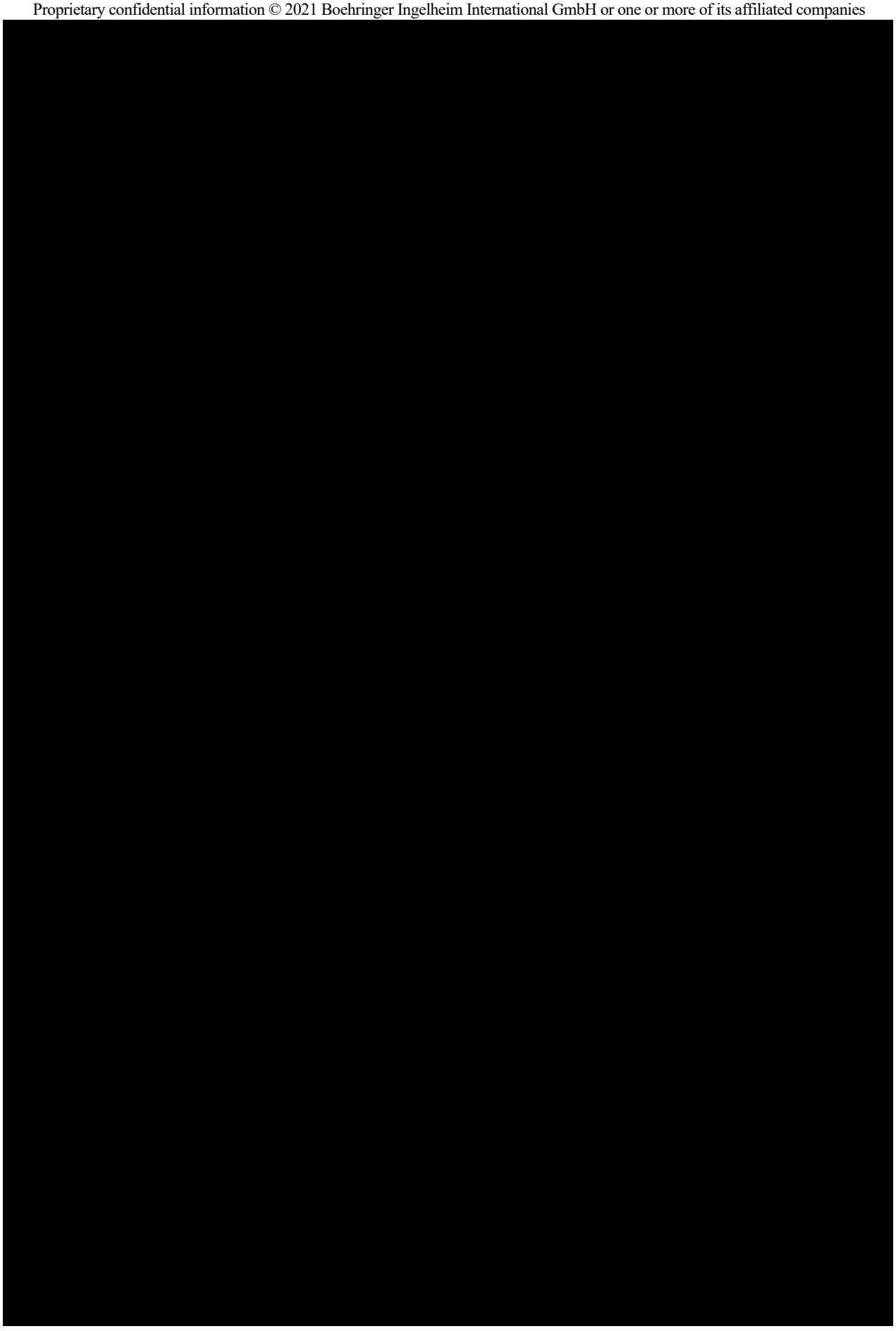

