TRIAL STATISTICAL ANALYSIS PLAN

(Part 1 of 1368-0098)

Document No.:	**c43421787-01**
BI Trial No.:	1368-0098
Title:	Randomised, double-blind, placebo-controlled, Phase IIb/Phase III study to evaluate the efficacy and safety of spesolimab in patients with moderate to severe hidradenitis suppurativa
Investigational Product(s):	Spevigo®, spesolimab
Responsible trial statistician(s):	[redacted] Tel.: [redacted] Fax: [redacted]
Date of statistical analysis plan:	13-08-2024
Version:	1.0
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[redacted]

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2. LIST OF ABBREVIATIONS

Term	Definition / description
ADA	Anti-drug antibodies
ADS	Analysis dataset
AE	Adverse event
AESI	Adverse event of special interest
ALQ	Above the upper limit of quantification
ALT	Alanine aminotransferase
AdT	Abscess and draining tunnel
AN	Abscess and inflammatory nodule
ANdT	Abscess, inflammatory nodule and draining tunnel
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
ATC3	Anatomical-Therapeutic-Chemical classification level 3
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
BI	Boehringer Ingelheim
BLQ	Below the lower limit of quantification
BMI	Body mass index
BSA	Body surface area
CARE	Clinical data analysis and reporting environment
CGI	Clinical Global Impression
C_{max}	Maximum measured concentration of the analyte in plasma
CRF	Case report form
CRP	C-reactive protein
CTIS	Clinical Trials Information System
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Arithmetic coefficient of variation
DBLM	Database lock meeting
DNA	Deoxyribonucleic acid

Term	Definition / description
dT	Draining fistula/tunnel
EC	Estimand concept
ECG	Electrocardiogram
eCRF	Electronic case report form
EMA	European Medicines Agency
ES	Enrolled set
FACIT	Functional Assessment of Chronic Illness Therapy
FUP	Follow-up
gCV	Geometric coefficient of variation
GCP	Good Clinical Practice
gMean	Geometric mean
GPP	Generalized pustular psoriasis
HASI	HS Area and Severity Index
HS	Hidradenitis suppurativa
HS-PGA	HS Physician Global Assessment
HiSCR	Hidradenitis suppurativa clinical response
mHiSCR	Modified - Hidradenitis suppurativa clinical response
HS-CRP	High-Sensitivity C-Reactive Protein
IHS4	International Hidradenitis Suppurativa Severity Score System
IL-36	Interleukin 36
IL-36R	Interleukin 36 Receptor
NRS	numerical rating scale
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
HiS-QoL	Hidradenitis suppurativa quality of life
iPD	Important protocol deviation
ICEs	Intercurrent events
i.v.	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
DLQI	Dermatology Life Quality Index
NRI	No response imputation
OC	Observed cases

Term	Definition / description
OR	Original results
OLE	Open Label Extension
PD	Pharmacodynamic(s), protocol deviation
PE	Primary endpoint
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic parameter set
PPS	Per protocol set
PT	Preferred term
Q1	1st quartile
Q3	3rd quartile
RAGe	Report appendix generator
REP	Residual effect period
RNA	Ribonucleic acid
RPM	Report planning meeting
SAE	Serious adverse event
SD	Standard deviation
SDL	Subject data listing
SI	Système international d'unités
SOC	System organ class
TS	Treated set
TSAP	Trial statistical analysis plan
UDAEC	User-defined Adverse Event Category
ULN	Upper limit of normal range
VAS	Visual analogue scale

3. INTRODUCTION

This TSAP describes the statistical analyses for Part 1 of study 1368-0098. [redacted]

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

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

SAS® Version 9.4 will be used for all analyses.

For Part 1 (Phase IIb):
Per CTP, the primary and interim analysis for Part 1 will be conducted after the last trial participant completes the Week 8 visit and Week 16 visit respectively. Separate iDBLs will be performed for primary and interim analysis and a respective team ("shadow team") independent of the main trial team will be formed to conduct the necessary analyses and ensure to maintain the blind and restrict access to the randomization codes from the main trial team for both primary and interim analysis. Details of this process will be described in a separate data logistics plan which will also specify details on data access.

Analyses of the skin and blood biomarkers will be described in a separate biomarker SAP, unless otherwise specified in this document.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

All analyses stated in the CTP (latest version) will be performed as planned with the following adaptations.

The below further efficacy endpoints have been updated:

- Achievement of HiSCR50 at each scheduled assessment.
  HiSCR50 is defined as at least a 50% reduction from baseline in the total abscess and inflammatory nodule count, with no increase in the abscess or draining fistula count.

- Absolute change from baseline in Patient Global Impression of Change (PGI-C) score over time.
  This endpoint will be updated to:
  Patient Global Impression of Change (PGI-C) score at each scheduled assessment over time.

- Absolute change from baseline in Patient Global Impression of Severity (PGI-S) score over time.
  This endpoint will be updated to:
  Patient Global Impression of Severity (PGI-S) score at each scheduled assessment over time.

The below further efficacy endpoints, which were not specified in the CTP version 2.0, have been added:

- Achievement of HiSCR75 at each scheduled assessment.
  HiSCR75 is defined as at least a 75% reduction from baseline in the total abscess and inflammatory nodule count, with no increase in the abscess or draining fistula count.

- Achievement of HiSCR90 at each scheduled assessment.
  HiSCR90 is defined as at least a 90% reduction from baseline in the total abscess and inflammatory nodule count, with no increase in the abscess or draining fistula count.

- Achievement of mHiSCR at each scheduled assessment:
  mHiSCR is defined as at least a 50% reduction in total ANdT count relative to baseline. and at least 50% reduction in total dT count relative to baseline.

- Achievement of mHiSCR-AdT at each scheduled assessment:
  mHiSCR-AdT is defined as at least a 50% reduction in the total AdT count with no increase in inflammatory nodule count, no increase in abscess count, and no increase in dT count relative to baseline.

- Achievement of mHiSCR-AdT(2) at each scheduled assessment:
  mHiSCR-AdT (2) is defined as at least 50% reduction in the total ANdT count relative to baseline and at least 50% reduction in total AdT count relative to baseline.

- Achievement of 2 points reduction in Physician's Global Assessment (PGA) score from baseline at each scheduled assessment (only for patients with a PGA ≥ 2 at baseline).

- Achievement of at least 30% reduction from Week 1 measurement in Numerical rating scale in Patient's Global Assessment of HS pain at each scheduled assessment.

- Percent change from baseline in Numerical rating scale in Patient's Global Assessment of HS pain at each scheduled assessment

- Percent change from Week 1 in Numerical rating scale in Patient's Global Assessment of HS pain at each scheduled assessment

5. ENDPOINT(S)

5.1 PRIMARY ENDPOINT(S)

The primary endpoint of the study is defined in CTP as:

Part 1 (Phase IIb): Percent change from baseline in dT count at Week 8

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

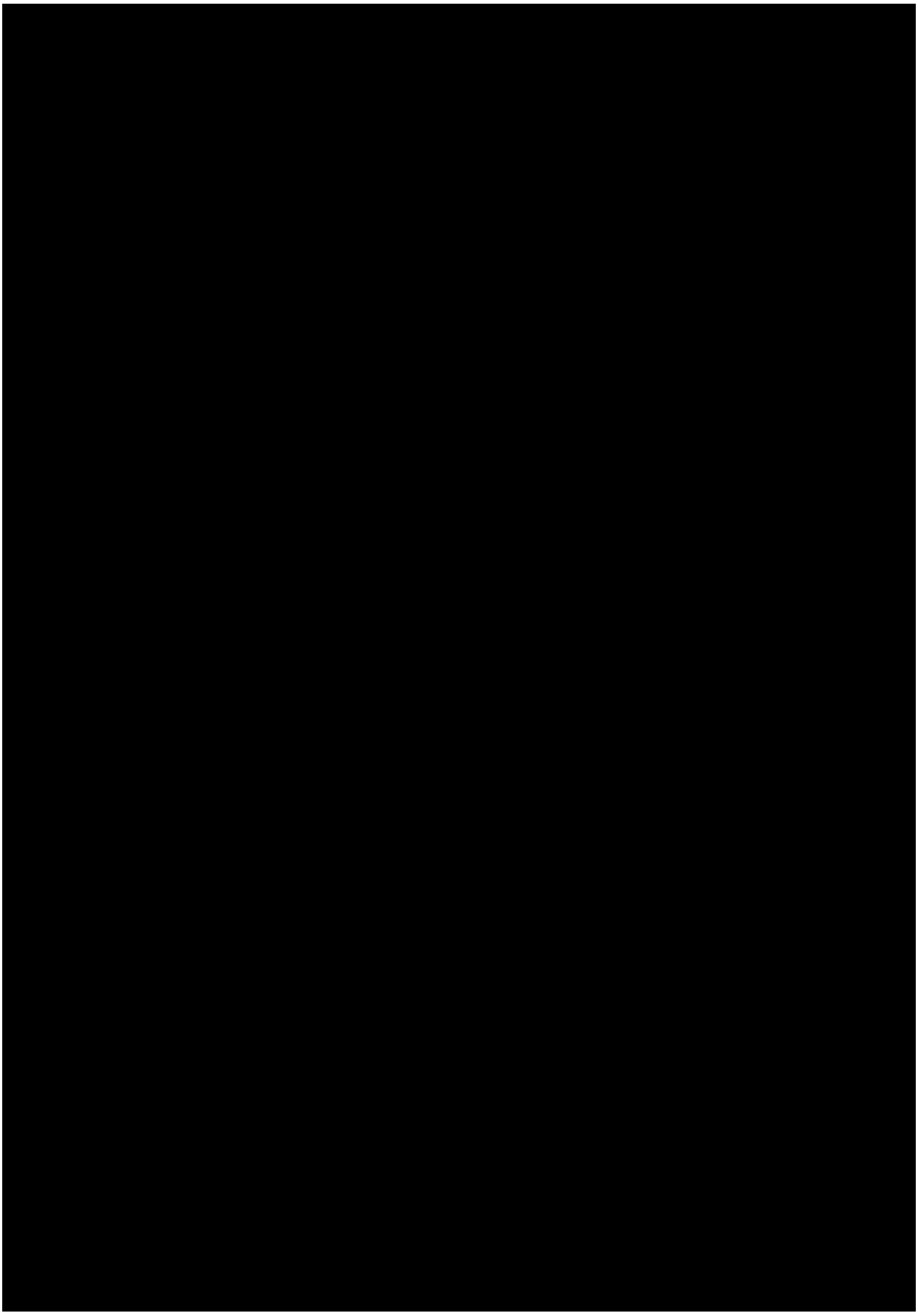
Part 1 (Phase IIb): Not applicable

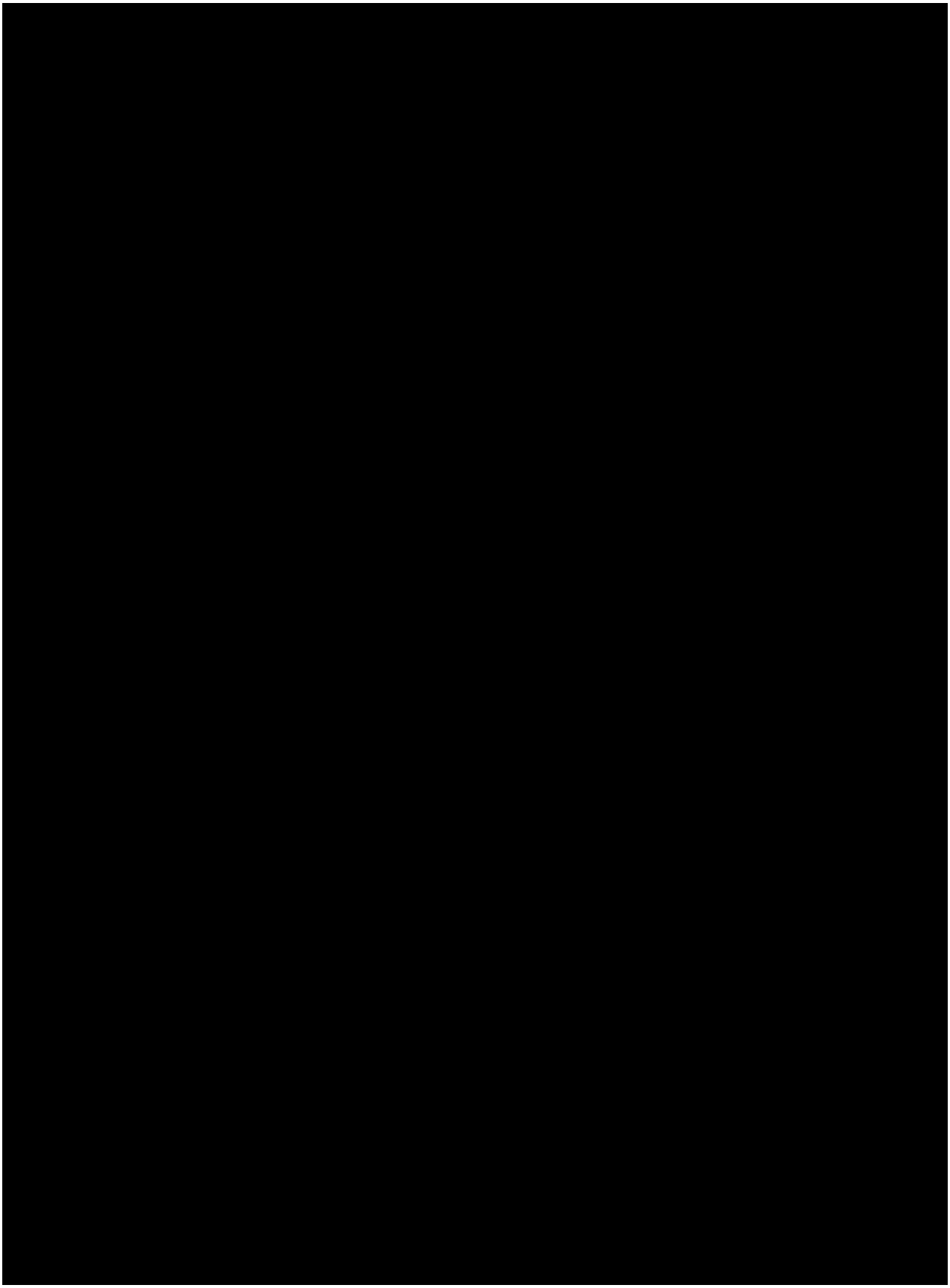
5.2.2 Secondary endpoint(s)

