# TRIAL STATISTICAL ANALYSIS PLAN

**c39181950-02**

| | |
|---|---|
| **BI Trial No.:** | 1368-0027 |
| **Title:** | Multi-center, randomized, parallel group, double blind, placebo controlled, Phase IIb dose-finding study to evaluate efficacy and safety of BI 655130 (spesolimab) compared to placebo in preventing generalized pustular psoriasis (GPP) flares in patients with history of GPP<br>Including Revised Protocol # 4 [c28020464-04] |
| **Investigational Product(s):** | Spesolimab, BI 655130 |
| **Responsible trial statistician(s):** | [redacted]<br>Tel.: [redacted]<br>Fax: [redacted] |
| **Date of statistical analysis plan:** | 2 Dec 2022 |
| **Version:** | 2.0 Final |

# 1. TABLE OF CONTENTS

[redacted]

[redacted]

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# 2. LIST OF ABBREVIATIONS

| Term | Definition / description |
|---|---|
| [redacted] | [redacted] |
| AE | Adverse event |
| ALT | Alanine aminotransferase |
| ALQ | Above the upper limit of quantification |
| AP | Alkaline phosphatase |
| AST | Aspartate aminotransferase |
| ATC3 | Anatomical-Therapeutic-Chemical classification level 3 |
| AUC0-∞ | Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity |
| 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 |
| Cmax | Maximum measured concentration of the analyte in plasma |
| CRF | Case report form |
| CRP | C-reactive protein |
| CTP | Clinical trial protocol |
| CTR | Clinical trial report |
| CV | Arithmetic coefficient of variation |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DBLM | Database lock meeting |
| DNA | Deoxyribonucleic acid |
| DLQI | Dermatology Life Quality Index |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| EM | Estimand for randomized maintenance period |
| EMR | Estimand for randomized maintenance period considering the use of restricted medication use for other purpose |
| EMA | European Medicines Agency |
| EN | Estimand for flare treatment period that considers intercurrent as non-responder |
| EN-ID8 | Estimand for flare treatment period that considers intercurrent as non-responder including data after the use of second flare treatment at R3/D8 |
| ES | Enrolled set |
| EC | Estimand that excludes data after the occurrence of intercurrent events during randomized maintenance period |
| EudraCT | European union drug regulating authorities clinical trials |
| gCV | Geometric coefficient of variation |
| gMean | Geometric mean |
| GPP | Generalized pustular psoriasis |
| GPPASI | Generalized Pustular Psoriasis Area and Severity Index |
| GPPASI 50 | Achievement of a ≥ 50 % reduction in GPPASI total score compared to baseline |

| Term | Definition / description |
|---|---|
| GPPASI 75 | Achievement of a ≥ 75 % reduction in GPPASI total score compared to baseline |
| GPPGA | Generalized Pustular Psoriasis Physician Global Assessment |
| IL | Interleukin |
| iPD | Important protocol deviation |
| KM | Kaplan-Meier |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MCP-Mod | The Multiple Comparison Procedures and Modeling |
| NOA | Not analyzed |
| NOP | No peak detectable |
| NOR | No valid result |
| NOS | No sample available |
| NRI | No response imputation |
| OC | Observed cases excluding data after intercurrent event |
| OC-ID8 | Observed cases excluding data after intercurrent event but include data after the use of second flare iv treatment at R3/D8 |
| OR | Original results |
| PD | Pharmacodynamic(s) |
| PGI-C | Patient Global Impression of Change |
| PGI-S | Patient Global Impression of Severity |
| PK | Pharmacokinetic(s) |
| PKS | Pharmacokinetic parameter set |
| PM | Primary method of censoring rule |
| PSS | Psoriasis symptom scale |
| Q1 | 1st quartile |
| Q3 | 3rd quartile |
| RAGe | Report appendix generator |
| REP | Residual effect period |
| RNA | Ribonucleic acid |
| RS | Randomized set |
| SAE | Serious adverse event |
| SD | Standard deviation |
| SDL | Subject data listing |
| SI | Système international d'unités |
| SM | Sensitivity method of censoring rule |
| SoC | Standard of Care |
| TPSS | Target Plaque Severity Score |
| ULN | Upper limit of normal range |
| UDAEC | User-defined Adverse Event Category |
| VAS | Visual analogue scale |
| WPAI-GPP | Work Productivity and Activity Impairment Questionnaire: GPP |

# 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 CTP and its amendments, 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 CTP. 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, and planning of sample size, and randomisation.