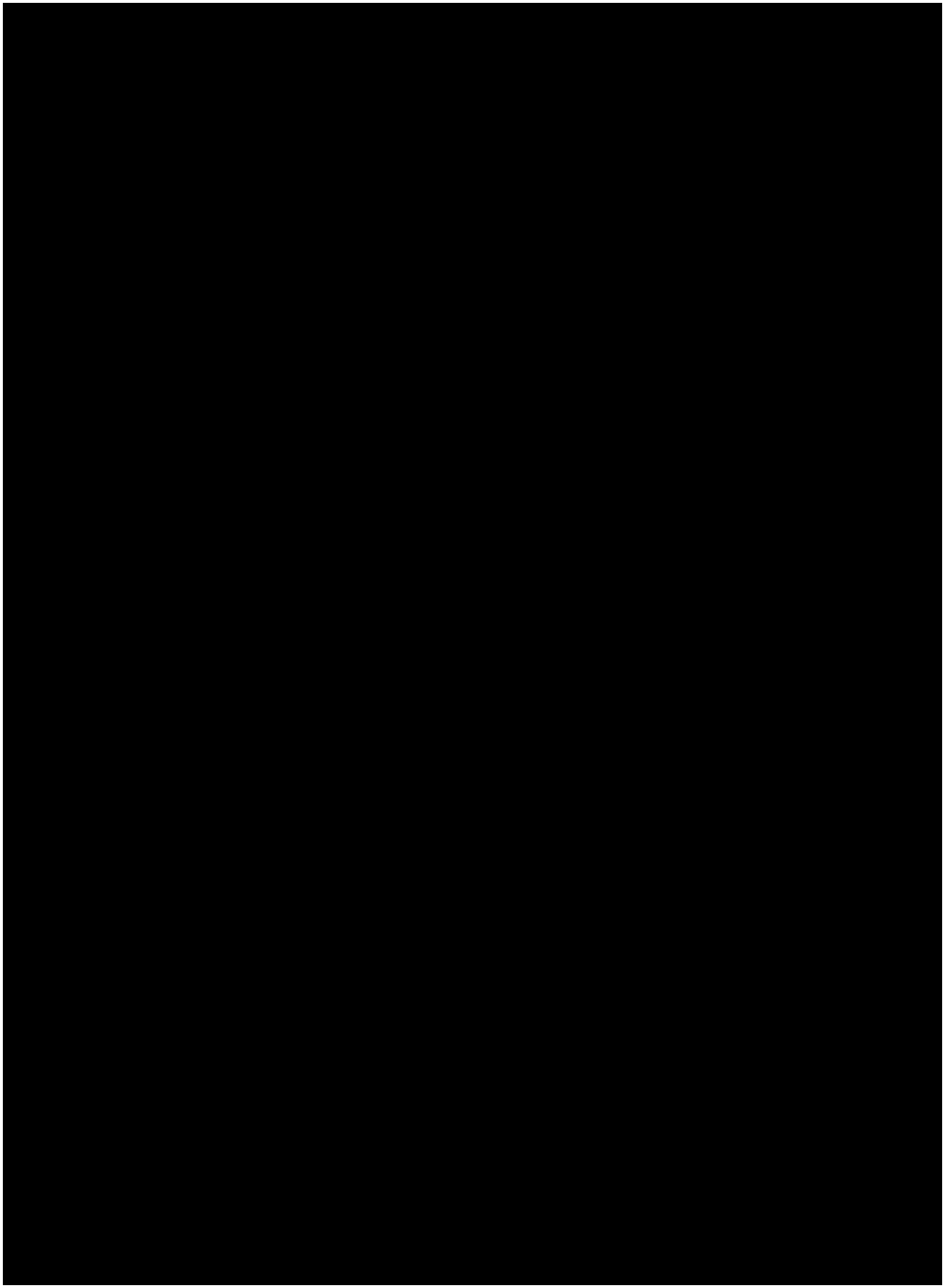

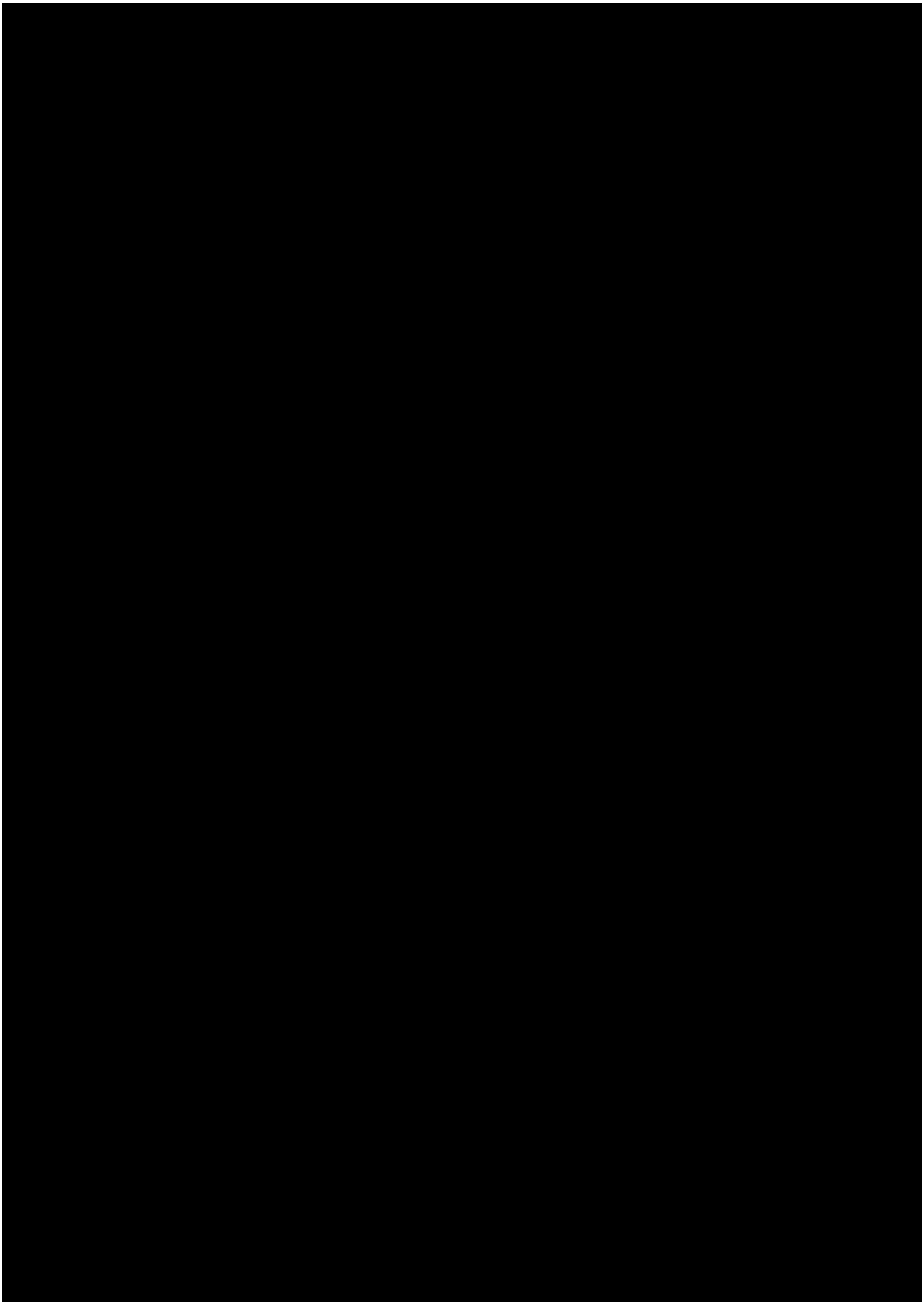