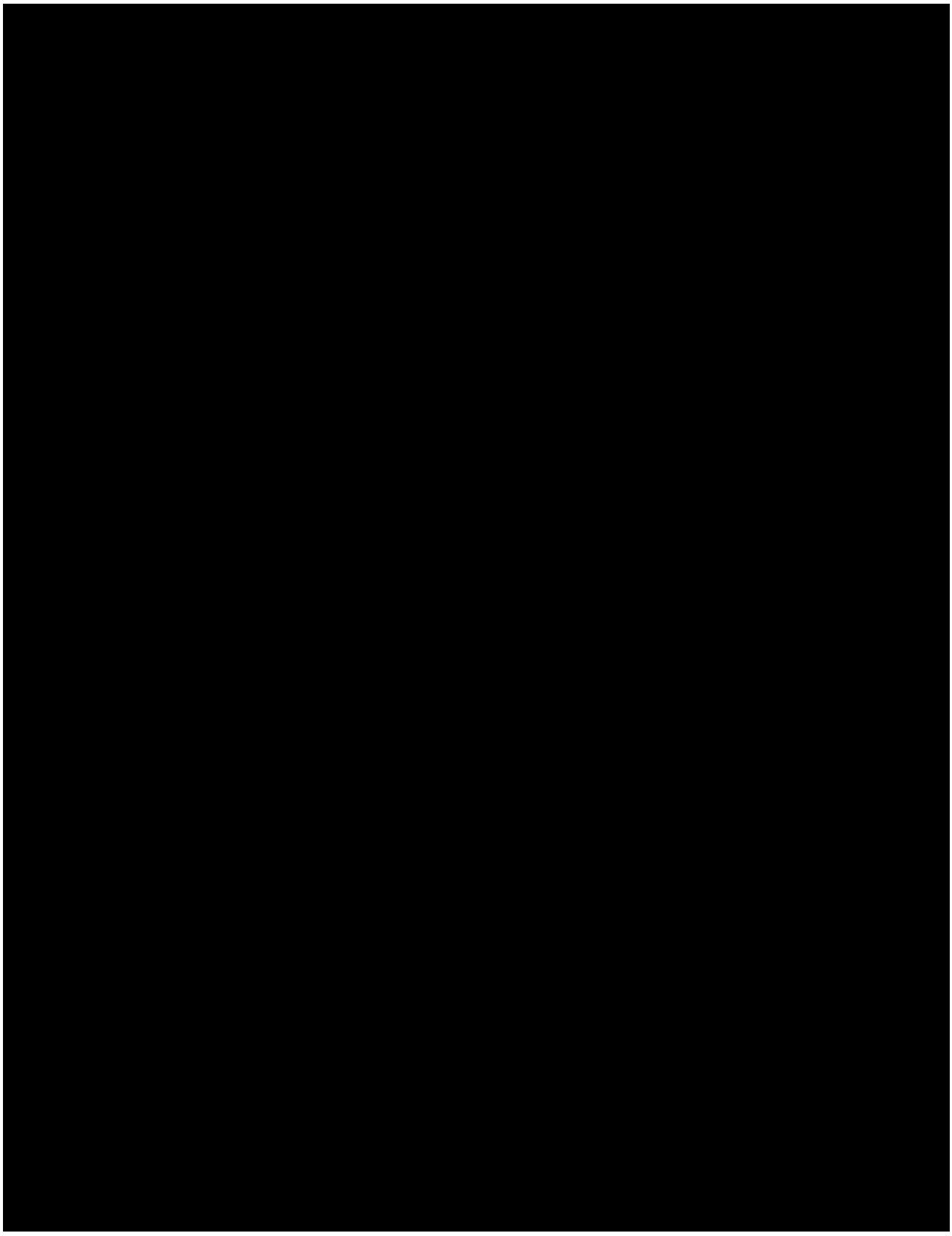
Part 1 (Phase IIb)
Efficacy

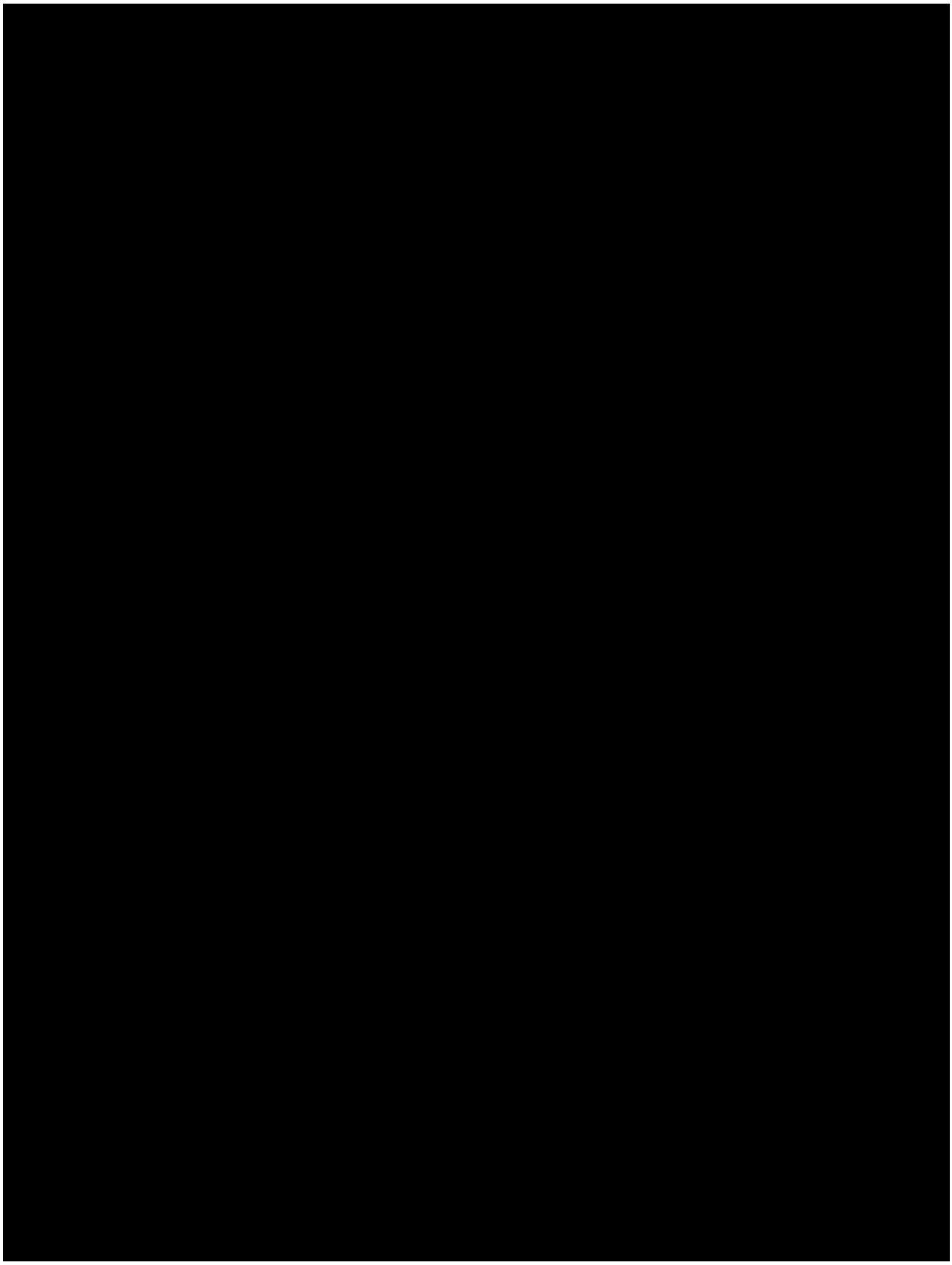
- Percent change from baseline in dT count at Week 16.
- Absolute change from baseline in IHS4 value at Week 8.
- Absolute change from baseline in IHS4 value at Week 16.

Safety
Occurrence of treatment emergent adverse events (TEAEs)









6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

Part 1 (Phase IIb)
The analysis periods are defined relative to the day of randomization (Day 1) in Table 6.1:1:

Table 6.1: 1 Flow chart of analysis periods of the study according to randomized treatment

Study analysis period	**Description**	**Start (included)**	**End (included)**
Screening period	Screening	Earliest of (Date of informed consent, first screening procedure)	Date/time of start of the first study dose minus 1 minute.
Loading period (from Day 1 to [redacted]	On-treatment period	Date/time of start of the first study loading dose (Day 1)	Earliest of i) Date/time of start of the first maintenance dose minus1 minute; ii) Date of end of last loading dose + 112 days at 11:59 p.m. if patient early discontinued study treatment before [redacted] visit; iii) last contact date on End of Study page at 11:59 p.m.
Maintenance period I (from [redacted] to Week 8)		Date/time of start of the first maintenance dose for [redacted] visit (if applicable)	Earliest of i) Date/time of start of the study maintenance dose for Week 8 visit minus 1minute; ii) Date of end of last maintenance dose + 112 days at 11:59 p.m. if patient early discontinued study treatment before Week 8 visit; iii) last contact date on End of Study page at 11:59 p.m.
Maintenance period II (from Week 8 to Week 16)		Date/time of start of the study maintenance dose for Week 8 visit (if applicable)	Earliest of i) Date/time of start of the study maintenance dose for Week 16 visit minus 1minute; ii) Date of end of last maintenance dose + 112 days at 11:59 p.m. if patient early discontinued study treatment before Week 16 visit; iii) last contact date on End of Study page at 11:59 p.m.
Maintenance period III (from Week 16 to [redacted])		Date/time of start of the study maintenance dose for Week 16 visit (if applicable)	Earliest of i) Date/time of the first treatment in OLE trial 1368.0130 minus1 minute if subject is rolled over; ii) Date of end of last maintenance dose + 112 days at 11:59 p.m. if patient early discontinued study treatment; iii) last contact date on End of Study page at 11:59 p.m.
Off-treatment phase[1] (if applicable)	Off-treatment period	Date of end of last study dose + 113 days at 0:00 a.m.	Latest of i) Date of EOS visit; ii) last contact date on End of Study page at 11:59 p.m.

Dates are defined individually per patient. If more than one date is associated with a specific visit, measurements associated with a specific date are assigned to a study analysis period according to the rules specified in the table. An analysis period will not extend beyond the start date of the following phase.
[1] The off-treatment period only exists for patients who early discontinued study treatment or choose not to enter the extension study 1368-0130, whose last contact date is after the date of end of last study treatment + 112 days.

The following labels for the treatment groups for all analysis is according to the randomized treatment up to Visit 14 (Week 16):

- **"Placebo"** (i.e. randomised to receive placebo);
- **"Speso Low"** ([redacted] [Week 16]);
- **"Speso Medium"** [redacted] [Week 16]);
- [redacted] [Week 16]);
- **"Speso Total"** (i.e. randomised to any of the spesolimab group);
- **"Overall Total"** (i.e. randomised to any treatment group regardless of placebo or Spesolimab group).

6.2 IMPORTANT PROTOCOL DEVIATIONS

Each protocol deviation must be assessed to determine whether it is an important protocol deviation(iPD). For definition of iPDs, and for the process of identification of these, refer to the BI reference document "Identify and Manage Important Protocol Deviations (iPD)" (9.6).

Handling of iPDs in analysis is included in the DV domain specifications and stored within the Trial Master File (TMF) in Electronic Document Management System (EDMS). iPDs may lead exclusion of subjects from the Per-Protocol set (PPS), which will be specified in DV domain specifications.

6.3 INTERCURRENT EVENTS

The expected intercurrent events of interest in this trial are:
Use of rescue medication
Treatment discontinuation due to AE/lack of efficacy
Treatment discontinuation due to other reasons, e.g. relocating or other logistical reasons.
Use of restricted medication
Death

The strategies for handling intercurrent events up to Week 16 visit are as follows:
- Treatment policy (ET): Use of "treatment policy" approach disregards the intercurrent event and uses the value of the variable regardless of the occurrence of the intercurrent event.
- Hypothetical approach (EH): Data after the intercurrent events will be censored.

- Composite strategy (EC): Use of composite approach, where data after the intercurrent events were treated as a non-responder.

If multiple intercurrent events occur to the same patient up to Week 16 visit, the intercurrent event with composite strategy will be considered.

Summary of intercurrent events and handling strategy for primary endpoint are listed in Table 6.3: 1.

Table 6.3: 1 Summary of intercurrent events and handling strategy for primary endpoint

Intercurrent Events	Primary Estimand (ET)	Supplementary Estimand (EH)
Use of rescue medication	ET	EH (Censor*)
Treatment discontinuation due to AE/lack of efficacy	ET	EH (Censor*)
Treatment discontinuation due to other reasons	ET	EH (Censor*)
Use of restricted medication	ET	EH (Censor*)
Death	EH	EH (Censor*)

*Data after the time when intercurrent event happens will be censored.

Summary of intercurrent events and handling strategy for **continuous secondary and further endpoints** are listed in Table 6.3: 2.

Table 6.3: 2 Summary of intercurrent events and handling strategy for continuous secondary and further endpoints

Intercurrent events	Primary Estimand (ET)
Use of rescue medication	ET
Treatment discontinuation due to AE/lack of efficacy	ET
Treatment discontinuation due to other reasons	ET
Use of restricted medication	ET
Death	EH

Summary of intercurrent events and handling strategy for **binary further endpoints** are listed in Table 6.3: 3.

Table 6.3: 3 Summary of intercurrent events and handling strategy for binary further endpoints

Intercurrent events	Primary Estimand (EC-ET)
Use of rescue medication	EC
Treatment discontinuation due to AE/lack of efficacy	ET
Treatment discontinuation due to other reasons	ET
Use of restricted medication	EC
Death	EC

Primary Imputation Approach for binary endpoints – No Response Imputation [NRI]:
- If there are data at visits both before and after the visit with a missing outcome, then impute as success only if both neighbouring visits also represent a success (independent of whether the preceding and following observations were selected for analysis based on time windows described in Section 6.7 and no rescue treatment has been given during this period).
- Otherwise, impute as a failure.

6.4 SUBJECT SETS ANALYSED

The following analysis sets will be defined for statistical analyses:
Enrolled Set (ES):
This patient set includes all patients who signed informed consent. The ES will be used for the analyses of patient disposition.

Randomized Set (RS):
This patient set includes all patients who were randomized in the trial. Treatment assignment will be as randomised. It will be used for analyses of subject for baseline demographics, disease characteristics and iPD etc.

Full Analysis Set (FAS):
This patient set includes all randomized patients and received at least one dose of study drug. This is the main analysis set for presentation of efficacy data. Patients will be analysed according to their planned treatment group.

- Full Analysis Set (FAS-Post16):
  This patient set includes all randomized patients and received at least one dose of study drug during the maintenance period III (from Week 16 to [redacted]. This is the main set for presentation of efficacy data post week 16.

Safety Analysis Set (SAF):
This subject set includes all subjects who were randomized and received at least one dose of study drug. This is the main analysis set for safety. Subjects will be analysed according to the actual treatment received at Day 1.

Per-Protocol Set (PPS):
This subject set includes all subjects in the randomized set who adhered to the CTP without any iPDs which are flagged for exclusion from the PPS. The PPS will be used for sensitivity analysis on the primary endpoint.

The discussion of all exceptional cases and problems and the decisions on the allocation of patients to populations will be made at latest at the DBLM. A separate DBLM will be performed prior to each database snapshot of this trial.

PK Parameter Analysis Set (PKS) (if applicable):
This patient set includes all patients in the RS who provide at least one evaluable observation for the Spesolimab concentration, which was not flagged for exclusion. The PKS will be used for the display of concentrations.

ADA Analysis Set:
This patient set includes all patients in the RS who provide baseline and at least one reportable post-baseline ADA data.

Biomarker Set (BMS) (if applicable):
This patient set includes all patients in the RS who have analyzable data (observed or imputed) in at least one biomarker.

Handling of Treatment Misallocations in Analysis Sets

If a subject is treated but not randomized, they will be excluded from the efficacy analysis and safety analysis by definition. However, subjects under such circumstances will be described in the final clinical trial report.

If a subject is randomized but takes incorrect treatment during the study, then:

- For efficacy analyses according to RS and PPS, they will be reported under their randomized treatment groups.
    - In the case of stratification error at randomization, the subjects will be analyzed according to the stratum to which they actually belong to (regardless of any mis-assignment to treatment based on identification of the wrong stratum from IRT), as such an error occurs before randomization and is therefore consistent with regulatory guidance.
- For the safety analysis based on SAF, the actual treatment will be used as below:

- If a subject is planned to receive administration of Spesolimab (randomized to Speso) at day 1, then patients will be reported under their randomized treatment group for safety analysis because the overall safety profile is expected to be driven by the amount of Spesolimab received in totality over the entire treatment duration. It is not expected that the safety profile will deviate from the planned treatment regimen if the subject receives only a few vials of the incorrect medication at only some dosing occasions.

- If a subject is planned to receive placebo treatment at day 1, then they will be reported under the placebo arm if they are treated and receive no vial of randomized Spesolimab. If the subject receives >= 1 vial of randomized Spesolimab before week 16, then the patient will be handled differently for efficacy analysis and safety analysis. It will keep as placebo for efficacy reporting. For safety, then the patients will be reported as their treated Spesolimab group.

Table 6.4: 1 Subject sets analyzed

	Subject Set							
Class of endpoint	ES	RS	FAS	SAF	PPS	PKS	ADA	BMS
Disposition	X							
Demographic and baseline characteristics			X					
Baseline condition / Medical history			X					
Compliance and Exposure				X				
Concomitant medication/therapy			X					
iPD		X						
Primary endpoint			X[a]		X[b]			
Secondary endpoints			X					
Further endpoints			X[c]					
Safety endpoints				X				
Concentration (if applicable)						X		
Anti-drug antibody							X	
Biomarker (if applicable)								X

a Primary analysis; b Sensitivity analysis; c FAS including FAS-post 16.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Section 7.3 of the CTP describes the handling of missing data.

Missing or incomplete AE dates are imputed according to BI standards (9.1).
Missing data and outliers of PK data are handled according to BI standards (9.2).