The statistical analyses will be performed within the validated working environment CARE, including SAS™ (current Version 9.4, by [redacted]), and SAS™-based tools (e.g., macros for the analyses of AE data or laboratory data; Report Appendix Generator system (RAGe) for compilation/formatting of the CTR appendices). R version 4.1.1 with "DoseFinding" package will be used for analysis based on MCP-Mod.

Study data will be stored in a trial database within the BRAVE system.

[redacted]

The primary analysis of the double-blinded randomize period this trial is planned to be performed once all randomized subjects have completed or early discontinued the 48-week study period. The final analysis is planned to be performed once all randomized subjects have completed the study (including any residual effect period). Both are described in this TSAP.

To support a potential spesolimab early acute flare treatment submission, interim analyses of the open-label clinical efficacy and safety data following occurrence of a first GPP flare treated with open-label spesolimab use will be performed. Data cut-off for the interim analyses will be described in a separate document.

# 4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

For JDA severity index, the categorization for the laboratory findings WBC count, CRP and serum albumin will be done based on the results of the central laboratory measurements not eCRF pages. If central laboratory values are not available, eCRF results will be used.

# 5. ENDPOINTS(S)

The primary and secondary objectives are defined in CTP as:

*the primary objective of this trial is to demonstrate a non-flat curve and evaluate the dose response relationship for 3 subcutaneous dosing regimens of spesolimab versus placebo, on the primary endpoint, the time to the first GPP flare onset up to week 48.*

*The secondary objective is to demonstrate superiority versus placebo for each of BI 655130 300 mg q4 weeks and BI 655130 300 mg q12 weeks on the primary endpoint, the time to the first GPP flare onset up to week 48, as well as the key secondary endpoint, the occurrence of at least one GPP flare up to 48 weeks.*

To align with the documentation of flare treatment submission, in this trial statistical analysis plan (TSAP) and future clinical trial report (CTR), “flare treatment period” will be used in replacement of “rescue treatment period”. The “flare treatment” is equivalent to “rescue treatment” or “rescue medication” in the following text. All of them indicate the open label (OL) i.v. dose of spesolimab to treat the first GPP flare during the randomized treatment period.

## 5.1 PRIMARY ENDPOINT(S)

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

*Time to first Generalized Pustular Psoriasis (GPP) flare (defined by increase in Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) score by ≥ 2 from baseline and the pustular component of GPPGA ≥ 2) up to week 48.*

A composite strategy will be applied as the primary Estimand for randomized maintenance treatment period (abbreviated to **EM**). Under EM Estimand, in addition to the event defined by *increase in Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) score by ≥ 2 from baseline and the pustular component of GPPGA ≥ 2*, any intercurrent events, i.e., any use of rescue medication with OL i.v. spesolimab, or investigator-prescribed Standard of Care (SoC) to treat GPP worsening, will be considered to represent the onset of a GPP flare.

[redacted]

The strategies for handling intercurrent events under Estimands are summarized as follows in Table 5.1:1.

Table 5.1: 1 Summary of intercurrent events handling for time-to-event endpoints during the randomized maintenance treatment period

| *Intercurrent events* | *Composite* ***EM*** | [redacted] |
|---|---|---|
| Use of rescue medication with i.v. spesolimab | Composite (Event*) | |
| Investigator-prescribed Standard of care to treat GPP worsening | Composite (Event*) | |
| Use restricted medication for other indications | Treatment Policy | |

*The subject will be set as an event or censored at the time intercurrent event happens

Per CTP Section 2.1,
*the treatment comparison within the randomized maintenance period will be made for randomized subjects regardless of treatment adherence or discontinuation.*

Treatment discontinuation is not considered as an intercurrent event in this trial. Any events occurred up to week 48 will be considered, regardless of treatment adherence or discontinuation.