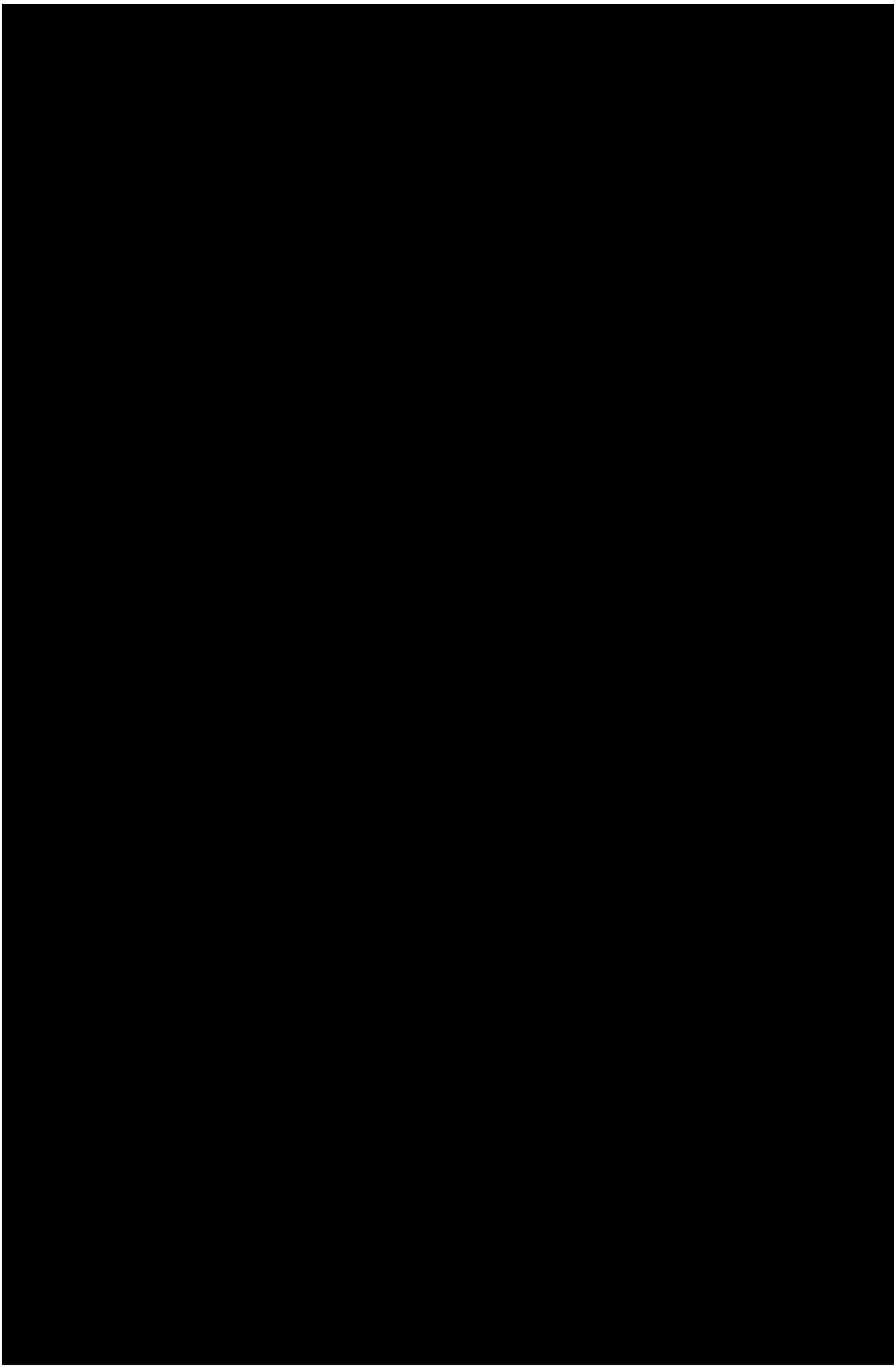