For incomplete information on the date of first diagnosis, time since first diagnosis will be calculated as follows:

- If the year of first diagnosis is unknown, time since first diagnosis will be set to missing.
- If day and month of the first diagnosis are unknown, time since first diagnosis will be calculated as if diagnosed on the 30th June of that year.

- If only the day of the first diagnosis is unknown, time since first diagnosis will be calculated as if diagnosed on the 15th of that month.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Unless otherwise specified, measurements reported with date and time and taken prior to start of administration of trial treatment will be considered pre-treatment values; measurements reported with a date only (and no time) and taken on the day of first administration of trial treatment will also be considered pre-treatment values. These pre-treatment values will be assigned to visits according to the nominal visit number as recorded on the eCRF or as provided by the laboratory.

Patient reported output (PRO) measurements reported prior to/on the date of the drug administration will be taken as pre-treatment values, regardless the time of measurements taken if there exist.

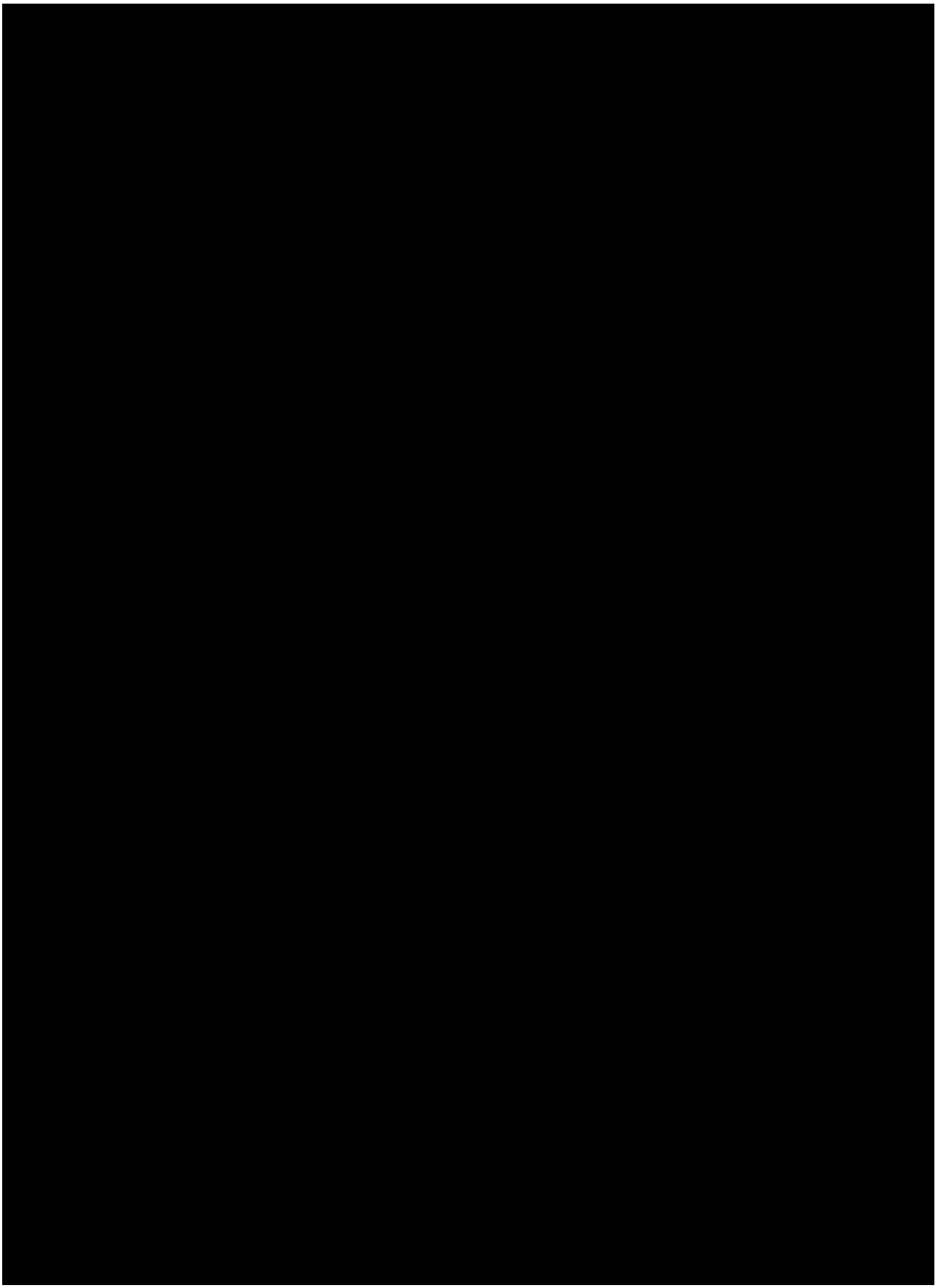
Baseline, unless otherwise specified, is defined as the last measurement collected prior to the start of administration of the trial treatment.

Measurements taken after start of administration of trial treatment will be considered either on- or off-treatment values based on the definition in Section 6.1, and will be assigned to visits for statistical analysis, if applicable, as defined below.

Analysis of AE data, potentially clinically significant abnormal laboratory values, concomitant medication or non-drug therapies, as well as use of rescue medication will not be based on visits. Frequency tables for these data will be using on-treatment data and categorized based on their occurring/starting dates. Therefore, no assignment to time windows will be necessary for such data.

The derivation of the last value, minimum value and maximum value of laboratory and vital signs data will consider all on-treatment values (whether or not selected in any time window; see Table 6.1: 1 for definition of the on-treatment period) within the period of interest; these will be derived for analysis of laboratory and vital signs data.

All other safety, efficacy and biomarker measurements will be assigned to visits based on extended time windows around the planned visit dates, defined relative to the day of first trial treatment (which is scheduled for Visit 2). These extended time windows are defined in Table 6.7: 1 and Table 6.7: 2.



7. PLANNED ANALYSIS

The primary objective for dose finding Phase IIb (Part 1) are as follows:
(1) to demonstrate a non-flat dose response curve, evaluate the quantitative treatment effect size, and evaluate the dose-response relationship based on the primary endpoint of percent change from baseline in dT count at Week 8;
(2) to determine an optimal dose candidate for Part 2 by incorporating information of available safety and of efficacy based on the primary endpoint of percent change from baseline in dT count at Week 8.

The primary and interim analysis for Part 1 will be conducted after the last trial participant completes the Week 8 visit and Week 16 visit respectively. Final trial analysis is planned to be performed at the end of the study once all randomized patients have completed the study (including any follow-up period). If applicable, details of biomarker analyses will be provided in a separate Biomarker Statistical Analysis Plan.

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

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 treatment group (unless otherwise specified, all subjects in the respective subject set regardless of whether they have non-missing values or not).

The precision for percentages should be one decimal point, unless the denominator is smaller than 100 (in all treatment columns), in which case percentages are given in integer numbers. The category missing will be displayed only if there are actually missing values.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

Descriptive statistics will be presented by treatment for demographic variables and baseline characteristics, based on the FAS. More details could refer to Section 5.4.1.

For continuous demographic variables listed in Table 7.1:1, they will be presented by the number and percentage of patients in the categories defined in Table 7.1:1.

Table 7.1: 1 Categories for demographic variables and baseline characteristics

Variable	Categories
Age	< 30 years 30 to < 65 years ≥ 65 years
Weight	≤60 kg >60 to ≤90 kg >90 kg
Weight based on popPK model #	<72kg 72 to ≤122kg >122kg
BMI	< 25 kg/m2 25 to < 30 kg/m2 ≥ 30 kg/m2
Time since first diagnosis	≤ 1 year > 1 to ≤ 5 year > 5 to ≤ 10 years > 10 years
Baseline dT count	≤ 3 ≥ 4 to ≤ 10 > 10
Neutrophil level	High > 7.23 X10^9 /L Low ≤ 7.23 X10^9 /L
Baseline neutrophil/lymphocyte ratio	1 to <=2 >2 to <=3 >3
IHS4 severity	Mild: ≤ 3 Moderate: >3 to ≤ 10 Severe: >10

The cut-off values of weight are based on the body weight values corresponding to the range of 80% to 125% of steady-state AUC0- τ (any dosing regimen) using 94 kg as a reference, according to the population PK model.

7.2 CONCOMITANT DISEASES AND MEDICATION

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

Concomitant diseases (i.e., baseline conditions) and concomitant non-drug therapies will be coded according to the most recent version of Medical Dictionary for Drug Regulatory Activities (MedDRA). Concomitant medications will be coded according to the most recent version of the World Health Organization – Drug Dictionary (WHO-DD).

Concomitant diseases which are present at start of the study will be descriptively summarized by treatment based on the FAS.

A medication/non-drug therapy will be considered concomitant to treatment, if it

- Is ongoing at the start of first study dose or
- Starts within the on-treatment period (see Section 6.1 for the definition)

A medication/non-drug therapy will be considered as prior medication/non-drug therapy, if the end date of the medication/therapy is at any time prior to the start of first study dose.

Concomitant medication use (excluding rescue medication) taken at any time during the on-treatment period (cf. Section 6.1) will be summarized by treatment based on FAS, with frequency and percentage of patients by Anatomical Therapeutic Chemical 3 (ATC3) class and preferred name.

Concomitant use of non-drug therapies (excluding rescue therapy) taken any time during the on-treatment period (cf. Section 6.1) will be summarized by treatment based on FAS, with frequency and percentage of patients.

Use of rescue medication will be summarized separately based on FAS.

7.3 TREATMENT COMPLIANCE

Only descriptive statistics are planned for this section of the report. Treatment compliance (see Section 5.4.2 for the definition and calculation) will be summarized by treatment and period on SAF using descriptive statistics (N, mean, SD, minimum, median, maximum).

7.4 PRIMARY OBJECTIVE ANALYSIS

7.4.1 Main analysis

Part 1 (Phase IIb)
The main analysis of the primary endpoint will use a treatment policy estimand. Details of handling the intercurrent events are addressed in Section 7.2.2 of the clinical trial protocol and Table 6.3.1. This main analysis of the primary efficacy endpoint will be performed on the full analysis set. Subjects will be analyzed according to the stratum to which they actually belong. Missing data will be handled using a mixed effects model with repeated measures (MMRM) under the assumption of missing at random.

The descriptions below are based on the primary objective and secondary objective, respectively.

Primary Objective: Dose Finding

For the primary endpoint analysis, first a mixed effect model for repeated measurements (MMRM) is calculated to estimate the treatment effects and the corresponding covariance matrix. Using the MCPMod approach (9.4, 9.5), these estimates are then further used to
(1) test for a non-flat dose response curve
(2) identify suitable dose-response shapes out of a selection of candidate models.

The final dose-response model is derived as a weighted average over all significant model shapes. Planned total dose before Week 8 will be used to evaluate dose response curve.

Details on both the specification of the MMRM and the MCPMod approach are given in the CTP Section 7.2.2.

MMRM analysis

The % change in dT count from baseline (Visit 2), at Visits 4, 6, 8 and 10 ([redacted], 8) will be evaluated using an MMRM accounting for the following sources of variation: fixed, categorical effects of treatment at each visit, TNFi status at baseline and categorical baseline dT count at each visit. The unstructured covariance structure will be used to model the within patient measurements. To estimate denominator degrees of freedom the Kenward-Roger approximation will be used.

SAS code for MMRM for the endpoint of dT count:

```
PROC MIXED DATA=alldat cl method=reml;
CLASS dt_base_categorical visit trt TNFi subject;
MODEL ept = TNFi visit*trt dt_base_categorical *visit/ddfm=kr s CL;
REPEATED visit / subject= subject type=un r rcorr;
LSMEANS visit*trt / pdiff=all om cl alpha=0.05 slice=visit;
RUN;
```

Results of the MMRM (N, mean, SE and 95% CI per dose group and timepoint) will be presented in tables and displayed graphically.

MCPMod Analysis

For the primary analysis the dose-response relationship will be modeled using the total doses. Here, the total is the sum of all doses administered to the patient prior to the week 8 visit including both loading and maintenance phase. Thereby, it is assumed that the cumulative concentrations over time (AUC) and thus the cumulative total dose is the key driver of the efficacy response in the modelling part of MCPMod. Table 7.4: 1 shows the calculated total doses per treatment arm.

Table 7.4: 1 Total dose per treatment arm

Treatment arm	**Total dose**
High dose regimen (Arm 1)	[redacted] Total dose: [redacted] Spesolimab
Medium dose regimen (Arm 2)	[redacted] Total dose: [redacted] Spesolimab
Low dose regimen (Arm 3)	[redacted] Total dose: [redacted] Spesolimab
Placebo (Arm 4)	Placebo at [redacted] Total dose: 0 mg Spesolimab

W: Week.

The multiple comparison procedure will then be implemented using optimal contrast tests, which control the family-wise type I error rate at a one-sided $\alpha = 0.05$. The optimal contrasts corresponding to each candidate model in the trial design stage are shown in Table 7.4: 2.

Table 7.4: 2 Contrast coefficients

	Contrast coefficients for (total) dose			
Model	Placebo	Low dose: [redacted] BI	Medium dose: [redacted] BI	High dose: [redacted] BI
Linear	0.592	0.254	-0.085	-0.761
Exponential	0.458	0.304	0.071	-0.832
Emax	0.820	-0.037	-0.293	-0.490
SigEmax	0.641	0.302	-0.307	-0.635
BetaMod	0.664	0.214	-0.692	-0.185

BI: Spesolimab total dose, i.e., sum of all loading and maintenance doses administered before week 8

For the final evaluation, these contrasts will be updated using the expected model means from the candidate set and the estimated variance-covariance matrix extracted from the MMRM model. The final contrasts will be presented in the CTR.

A non-flat dose response curve is established if at least one dose-response model is statistically significant, i.e., rejecting the null hypothesis of a flat dose-response curve

indicates a benefit of spesolimab over placebo. If a non-flat dose response is established, the statistically significant models from the above candidate set are refitted to the data without any parameter assumptions to generate new estimates for all model parameters.

The final model is derived as a weighted average over all significant model shapes. Here, the weights for each significant model (M_k) are given by

$$w(M_k) = \frac{\exp(0.5 \cdot \mathrm{AIC}(M_k))}{\sum_{i=1}^{k} \exp(0.5 \cdot \mathrm{AIC}(M_i))},$$

Where $\mathrm{AIC}(M_k)$ is the Akaike Information Criterion (AIC) of model M_k.