See Section 10.1.2 for details on the derivation of the GPPGA total score.

## 5.2 SECONDARY ENDPOINT(S)

### 5.2.1 Key secondary endpoint(s)

The key secondary endpoint of the study is defined in CTP Section 2 as:

*The occurrence of at least one GPP flare (defined by increase in GPPGA score by ≥ 2 from baseline and the pustular component of GPPGA ≥ 2) up to week 48.*

This endpoint is considered as key secondary endpoint for secondary objective (i.e., demonstrate the superiority of spesolimab versus placebo), while for the primary objective (i.e., dose-finding analysis), is considered as secondary in nature only instead of key secondary.

Per CTP Section 7,
*This (the key secondary endpoint) is a monotone increasing variable, so once a flare has occurred by a particular visit, all subsequent visits will also by definition have had a preceding flare.*

Once the first GPP flare occurs, all subsequent visits will be regarded as the occurrence of GPP flare. The Estimands applied for primary endpoint are also applicable for the key secondary endpoint. The detailed handling of intercurrent events under different Estimands for the key secondary endpoint is described in Table 5.2: 1, which also applies to the secondary and further binary endpoints. The missing data handling for the visits after censoring will be described in Section 6.6.2

Under the primary Estimand **EM**, for the key secondary endpoint, the occurrence of the first GPP flare (defined by increase in GPPGA score by ≥ 2 from baseline and the pustular component of GPPGA ≥ 2) is a treatment failure while the use of rescue treatment of i.v. spesolimab or use of investigator-prescribed SoC will also lead to treatment failure.

Table 5.2: 1 Summary of handling intercurrent events for binary endpoint during the randomized maintenance treatment period

| *Intercurrent events* | *Composite EM* | *C r E* |
|---|---|---|
| Intercurrent event | | |
| Use of rescue medication with i.v. spesolimab | Composite (Treatment failure [a]) | ( |
| Investigator-prescribed Standard of care to treat GPP worsening | Composite (Treatment failure [a]) | ( |
| Use restricted medication for other indications | Treatment Policy | ( |

[a] Treatment failure indicates the occurrence of GPP flare for key secondary endpoint. For the binary endpoints that indicate positive disease outcome, such as sustained remission, no PSS sub score>1 and DLQI of 0 or 1, the treatment failure indicates that the prespecified endpoint is not achieved.
[b] Data will be censored (set as missing) after the specified intercurrent event.

### 5.2.2 Secondary endpoints

Three efficacy endpoints and one safety endpoint are defined as secondary endpoints.

Per CTP Section 2, the below-defined secondary endpoints, for the secondary objective of the trial, are included in the formal testing along with the primary endpoint and the key secondary endpoint:

- *Time to first worsening of Psoriasis Symptom Scale (PSS) up to week 48 defined as a 4-point increase in total score from baseline.*
- *Time to first worsening of Dermatology Quality of Life Index (DLQI) up to week 48 defined as a 4-point increase in total score from baseline.*

The Estimands specified for primary endpoint will be applied to the secondary time-to-event endpoints per Table 5.1:1.

For further details on the derivation of the PSS score, and the DLQI score, refer to Sections 10.1.5, and 10.1.6, respectively.