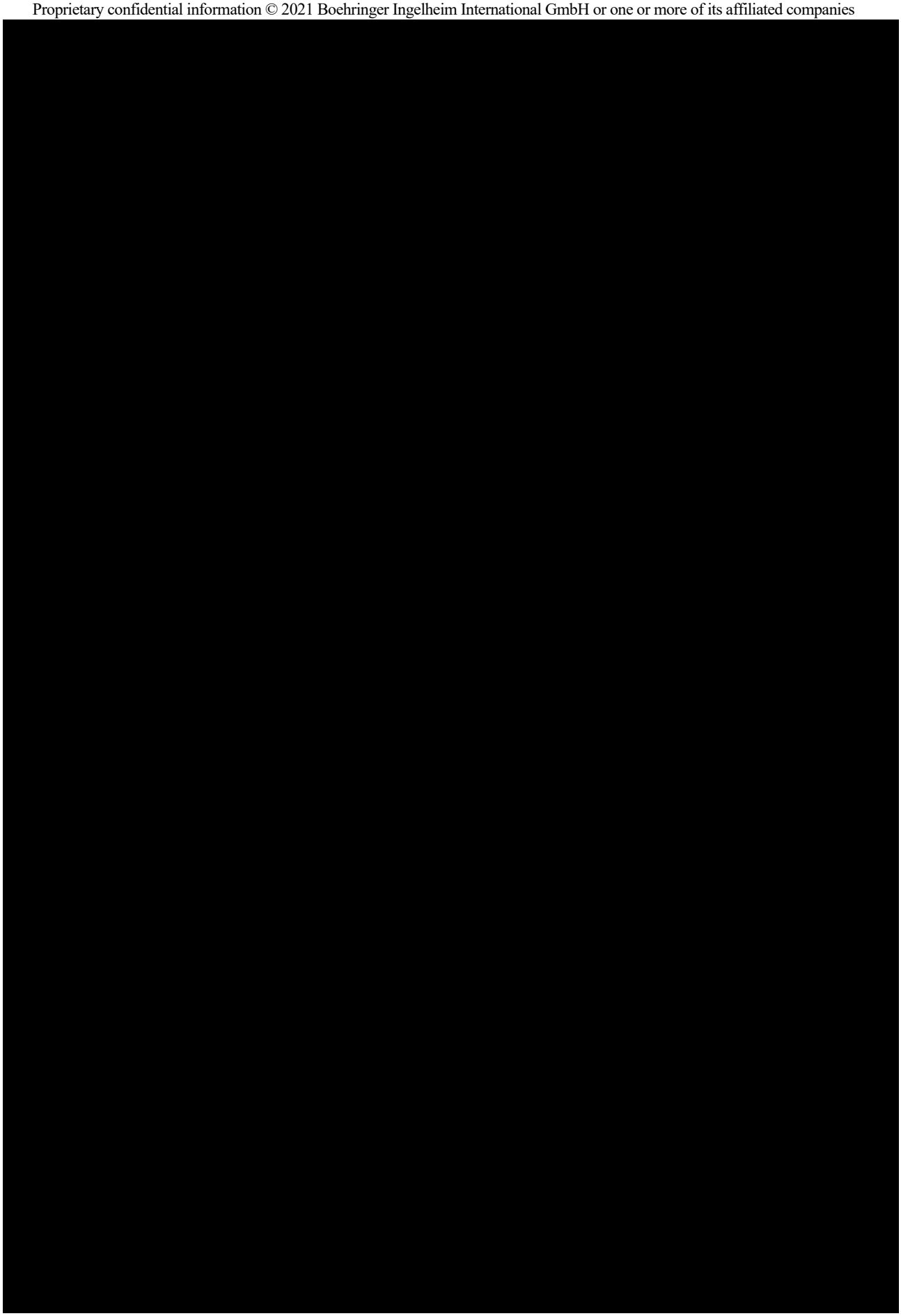

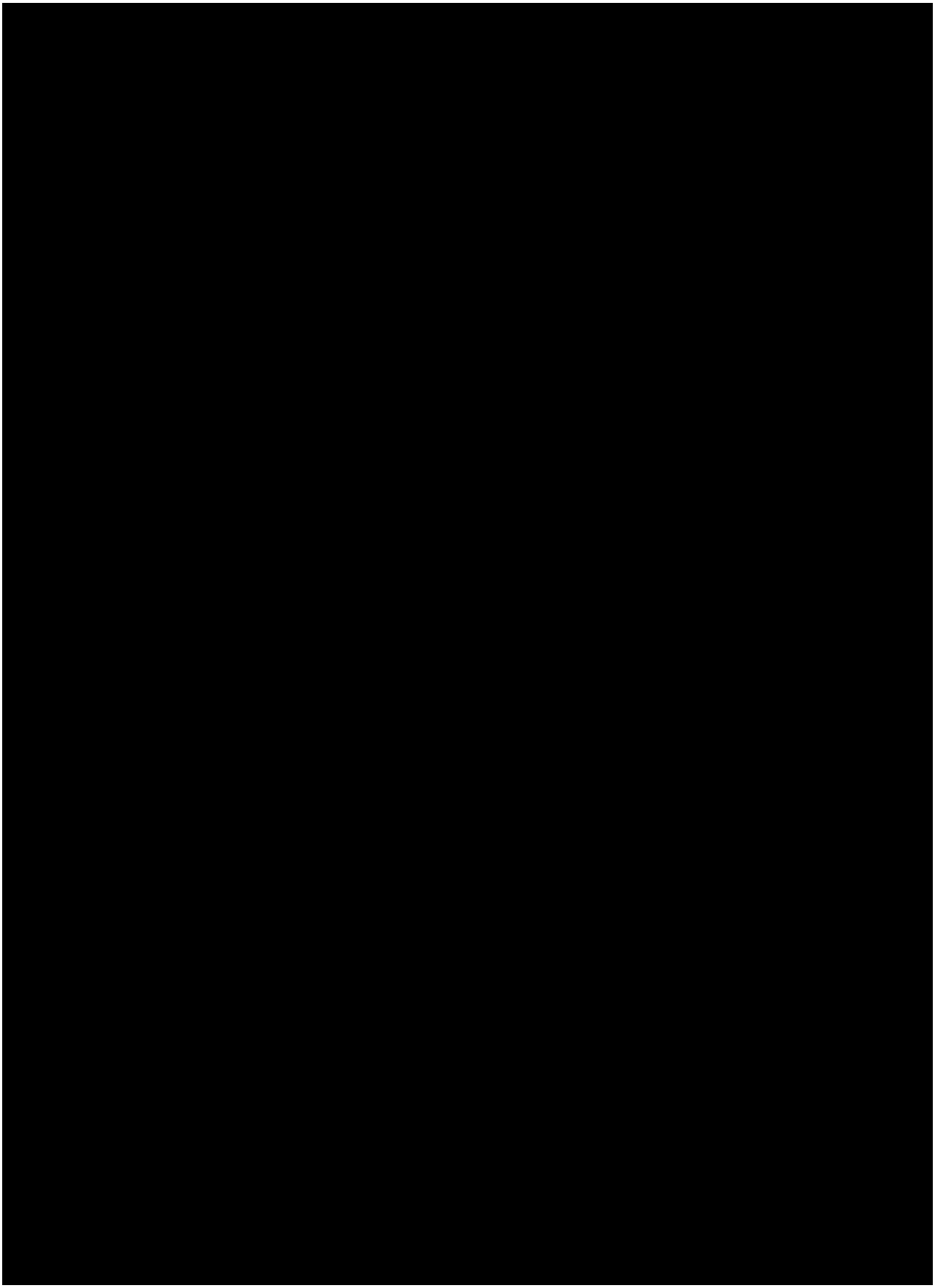