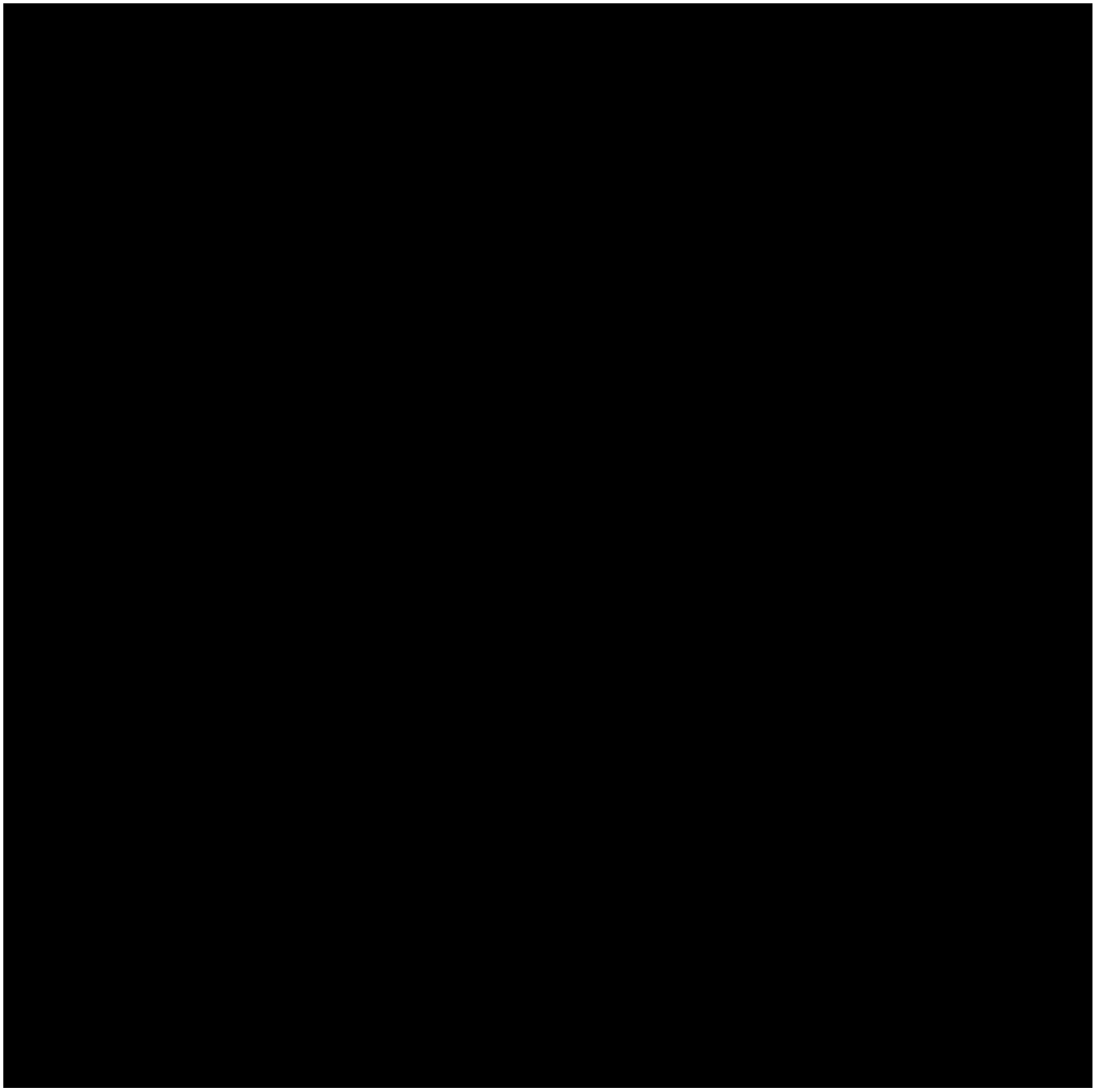
Estimates for each dose group will be calculated and final dose-response curve will be based on the final model. The confidence band for the final model will be based on parametric bootstrap approach by sampling from the multivariate normal distribution underlying the MMRM estimates and then fitting each of the models to each of these samples.

[redacted]

R code to perform the evaluations is available in Section 10.3.

The following displays are planned:
- Table of the updated contrast coefficients per dose group and candidate model, together with the MCPMod test statistics and p-values for each model and the critical value.
- For averaging model, figure of the dose-response curve and 95% confidence band for the bootstrap sampling.
- For all significant model shapes, figures of the dose-response curve plus 95% confidence band (of the predicated shape) and 95% CI per dose (estimated from MMRM).

[redacted]



7.5 SECONDARY OBJECTIVE ANALYSIS

7.5.1 Key secondary objective analysis

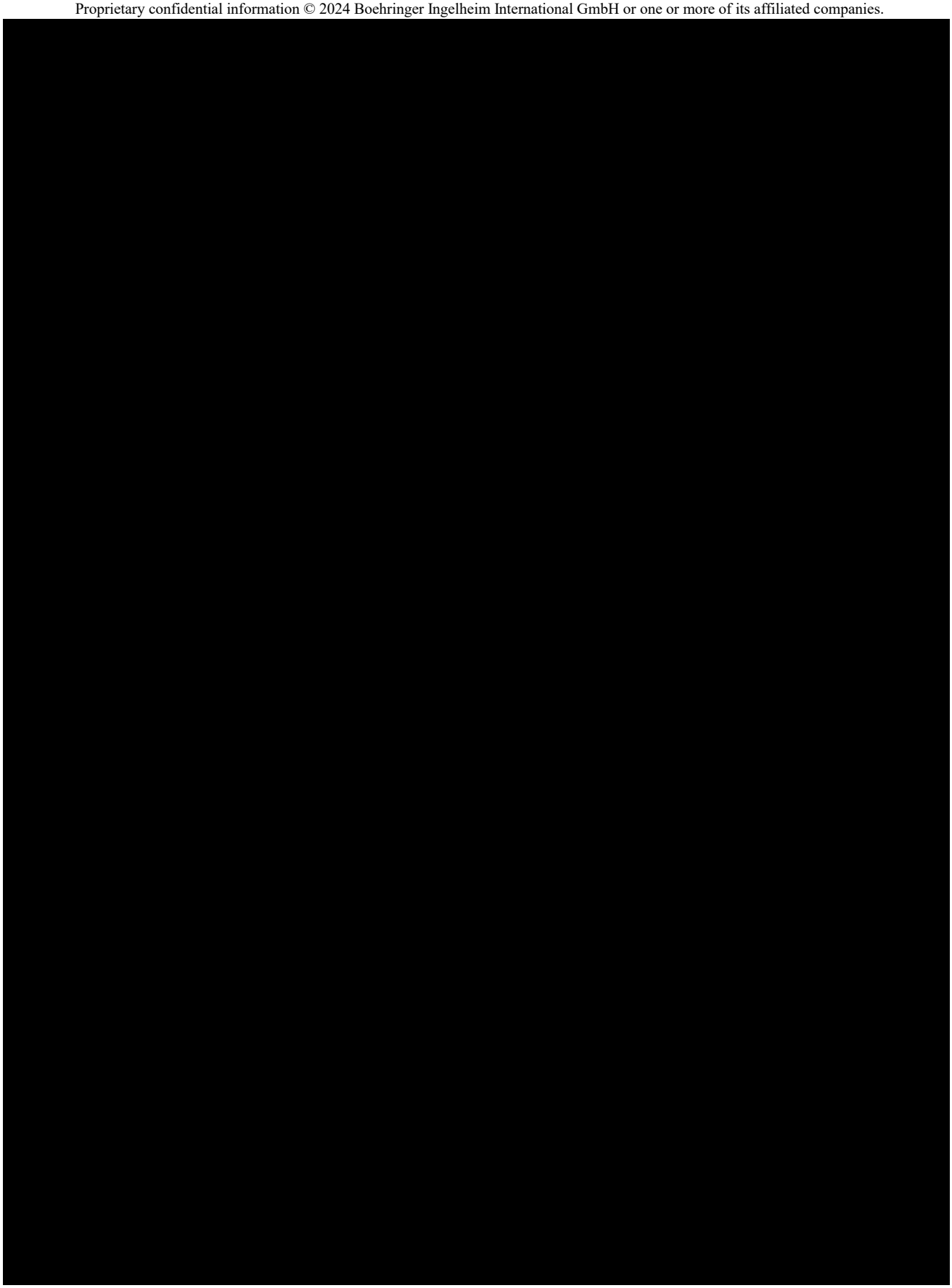
For part I, this section is not applicable as no key secondary endpoint has been specified in the protocol.

7.5.2 Secondary objective analysis

For part 1, for each of the secondary endpoint, treatment policy will be used as the primary strategy to handle intercurrent events as for the primary endpoint.

Continuous secondary endpoints
All secondary endpoints for part 1 are continuous endpoints, which will be analyzed using a MMRM approach based upon the model specification similar as described for the primary endpoint. Also, absolute change from baseline in IHS4 at week 8 is selected to use MCPMod to demonstrate a non-flat dose response curve.

SAS code for MMRM for the endpoint of IHS4:
The following SAS code will be used to calculate the MMRM.
PROC MIXED DATA=all at cl method=reml;
CLASS dt_base_categorical visit trt TNFi subject;
MODEL ept = TNFi dt_base_categorical visit*trt base*visit/ddfm=kr s CL;
REPEATED visit / subject= subject type=un r rcorr;
LSMEANS visit*trt / pdiff=all om cl alpha=**0.05** slice=visit;
RUN;



[redacted]

[redacted] week 8, week 16 and [redacted]

[redacted]

7.7 EXTENT OF EXPOSURE

The exposure to study medication will be analyzed based on SAF. The number of subjects who received a dose of trial drug will be tabulated. The amount of total dose and duration of exposure will be summarized by descriptive statistics (N, mean, SD, minimum, median, maximum) for the overall on-treatment period, the loading stage, whole maintenance stage, maintenance stage I, maintenance stage II, maintenance stage III as described in Table 6.1:1. The duration of exposure will also be summarized with the following categories:

- <= [redacted]
- > [redacted] to <= 8 weeks
- > 8 weeks to <= 16 weeks
- >16 weeks to <= [redacted]
- [redacted] to <= [redacted]
- [redacted]

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the SAF following BI standards. Data will be summarized descriptively without any imputation based on data available.

As the onset time of an AE will not be collected in the trial, any AE which occurs on the same day as a treatment dose will be assigned to the on-treatment period defined in Table 6.1:1. For safety assessments by visits, if time is not collected, data on the same day of a treatment dose will be treated to be “prior treatment” except for scheduled local tolerability and post-dose vital signs assessments.

Off-treatment data will be listed only.

7.8.1 Adverse Events

Unless otherwise specified, the analyses of AEs will be descriptive in nature, which will include all on-treatment events up to [redacted], week 8, week 16 treatment, as well as all events during the whole on-treatment period respectively. All analyses of AEs will be based on the number of subjects with AEs and NOT on the number of AEs.

AEs will be coded with the most recent version of MedDRA®. Patients will be analyzed according to the actual treatment received.

The analysis of AEs will be based on the concept of treatment emergent adverse events (TEAE). That means that all AEs occurring between first drug intake till 112 days after last drug intake will be assigned to the on-treatment period. All AEs occurring before first drug intake will be assigned to ‘screening’ and all AEs occurring after last drug intake + 112 days will be assigned to ‘follow-up’ (for listings only). For details on the treatment definition, see Table 6.1:1.

The exposure adjusted incidence rate (per 100 patient years) of a selected treatment emergent adverse event is defined as the number of patients experiencing the adverse event per

treatment group during time at risk divided by the total time of patients at risk in that treatment group to contribute the event to the analysis multiplied by 100 (per 100 patient years).

> Time at risk [patient years] = (date of onset of AE– first treatment start date within that treatment period + 1) / 365.25

If, for a patient, the selected treatment emergent adverse event didn't occur during the above defined treatment period (per Table 6.1:1) then the time at risk will be censored at the earliest of date of death, last contact date per EoS page, or the end of the above defined treatment period.

For each selected treatment emergent AE, the exposure adjusted incidence rate will be calculated as:

> Incidence rate [1/100 Patient years (pt-yrs)] = 100 * number of patients with TEAE / Total TEAE-specific time at risk [patient years].

The analyses of AEs will be descriptive in nature. Analyses of AEs will be based on the exposure adjusted incidence rates (per 100 patient years), as well as the number of patients with AEs. System organ classes (SOCs) (if applicable) will be sorted according to the standard sort order specified by the European Medicines Agency (EMA), preferred terms (PTs) (if applicable) will be sorted by total frequency (within SOC).

For further details on summarization of AE data, please refer to "Handling and summarization of adverse event data for clinical trial reports and integrated summaries" (9.8) and "Handling of missing and incomplete AE dates" (9.1).

An overall summary of AEs will be presented. This overall summary will also include summary for the class of investigator reported AESIs.

The following are considered as AESIs (see Sec 5.2.6.1 of CTP):

- Systemic hypersensitivity including infusion reaction and anaphylactic reaction
- Severe infections (according to CTCAE grading in Section 15 of the ISF)
- Opportunistic and mycobacterium tuberculosis infections
- Potential Severe Drug Induced Liver Injury (DILI)
- Peripheral neuropathy

In addition, user defined adverse event concepts (UDAEC) identified through specific search criteria will be reported separately (see Table 7.8.1:1).

Table 7.8.1: 1 Project MEDDRA search criteria for User Defined Adverse Events Concepts

User-defined AE category		Category
Hypersensitivity		
	Hypersensitivity ALL	All of the categories below
	Anaphylactic reaction, narrow	Narrow SMQ “Anaphylactic reaction”
	Angioedema, narrow	Narrow SMQ “Angioedema”
	Hypersensitivity, narrow	Narrow SMQ “Hypersensitivity”
Infections (serious/severe, opportunistic)		
	Infections 'ALL'	All of the categories below
	Opportunistic infections	Narrow SMQ "Opportunistic infections"
	Tuberculosis infections	Sub-BIcMQ “Tuberculosis related terms”, narrow BIcMQ "Infections", narrow sub-search 8.2 “Tuberculosis related terms”
	Severe infections	SOC "Infections and infestations" with AETOXGR >= 3 OR AESEV = 'Severe'. Not derived for studies where both severity variables are collected. SOC "Infections and infestations" – AEs of at least severe CTCAE grade (>= 3) or any severe events
	Serious infections	SOC “Infections and infestations” with [AECOND: AESER =1] SOC “Infections and infestations” – SAEs
Malignancies		
	Malignant tumours	Narrow sub-SMQ “Haematological malignant tumours”, Narrow sub-SMQ “Non-Haematological malignant tumours” Narrow Sub-SMQ “Malignant tumours”
	Malignant skin tumours	Broad Sub-SMQ “Skin malignant tumours”
	Skin melanomas	HLT Skin melanomas (excl. Ocular)
	Non-melanoma skin cancer (NMSC)	Broad Sub-SMQ “Skin malignant tumours” excluding HLT Skin melanomas (excl. Ocular)
	Malignancies excluding non-melanoma skin cancer (NMSC)	Sub-SMQ “Malignant tumours” excluding NMSC defined above
3 - point MACE for Monitoring		
	3-point MACE for Monitoring	BIcMQ “Major Adverse Cardiovascular Events” with Narrow sub-search 1.1 “3-point MACE (part1/2) for monitoring” Narrow sub-search 1.2 “3-point MACE (part2/2) for monitoring” and AE outcome=fatal *
Depression		
	Depression	Broad sub-SMQ "Depression (excl suicide and self-injury)"
Suicidal ideation and behavior (SIB)		
	sub-SMQ "Suicide/self-injury"	sub-SMQ "Suicide/self-injury"

User-defined AE category		Category
DRESS#		
	Narrow DRESS (Drug reaction with eosinophilia and systemic symptoms syndrome)	Narrow SMQ "Drug reaction with eosinophilia and systemic symptoms syndrome"
Peripheral Neuropathy, Narrow		
	Guillain-Barré Syndrome	Narrow SMQ “Guillain-Barré syndrome”
	Peripheral Neuropathy	Narrow SMQ “Peripheral Neuropathy”
	Demyelination	Narrow SMQ “Demyelination”

* This is achieved by retrieving all cases found either by running subsearch 1 in narrow scope (BIcMQ search ID 32019093) or subsearch 2 (BIcMQ serach ID 32019094).
# DRESS algorithmic search will be presented as a listing.

According to ICH E3 (9.9), 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.

The frequency of subjects with AEs will be summarized by treatment, primary system organ class and preferred term. AEs which were considered by the investigator to be drug related will be summarized separately. Separate tables will also be provided for subjects with SAEs, subjects with AEs leading to study drug discontinuation, subjects with AESIs, subjects with other significant AEs (derived based upon ICH E3 (9.9)), User-defined Adverse Event Concepts (UDAEC) (Table 7.8.1:1) and serious UDAEC. AEs will also be summarized by maximum intensity based on the CTCAE grading system.

For disclosure of AE data on ClinicalTrials.gov, the frequency of subjects with non-serious AEs occurring with an incidence of greater than 5% (in preferred terms) will be summarized by treatment, primary system organ class and preferred term. The frequency of subjects with SAEs will also be summarized.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (9.3). The up to Week 16 and overall on-treatment period for laboratory analyses will be provided. Note that data from the central laboratory will be used for all displays described below, unless otherwise specified.

For continuous safety laboratory parameters, normalized values will be derived.

Normalization means transformation to a standard unit and to a standard reference range. The process of normalization, handling of repeat values at the same visit for by-visit displays, as well as standard analyses for safety laboratory data are described in the BI guidance for the Display and Analysis of Laboratory Data. All analyses considering multiple times of the ULN (as described below) will be based on standardized and not normalized values. For continuous

safety laboratory parameters, differences to baseline will be calculated. For all outputs, the last assessment before the first treatment at Day 1 is chosen as the baseline value.

Only patients with at least one available post-baseline value will be included in the analysis of an individual laboratory parameter. All individual laboratory data will be listed. Values outside the reference range will be flagged.

For derivation of the last value, the minimum value, and the maximum value, all values during the on-treatment period will be considered. These will be derived for analysis of laboratory, vital signs and local tolerability data. For identification of potentially clinically significant abnormal laboratory values, all values during on-treatment period will also be considered.