Per CTP Section 2, the below-defined secondary endpoint, for the secondary objective of the trial, is not included in the formal testing procedure:

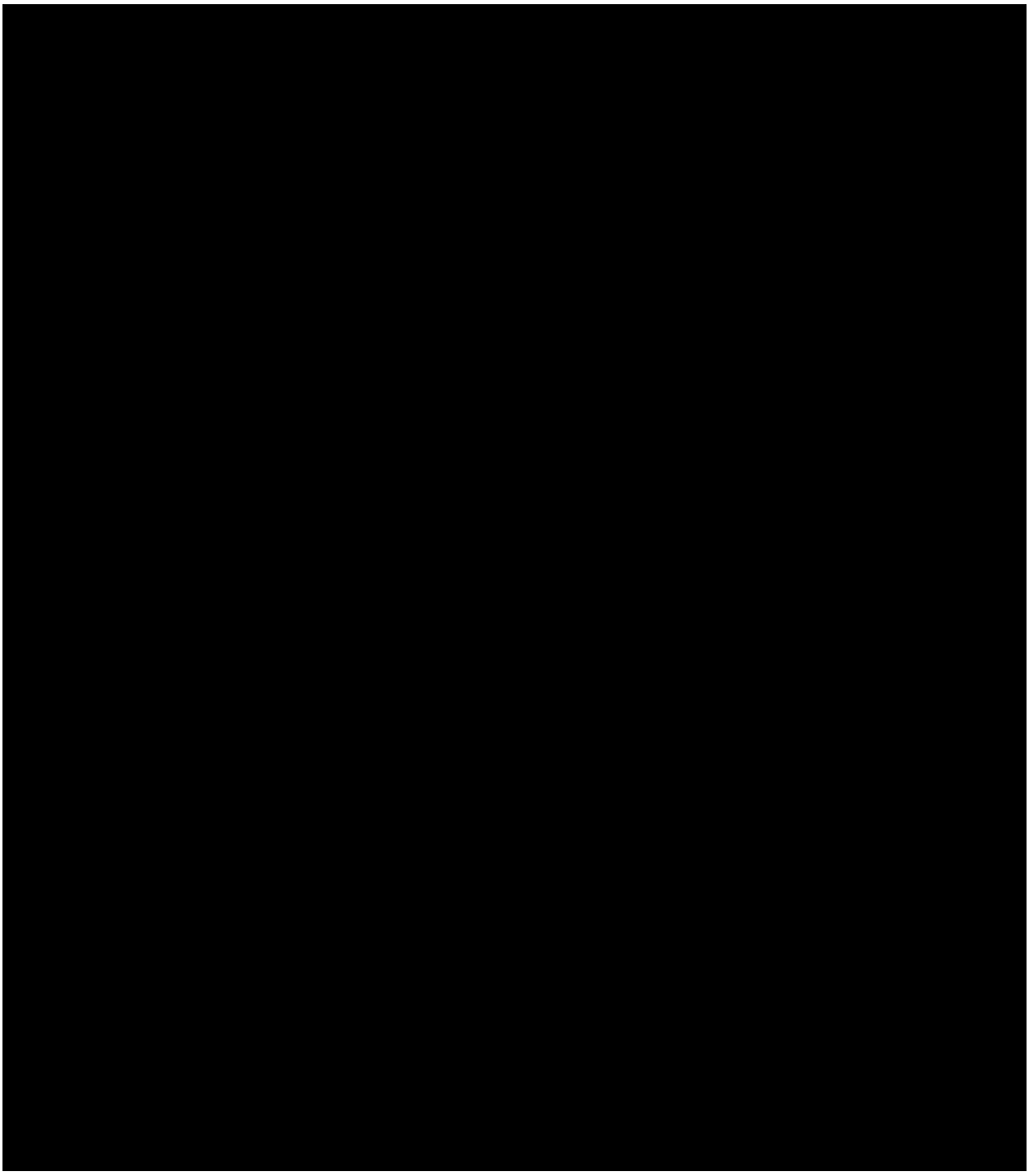
*Sustained remission, defined as a subject with a GPPGA score of 0 or 1 (clear or almost clear) at all visits up to week 48.*

As a binary endpoint, the Estimands applied in key secondary endpoint are also applicable to this secondary endpoint per Table 5.2:1.