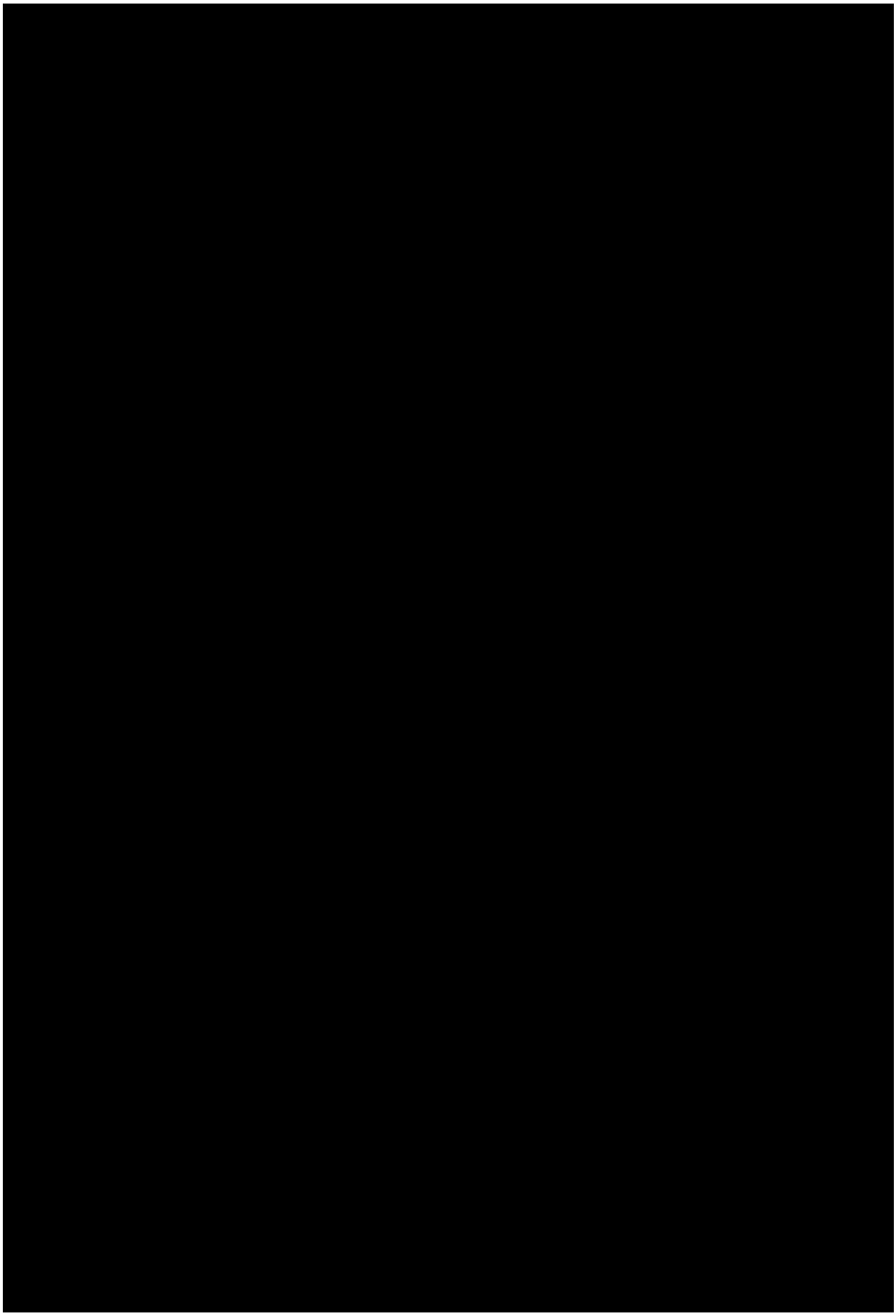