Descriptive statistics of laboratory values over time and for the difference from baseline on-treatment will be based upon normalized values, including summaries of the last value on treatment, the minimum value on treatment and the maximum value on treatment and corresponding change from baseline. Graphical displays via box plots/line plots will be produced for the last value, minimum and maximum value on treatment for each continuous laboratory endpoint.

Laboratory values will be compared to their reference ranges; shift tables will be provided for the number of patients with a specific CTCAE grade at baseline versus the CTCAE grade at the last measurement on treatment, as well as the worst grade on treatment; laboratory parameters with exception to this display type are described in the company standards (9.10). These analyses will be based on converted laboratory values. The display of laboratory data using the CTCAE grades will be done based on BI standards (9.10).

Potentially clinically significant abnormalities will be identified based on BI standard rules which are based on converted lab values, i.e. using SI units. These rules will be listed in the SDL appendix of the CTR. Frequency tables will summarize the number of patients with potentially clinically significant abnormalities. Patients having an abnormal lab value at baseline will be presented separately. A separate listing will present potentially clinically significant abnormal lab values; for each functional lab group all patient's lab values will be listed, if there exists at least one lab value with clinically significant abnormality within the group.

The frequency of patients with AST or ALT elevations $\geqslant$ 3xULN, $\geq$ 5xULN, $\geq$ 10xULN, and $\geq$ 20xULN will be displayed based on standardized laboratory values. To support analyses of liver related adverse drug effects, the frequency of subjects with AST and/or ALT $\geq$ 3xULN combined with the elevation of total bilirubin $\geq$ 2xULN, from samples drawn within 30 days of each other, will be displayed, stratified by alkaline phosphatase < 2xULN and $\geq$ 2xULN (a subject can potentially be in both alkaline phosphatase strata in case of multiple AST/ALT and bilirubin elevations). The start of the 30-day time span is triggered by each liver enzyme elevation above the defined thresholds. This analysis will be based on standardized laboratory values.

A graphical analysis of ALT and total bilirubin will be performed: the so-called eDISH plot. The peak total bilirubin is presented as a fold increase over the ULN against the peak ALT as a fold increase over the ULN, on a log10 scale. The measurements displayed for total bilirubin and ALT may, or may not, occur on the same date. Two reference lines, 2xULN for total bilirubin and 3xULN for ALT, are drawn onto the graph to divide the plane into four quadrants. Normal cases are in the lower left quadrant, potential DILI cases are in the upper right quadrant (potential Hy's Law quadrant), while the lower right quadrant is known as the Temple's corollary range (ALT ≥ 3xULN and total bilirubin < 2xULN). The display will be repeated for AST and total bilirubin.

The frequency of subjects with AST and/or ALT ≥ 3xULN combined with the elevation of INR ≥ 1.5xULN, from samples drawn within 30 days of each other, will be displayed. The start of the 30-day time span is triggered by each liver enzyme elevation above the defined thresholds. This analysis will be based on standardized laboratory values.

A graphical analysis of ALT and INR will be performed. The peak INR is presented as a fold increase over the ULN against the peak ALT as a fold increase over the ULN, on a log10 scale. The measurements displayed for INR and ALT may, or may not, occur on the same date. Two reference lines, 1.5xULN for INR and 3xULN for ALT, are drawn onto the graph to divide the plane into four quadrants for better visual representation; normal cases are in the lower left quadrant. The display will be repeated for AST and INR.

An additional display will be produced for the frequency of patients with an elevation of the ALT and/or AST ≥ 3-fold ULN, and with the appearance of one or more of the following TEAE:

- Fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

An occurrence is flagged if, within +/- 7 days of the onset of an AST and/or ALT elevation ≥ 3-fold ULN (including events which start or are ongoing through this interval [i.e., including also assessment on the AE stop in addition to the start date]), at least one of the following TEAE terms (excluding PT terms on the secondary path) is observed:

- ADAE.AEHLT = "Gastrointestinal and abdominal pains (excl oral and throat)";
- ADAE.AEDECOD in ("Vomiting","Fatigue","Nausea","Pyrexia", "Right upper quadrant pain", "Abdominal pain upper", "Upper abdominal tenderness");
- ADAE.CQ16NAM = "Skin Rash (BIcMQ narrow);

An occurrence is also flagged if a >5% proportion in the ratio of eosinophils to total white blood cells is observed in the same sample as the detected AST/ALT elevation.

Clinically relevant findings in laboratory data will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator, and will be analyzed as such.

7.8.3 Vital signs

Descriptive statistics and graphical display are planned for this section of the report.

The analyses of vital signs (blood pressure, pulse rate, body temperature, respiratory rate) will be descriptive in nature. Descriptive statistics of vital signs over time and for the difference from baseline (see Section 6.7) will be provided, including the last value, the minimum value and the maximum value during on-treatment period.

Clinically relevant findings in vital signs data will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator, and will be analyzed as such.

7.8.4 ECG

Abnormal findings in 12-lead ECG will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator, and will be analyzed as such.

7.8.5 Local Tolerability

Local tolerability will be summarized during on-treatment period and by visit, with the frequency and percentage of patients who experienced any symptoms by severity/intensity.

7.8.6 Acne Episodes

In the final analysis, the occurrence and characteristics of historical acne episodes will be summarised by treatment with frequency and percentage of patients. The characteristics of any acne episodes which occur during the treatment period will be displayed overall; separate displays of the characteristics of those acne episodes which had a) a suspected medical history risk factor, b) a suspected concomitant medication risk factor, and c) a relatedness to spesolimab, will also be presented. If only few records for the acne episodes, listings will be provided instead of summary tables.

7.9 OTHER ANALYSIS

7.9.1 Biomarker analyses

The following biomarkers will be analysed and reported as a part of the CTR:

- [redacted]

For the analysis of [redacted] values below the lower limit of quantification (LLOQ) or above the upper limit of quantification (ULOQ) will be handled as follows:

Values < LLOQ and values > ULOQ that are reported as numerical values, will be kept as such. Entries reported as text (i.e. "< LLOQ" or "> ULOQ") and for which no value is provided, will be replaced by:

- For < LLOQ: 0.5*LLOQ
- For > ULOQ: ULOQ.

Results on other biomarkers (e.g. [redacted] of the data. In case they are reported outside the CTR the analysis will be defined in a separate document (otherwise the analysis will be described in the CTR).

For the analysis of biomarkers, log transformed data will be used where deemed necessary.

7.9.2 PK / PD analyses

No PK parameters will be calculated.

The descriptive analysis of Spesolimab plasma concentrations will be based on the SAF.

Exclusion of PK concentrations

The ADS ADPC (PK concentrations per time-point or per time-interval) contains column variables ACEXC or ACEXCO indicating inclusion/exclusion (ACEXC) of a concentration and an analysis flag comment (ACEXCO). Exclusion of a concentration depends on the analysis flag comment ACEXCO. For example, if ACEXCO is set to 'ALL CALC', the value will be excluded for all types of analyses based on concentrations. If ACEXCO is set to 'DESC STATS' the value will be excluded from descriptive evaluations per planned time point/time interval. If ACEXCO contains the addition 'TIME VIOLATION' or 'TIME DEVIATION' the value can be used for further analyses based on actual times.

Further details are given in (9.7). No formal analysis of pharmacokinetic/pharmacodynamic relationships is planned. [redacted]

Any further exploratory analyses, if done, will be described in the CTR or in a separate report.

7.9.3 Immunogenicity

The ADA status and titer as well as frequency of patients with ADA to Spesolimab will be presented by visit. Descriptive statistics of ADA titer (for ADA positive patients, when available) will be provided by visit. The number of subjects with ADA status positive/negative at any time will also be presented. ADA parameters (e.g. treatment-induced ADA positive subjects, transient ADA response and persistent ADA response) will also be presented by visit and cumulatively for the overall study duration. Further exploratory assessments of the ADA data will be performed once data is available and these will be described, if done, in the CTR.

Further analyses based on ADA data may be performed such as

- efficacy-based subgroup analysis for selected subgroups in Table 6.5: 1 for the following groups
  - ADA positive and ADA negative subjects (at Week 8 and Week 16 visit), or
  - NAb positive and NAb negative subjects (at Week 8 and Week 16 visit)
- Safety-based subgroup analysis (using e.g. hypersensitivity safety events) for the following groups
  - ADA positive and ADA negative subjects (at any time), or
  - NAb positive and NAb negative subjects (at any time), or

before ADA development (including subjects with events either before their first ADA positive sample or without ADA positive sample throughout) and after ADA development (including subjects with events from the time point of their first ADA positive sample onwards). This approach takes into account the time when ADA actually developed and when the safety event occurred in relationship to ADA.

8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

The treatment information will be released for interim analysis according to the details specified in the logistics plan.

Once the last patient has completed their *End-of-Treatment (EOT) visit* and all corresponding data has been entered and cleaned to the level documented in the "Data Delivery Request" (DDR) form, the data will be declared ready to be unblinded via the "Data Ready to be Unblinded and/or Final Trial Closure Notification" (RUN) form. Then the treatment information will be released for analysis.

The data col*lection for the off-treatment residual effect period un*til the End-of-Study (EoS) / Follow-Up visit will continue into the unblinded trial database. Once trial data collection has been completed and all data has been entered and cleaned as documented on the RUN form, a final data lock will be performed.

After the release of treatment information, it is expected that only trial data related to the off-treatment residual effect period will be entered and changed. Therefore, after the timepoint of release of treatment information, all changes affecting trial data up to the End-of-Treatment (EoT) visit will be documented and summarized in the CTR.