Note that, similar as the key secondary endpoint, i.e., the occurrence of GPP flare, the sustained remission is a monotone increasing variable. Once the remission (GPPGA total score 0 or 1) is not achieved or the intercurrent event (can lead to treatment failure) has occurred by a certain visit, the status of sustained remission will be not achieved for all subsequent visits up to week 48.

Per CTP Section 2, the secondary safety endpoint is defined as:

*The occurrence of Treatment Emergent Adverse Events (TEAEs).*



### 5.4.1 Safety Endpoints

Safety endpoints are defined per CTP Section 5.2

Intensity of AEs was assessed during the trial according to Rheumatology Common Toxicity Criteria (RCTC) version 2.0. At the time of the data analysis, selected laboratory parameters will be assessed by Common Terminology Criteria for Adverse Events (CTCAE) in addition to RCTC grades, where possible. The specific definition of CTCAE grades is described in Section 10.3

### 5.4.2 Demographic and other baseline characteristics

The following demographic parameters will be defined: sex, ethnicity, race, sub-race of Asian, age, height, weight, BMI, smoking status, and region of sites.

Age [years] will be determined as the difference between year of birth and year of informed consent. BMI will be calculated as weight [kg] / height $[m]^2$ (based on the last available weight measurement prior to the first randomized dose on V2/D1).

Medical History for GPP include mutation status (IL36RN, CARD14 and AP1S3), as well as the details, if any, on the presence of concurrent chronic plaque psoriasis or chronic erythrodermic psoriasis will be summarized. The method by which diagnosis of GPP was confirmed is also collected.

Disease characteristics will include the details on typical flare, most severe flare, longest flare, and most recent flare prior to consent.

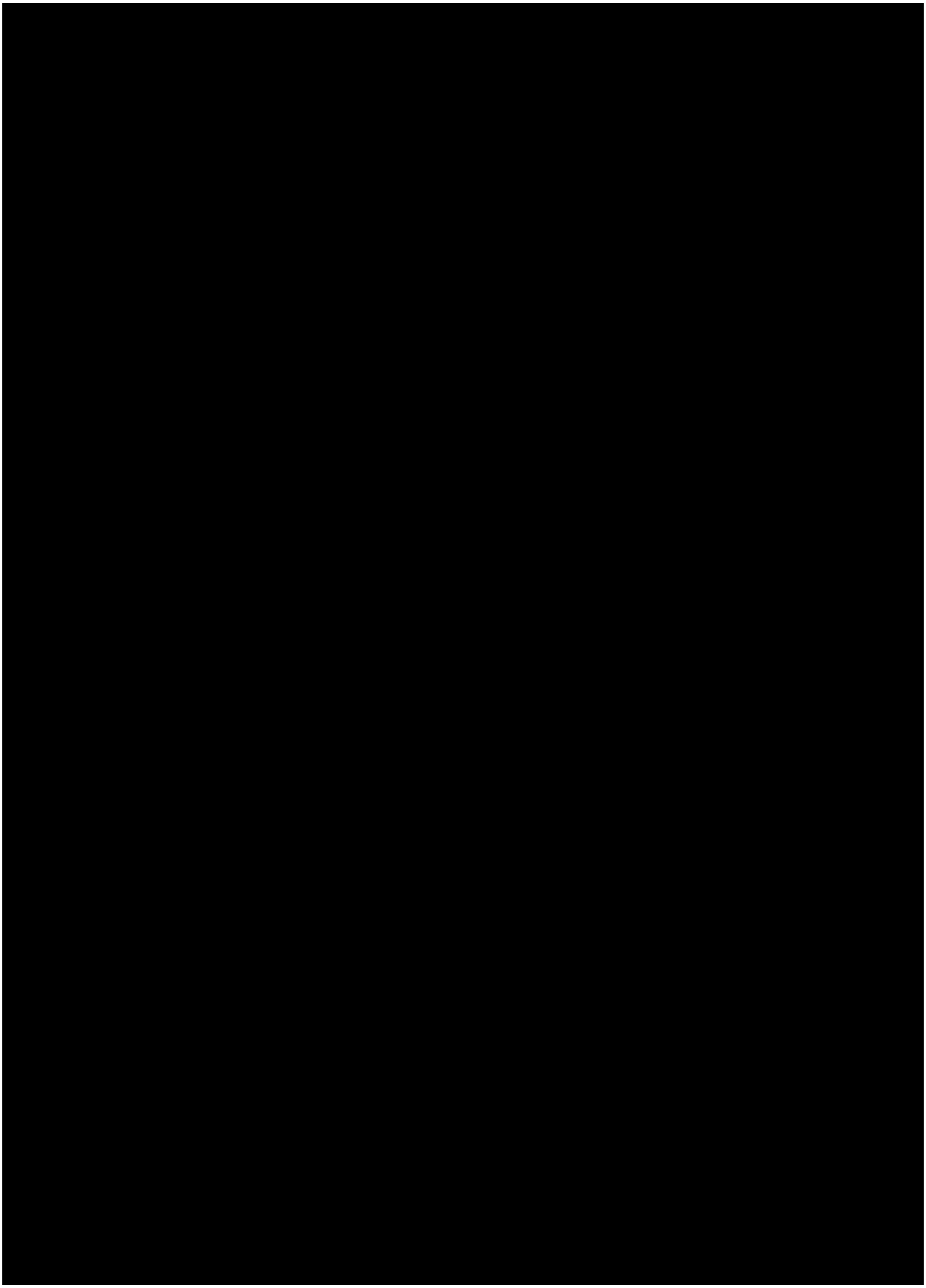
Time since first diagnosis [years] will be calculated as the difference between date of first diagnosis and date of informed consent, divided by 365.25. For calculation in the context of incomplete information on the date of first diagnosis, according to Section 6.6.8.