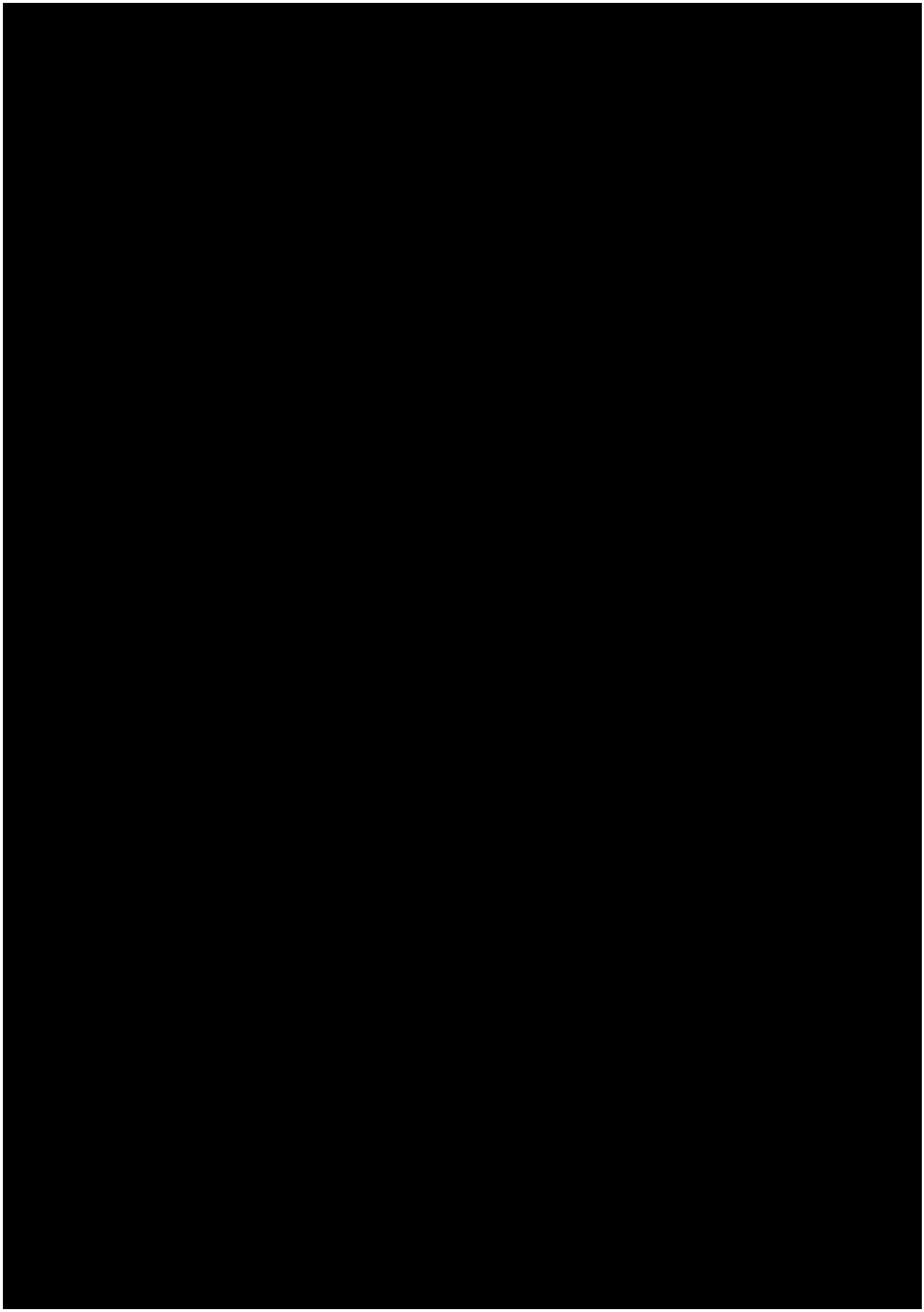

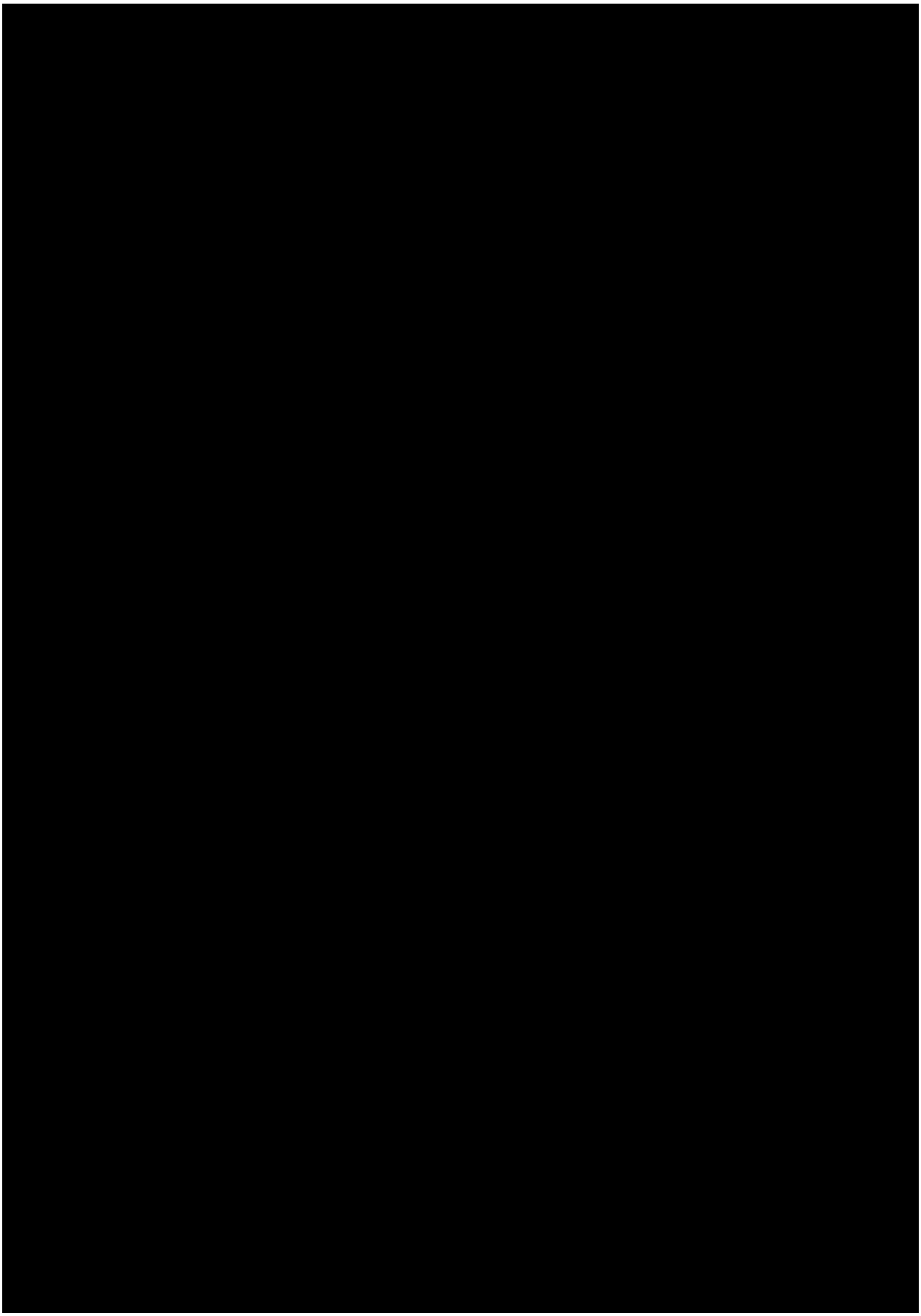

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	**18-Feb-2021**	[redacted]	None	This is the final TSAP