9. REFERENCES

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9.2	*BI-KMED-TMCP-HTG-0025:* "How to Guide: Standards and Processes for Analyses Performed within Clinical Pharmacokinetics/Pharmacodynamics", current version, KMED.
9.3	*BI-KMED-BDS-HTG-0042*: "How to Guide: Handling, Display and Analysis of Laboratory Data", current version, KMED.
9.4	*Pinheiro J, Bornkamp B, Bretz F.* Design and analysis of dose-finding studies combining multiple comparisons and modelling procedures. J Biopharm Stat 16 (5), 639-656 (2006).
9.5	*Pinheiro J, Bornkamp B, Glimm E, Bretz F.* Model-based dose finding under model uncertainty using general parametric models. Stat Med 33 (10), 1646 – 1661 (2014).
9.6	*BI-VQD-12045_40-413:* "Identify and Manage Important Protocol Deviations (iPD) ", current version, group / owning department "Med Clinical Development & Operations", DMS for controlled documents.
9.7	*001-MCS-36-472_RD-01:* "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies", current version; IDEA for CON.
9.8	*001-MCG-156:* "Handling and summarisation of adverse event data for clinical trial reports and integrated summaries", current version; IDEA for CON
9.9	*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.
9.10	*BI-KMED-BDS-HTG-0036*: "How to Guide: CTCAE Grading for Laboratory Values", current version, KMED.
9.11	*Heinze G, Schemper M.* A solution to the problem of separation in logistic regression. Statistics in Medicine 21: 2409-2419 (2002).
9.12	*Firth D.* Bias reduction of maximum likelihood estimates. Biometrika 80, 27–38 (1993)
9.13	*Greenland S, Robins M.* Estimation of a common effect parameter from sparse follow-up data, Biometrics 41, 55-68, 1985
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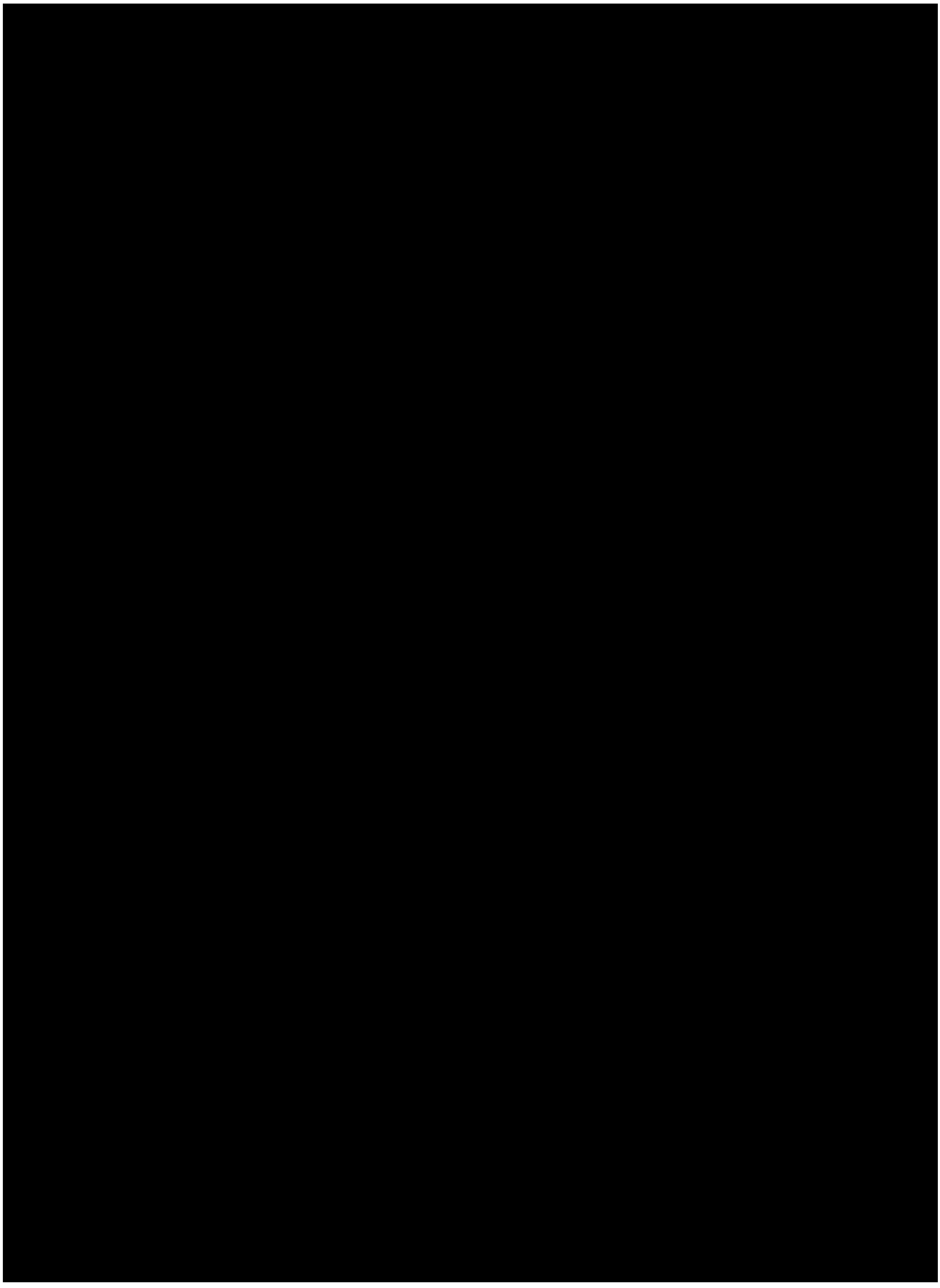
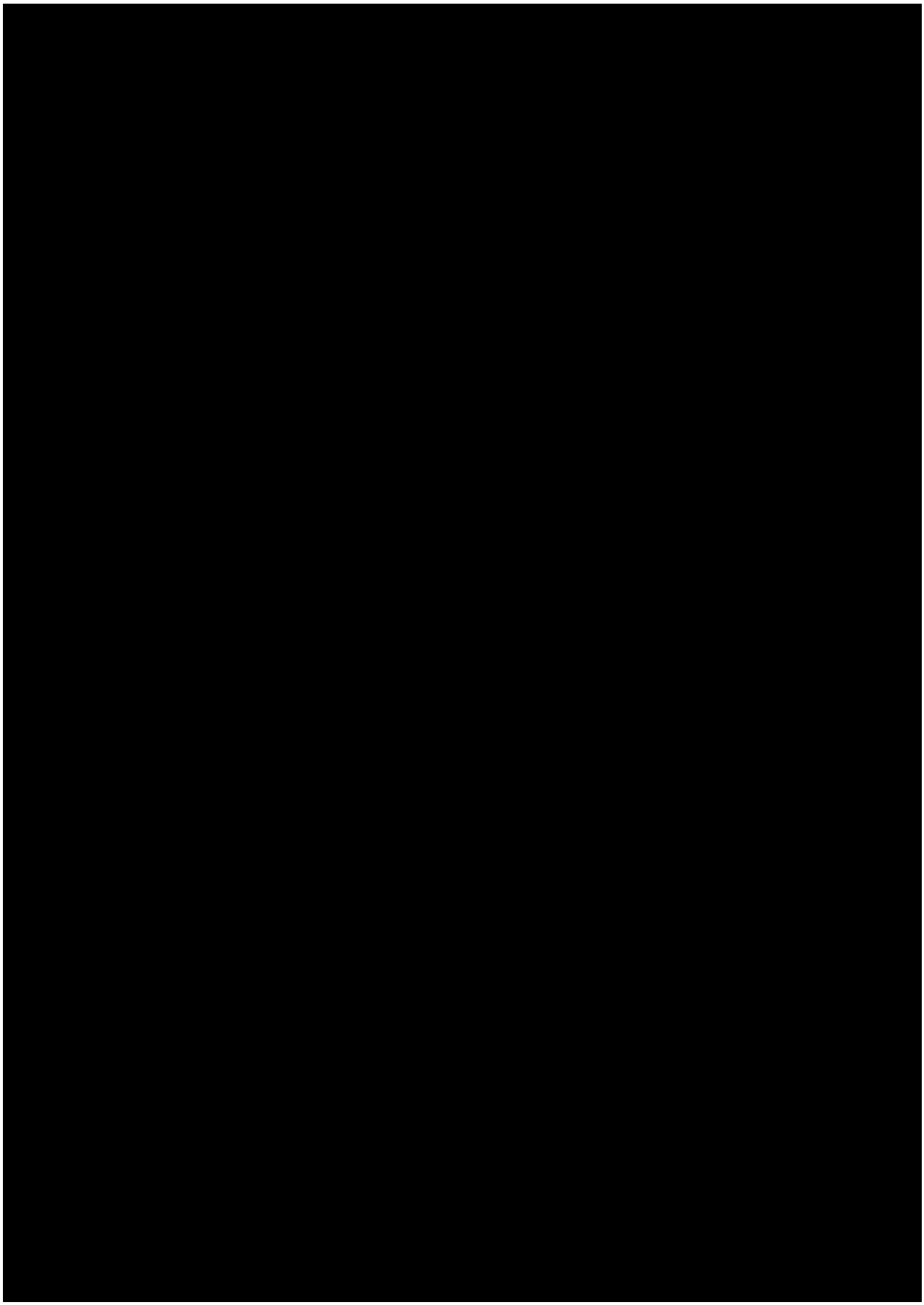
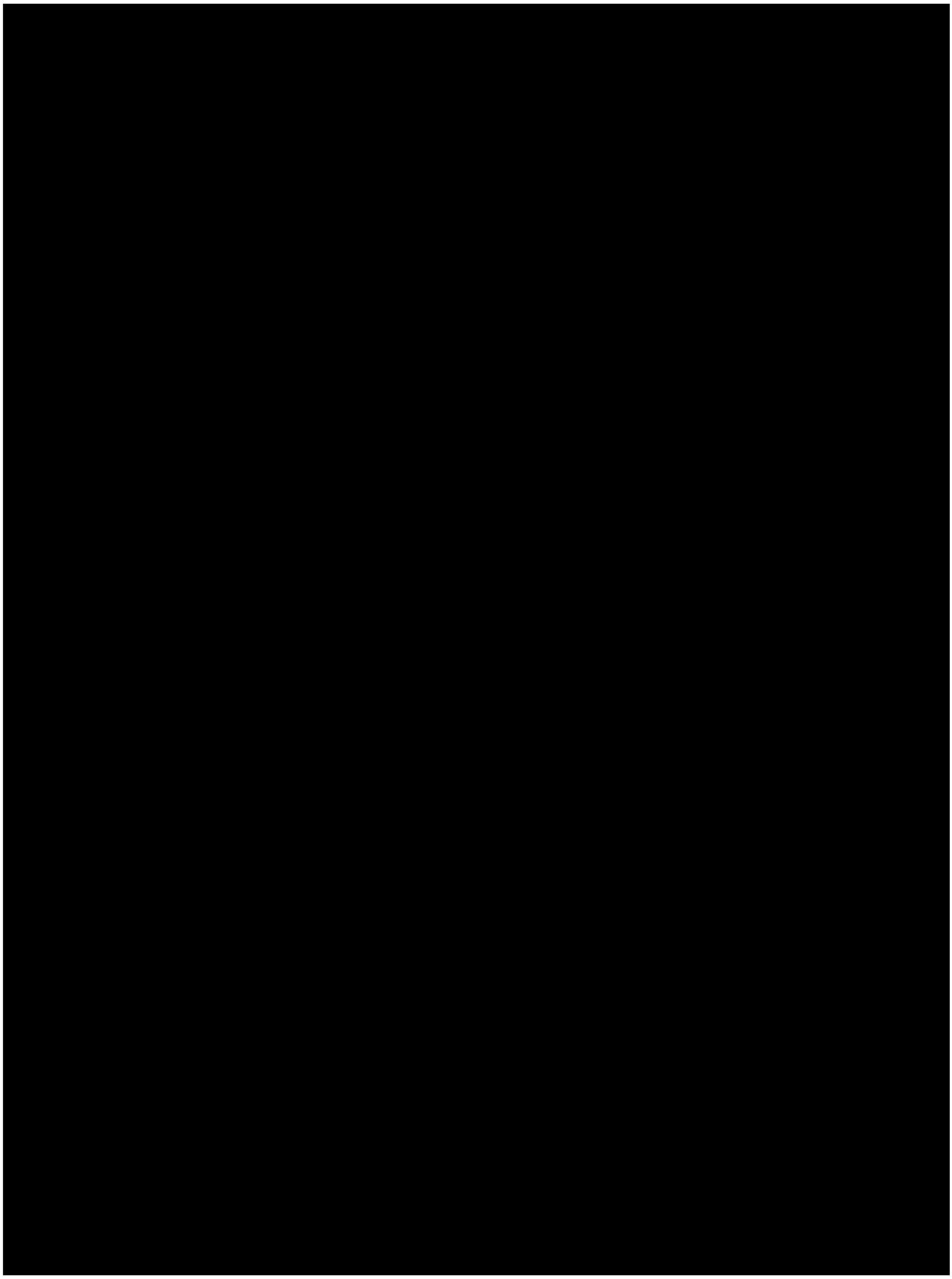
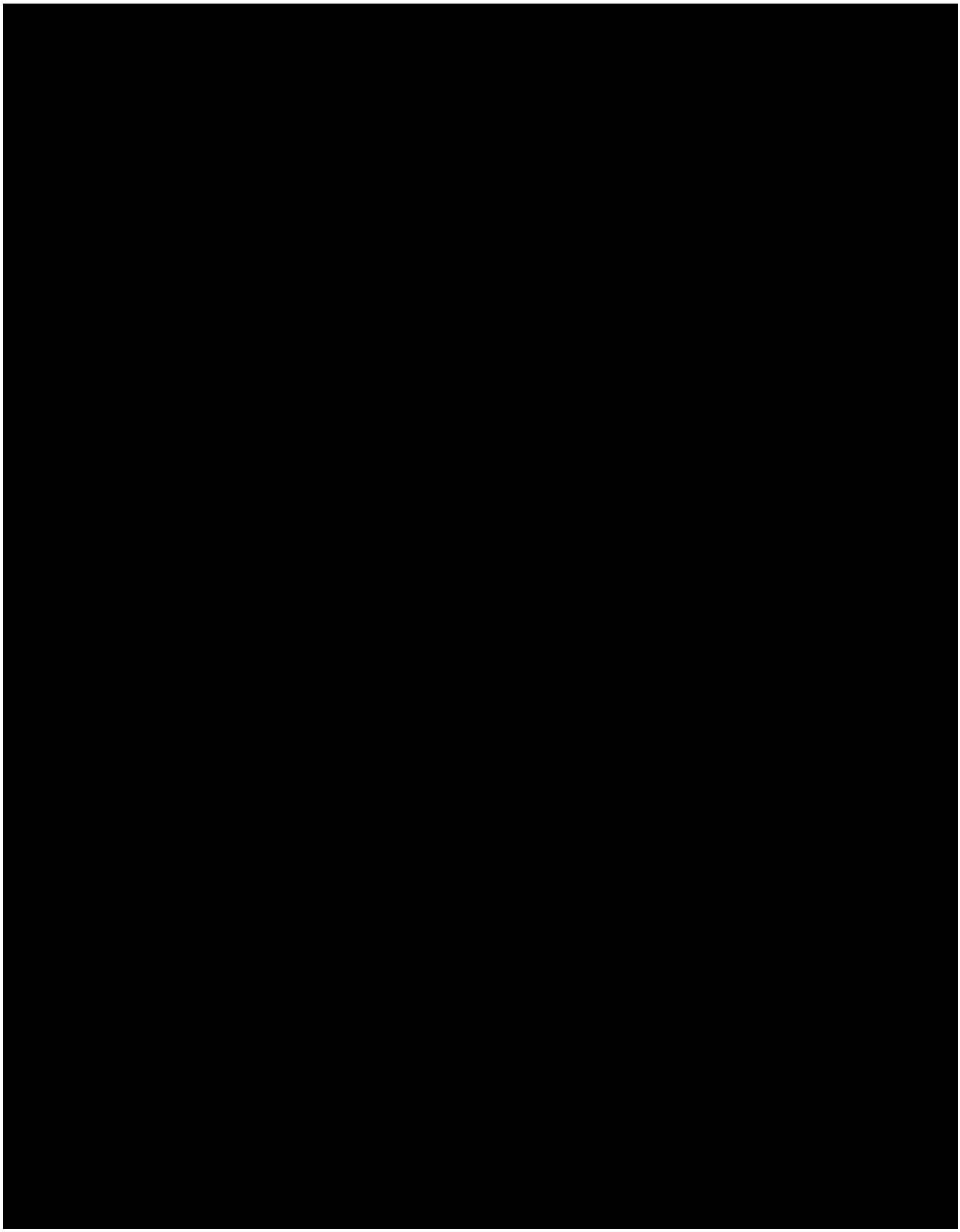
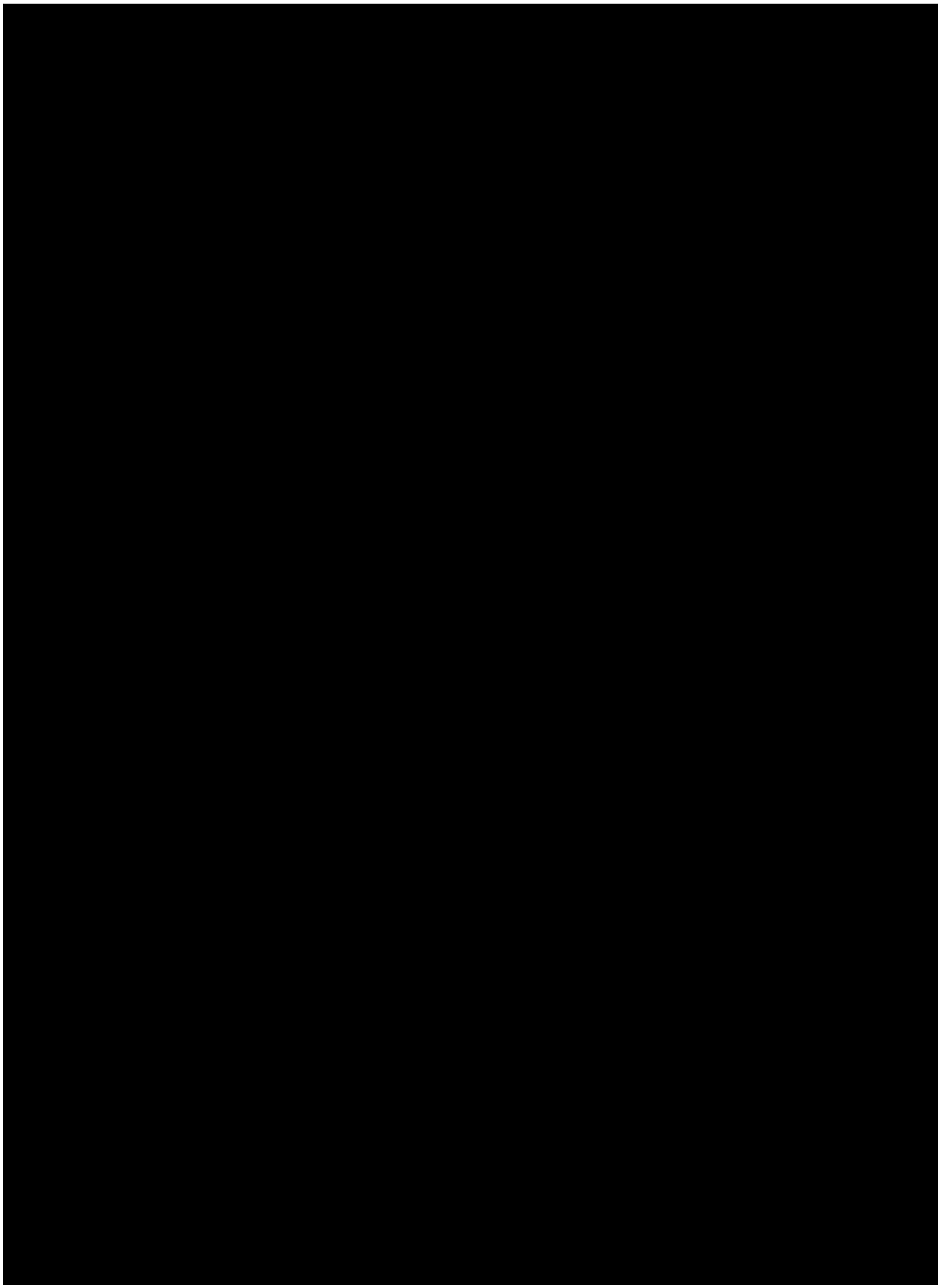
9.15	*Zouboulis C.C., Tzellos T., Kyrgidis A., Jemec G.B.E., Bechara F.G., et al.* European Hidradenitis Suppurativa Foundation Investigator Group. Development and validation of the International Hidradenitis Suppurativa Severity Score System (IHS 4), a novel dynamic scoring system to assess HS severity. Br J Dermatol. 2017 Nov; 177 (5): 1401-1409.
9.16	*Rubin, DB.* Multiple Imputation for Nonresponse in Surveys. New York: John Wiley &Sons. 1987. [R12-2378]

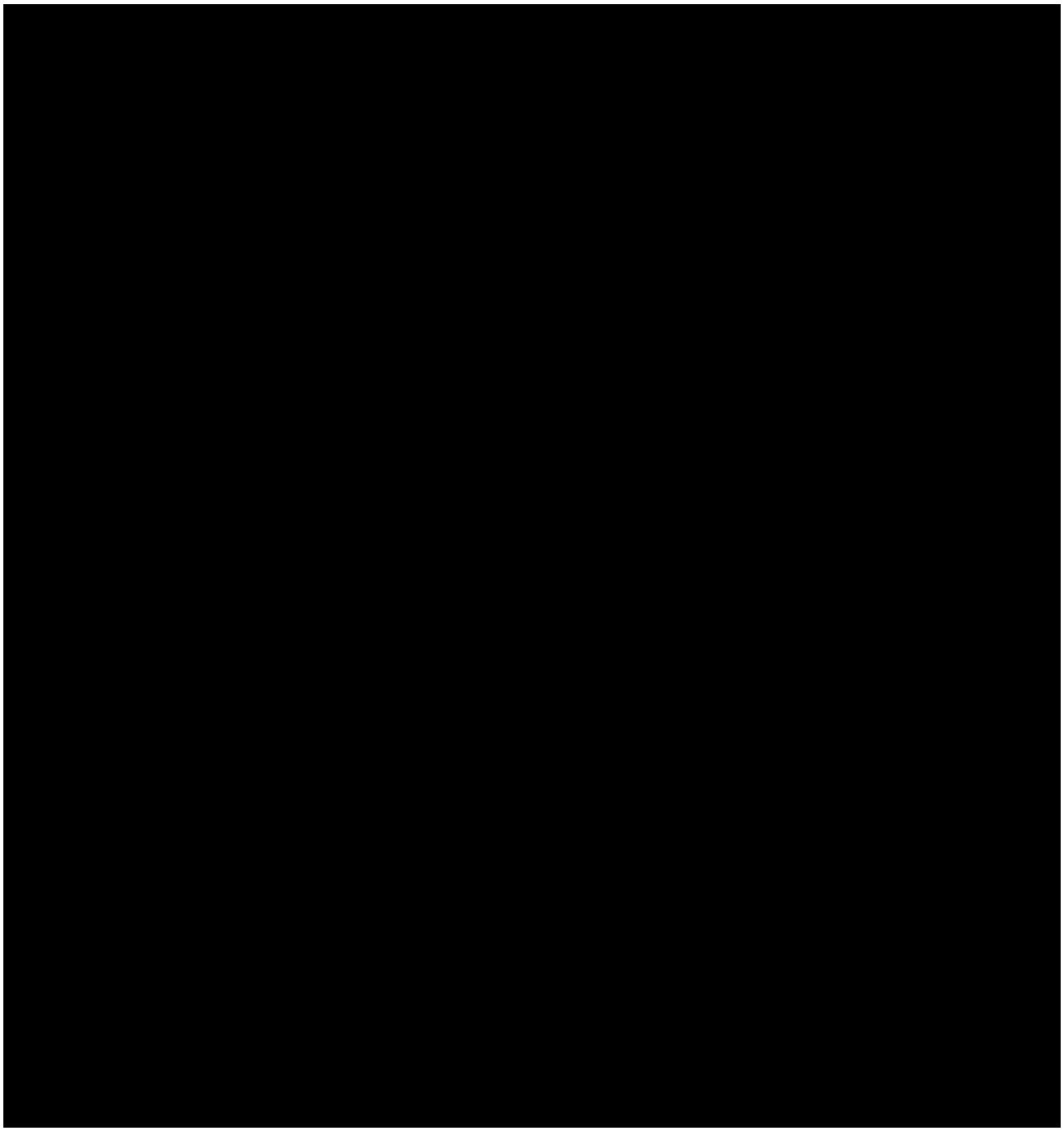


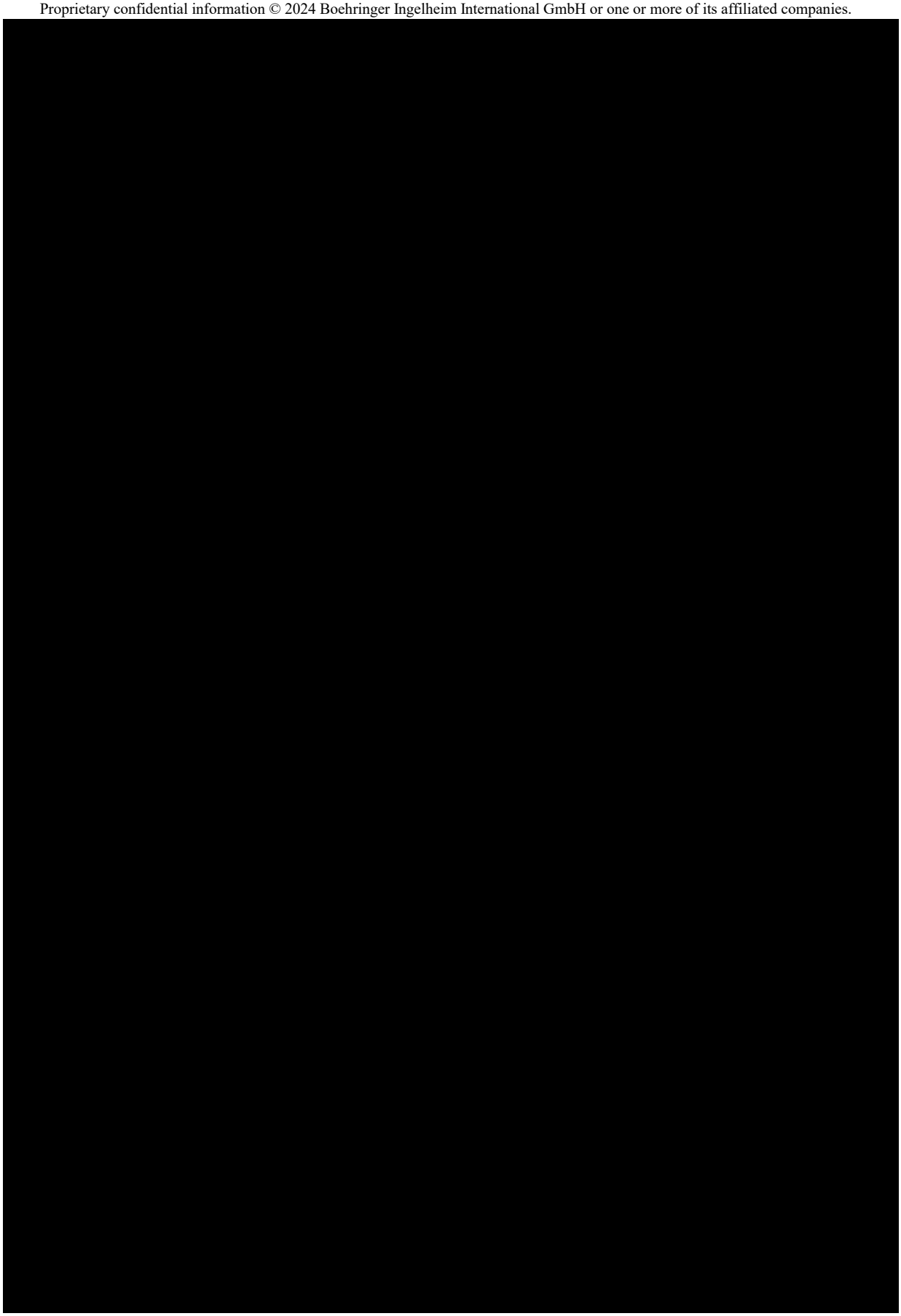


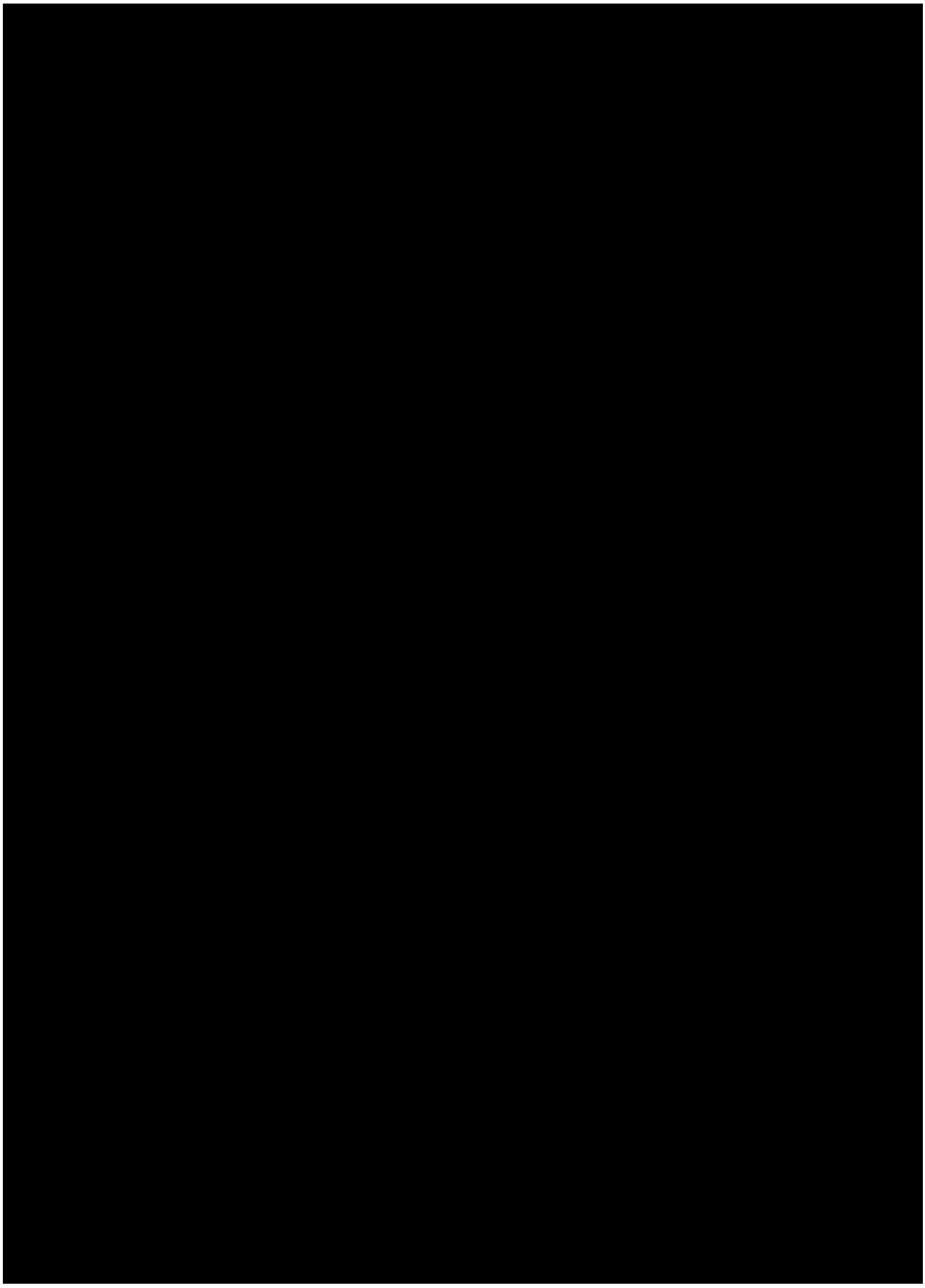


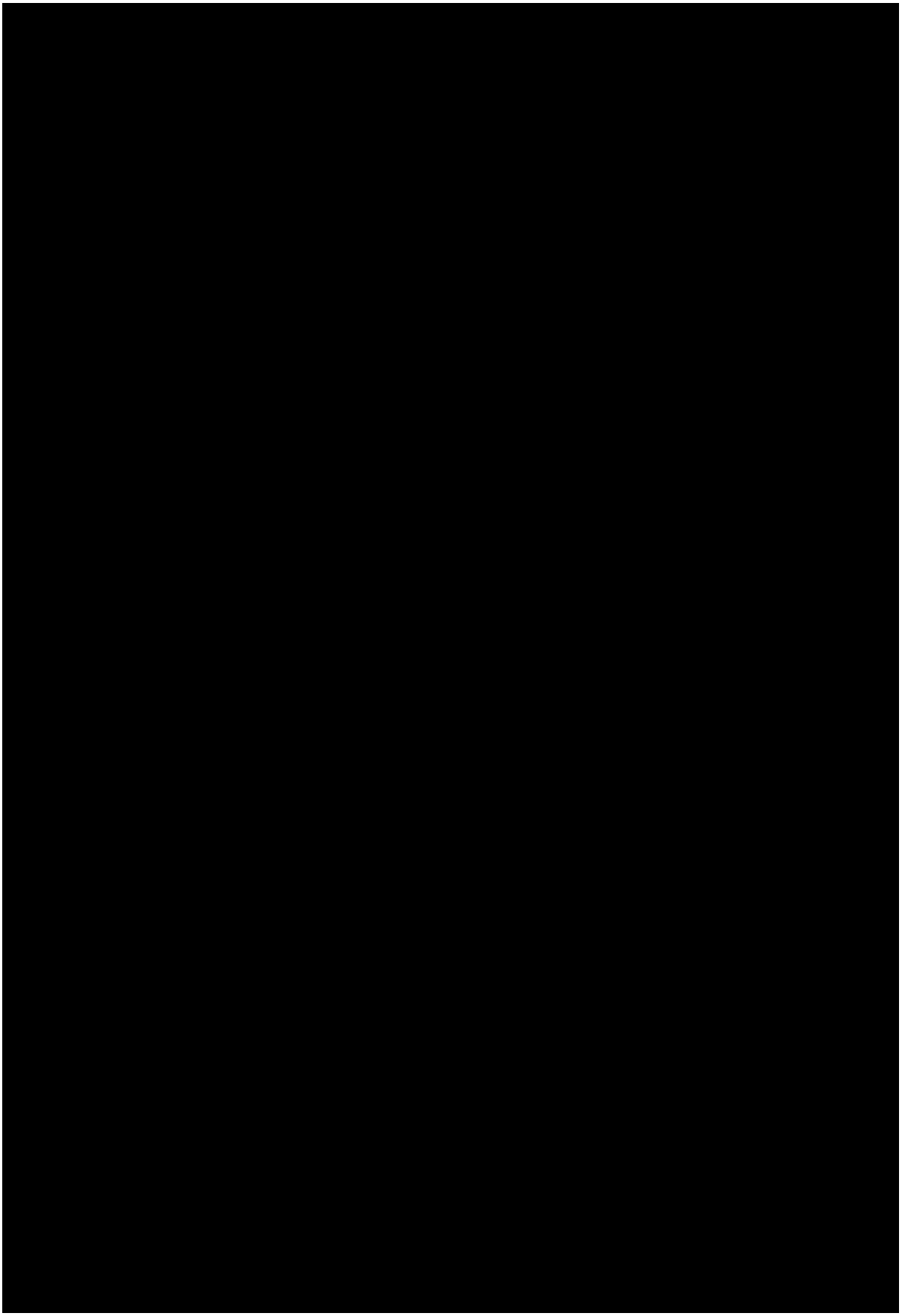


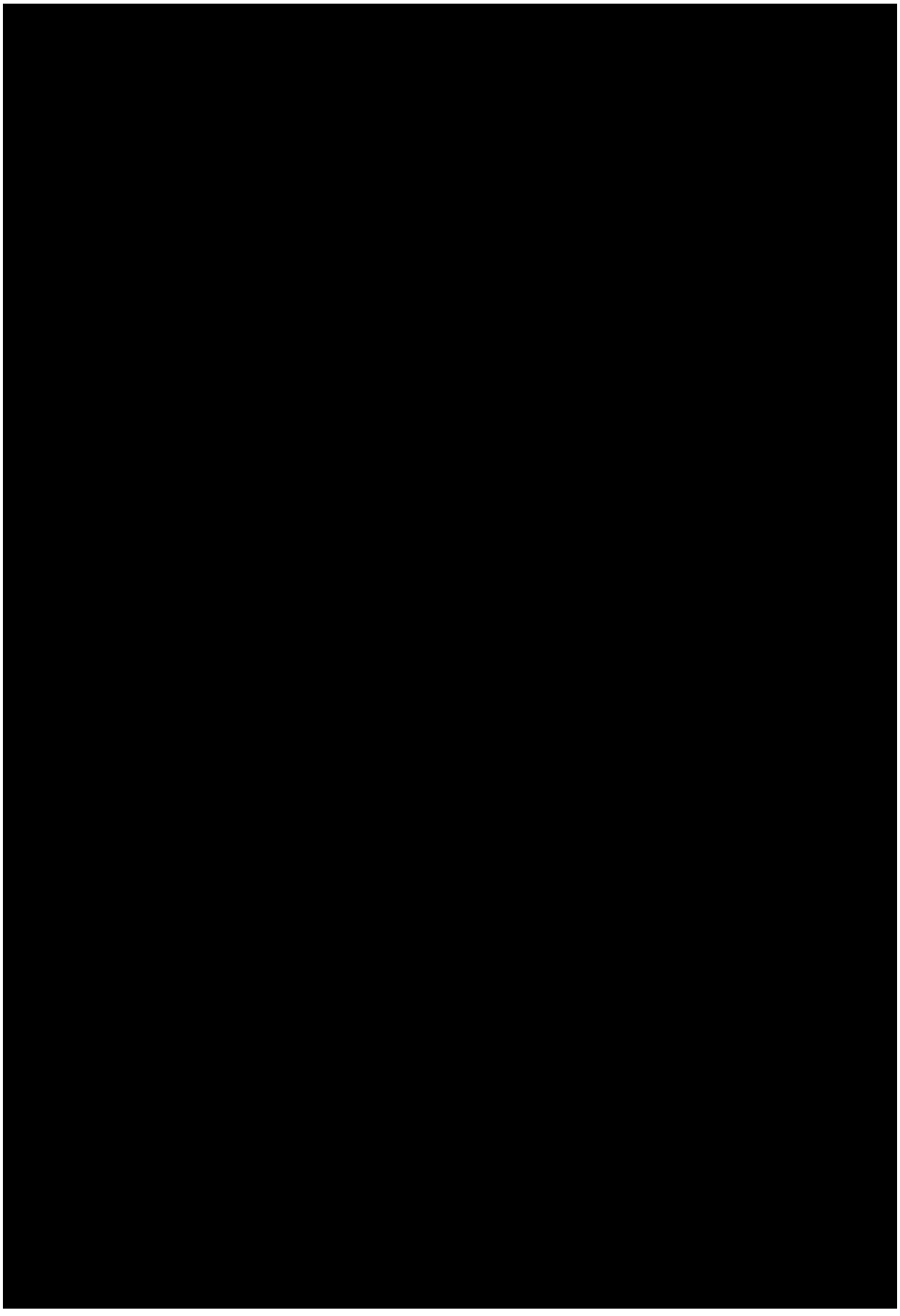


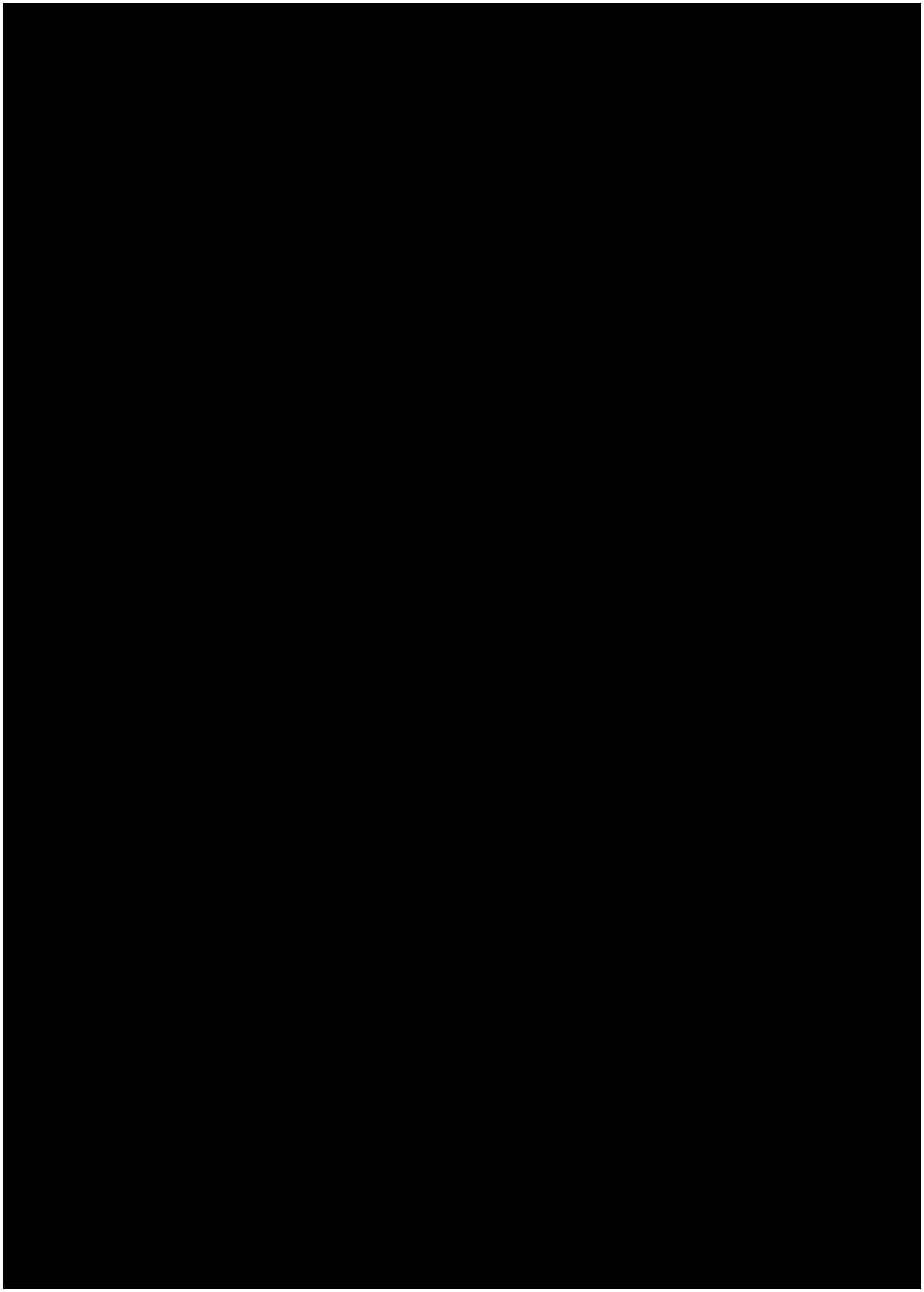


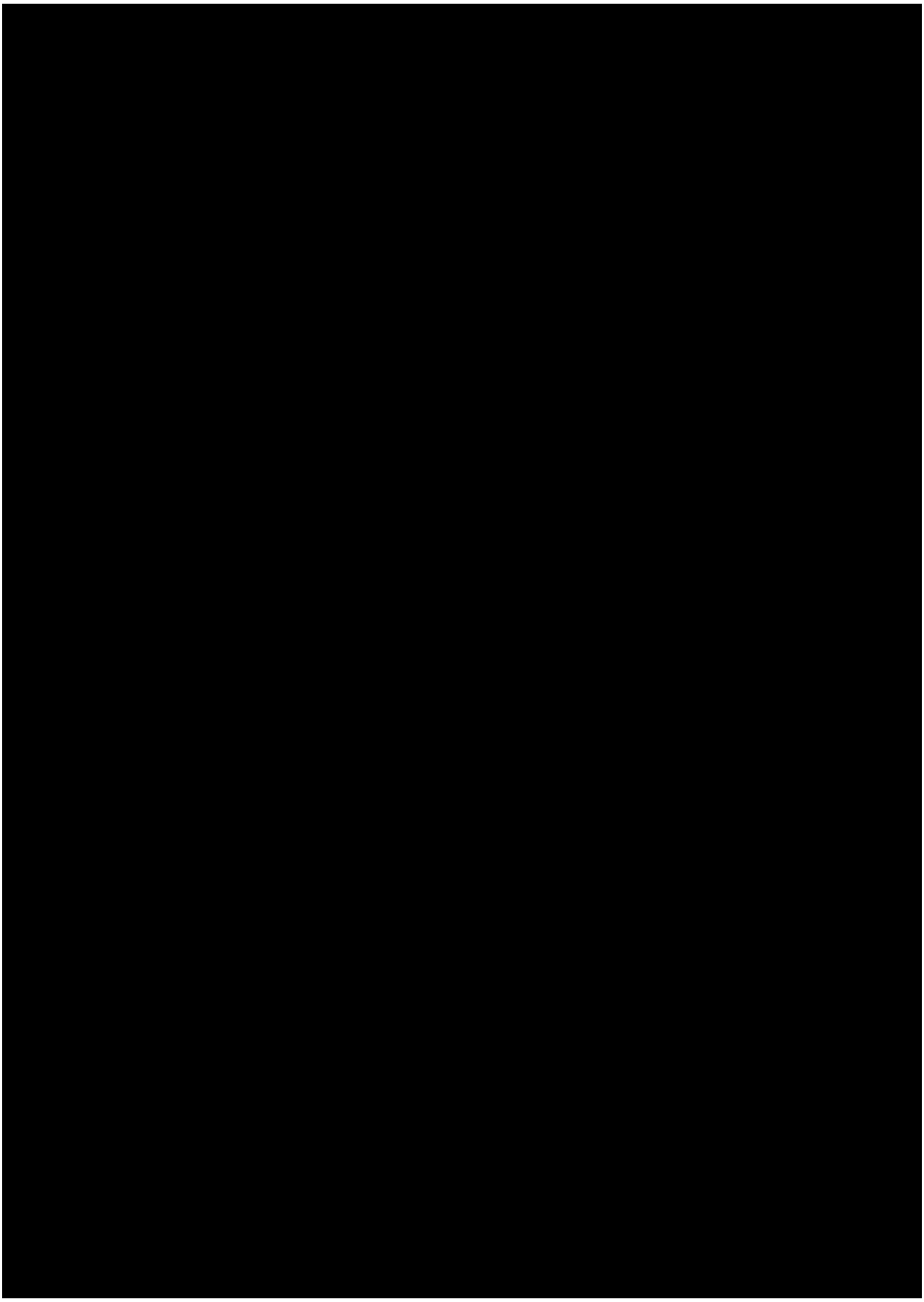


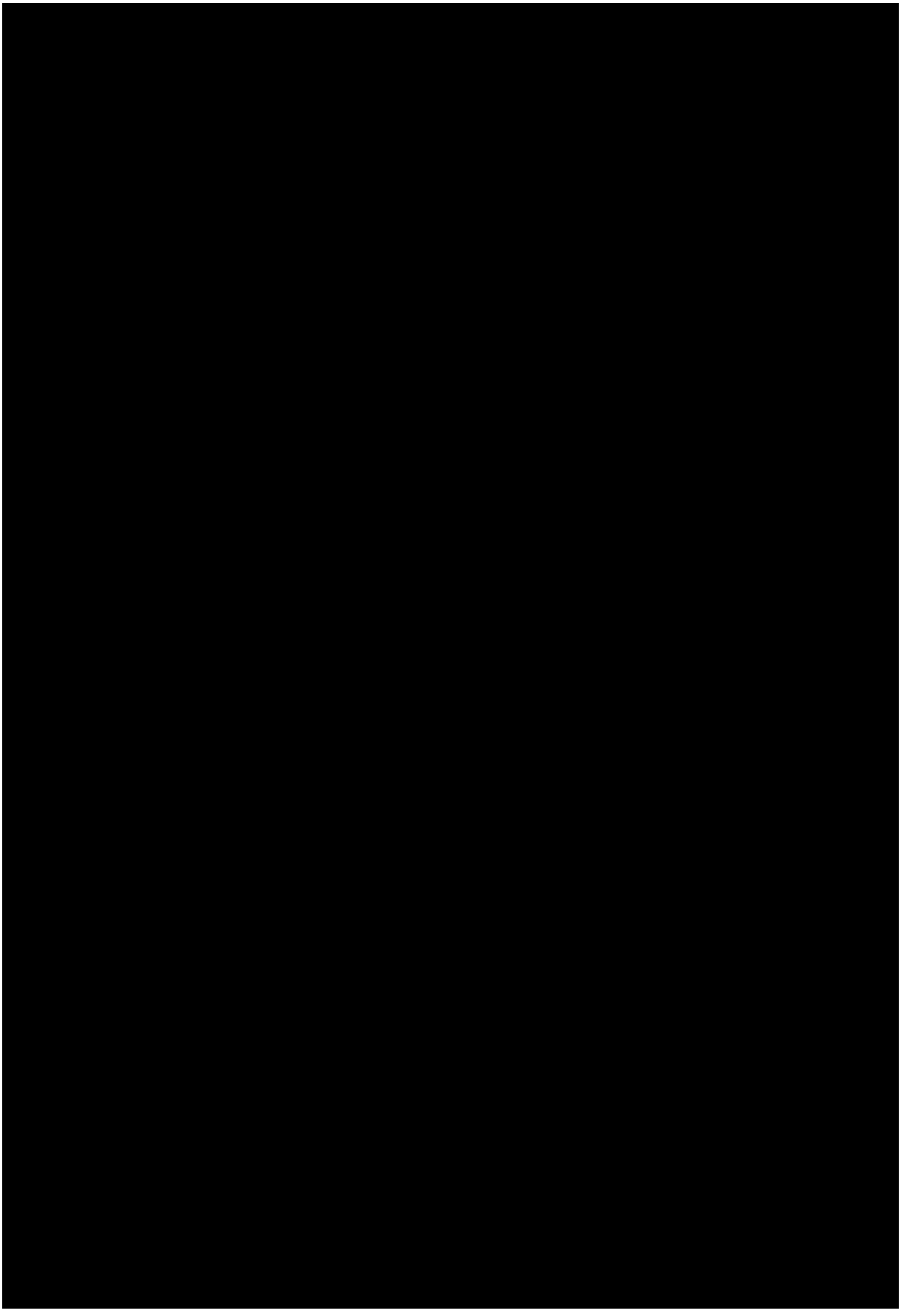


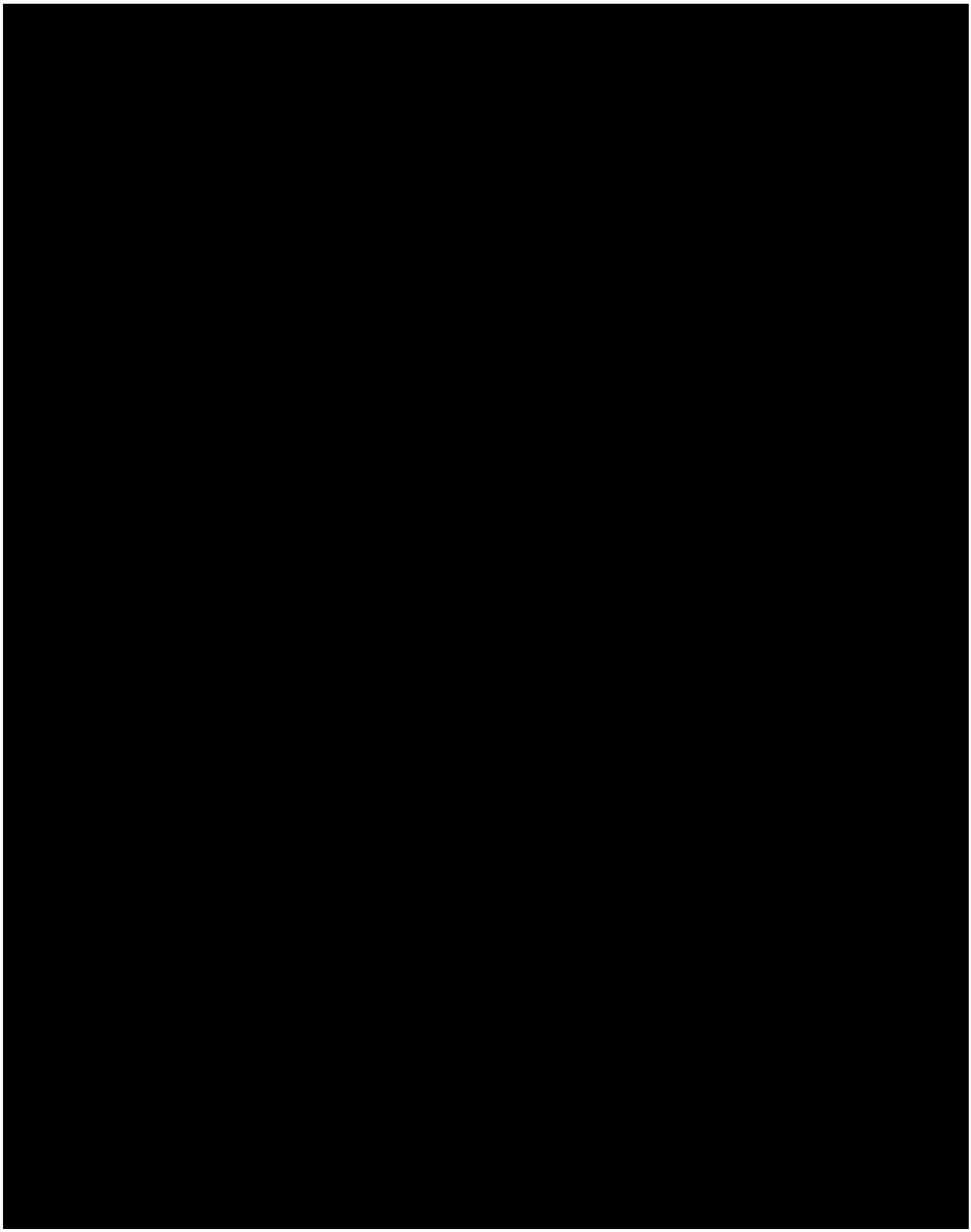












11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1.0	**13-08-2024**	[redacted]	None	This is the final TSAP.