In addition to the mutation status captured via the eCRF, the genes of interest also get re-sequenced. Hereby the mutation status will be defined based on the absence or presence of potential pathogenic IL36RN, CARD14 and AP1S3 variations based on existing functional or potential functional impact of the mutation. Based on this analysis the following groupings may be presented:

- Subjects with a mutation in any of the 3 genes vs. subjects with no mutation at all
- Subjects with a mutation in IL36RN (irrespective of the mutation status in the other genes) vs. subjects without an IL36RN mutation
- Subjects with a mutation in CARD14 (irrespective of the mutation status in the other genes) vs. subjects without an CARD14 mutation
- Subjects with a mutation in AP1S3 (irrespective of the mutation status in the other genes) vs. subjects without an AP1S3 mutation
- Subjects with a mutation in CARD14 or AP1S3 but no mutation for IL36RN vs. subjects not fulfilling this criterion

These re-sequenced results for the mutation status of IL36RN will be the basis for the subgroup classification as described in Section 6.4.

[redacted]



# 6. GENERAL ANALYSIS DEFINITIONS

## 6.1 TREATMENTS

For basic study information on the treatment to be administered, assignment to treatment, and selection of dose, refer to Section 3 and 4 of the CTP.

For the analysis of adverse event, the study phases are defined as in Table 6.1:1.

Table 6.1: 1 Flow chart of analysis phases of the study

| Study analysis phase | Description | Start (included) | End (included) |
|---|---|---|---|
| Screening phase | Screening | Earliest of (Date of informed consent, first screening procedure) | Date/time of start of the first randomized study treatment minus 1 minute |
| Randomized maintenance treatment phase | On randomized treatment period | Date/time of start of the first randomized study treatment (V2/D1) | Earliest of i) Date/time of start of the rescue treatment with i.v. spesolimab minus 1 minute. ii) Date of the end of last randomized study treatment + REP [2](112 days) at 23:59. iii) Date/time of the first treatment in OLE trial 1368.25 if the subject is rolled over, iv) last contact date on End of Study page at 23:59 if subject is not rolled over. |
| Flare treatment phase (if applicable) | On flare treatment period | Date/time of start of the first rescue treatment with spesolimab i.v. 900 mg | Earliest of i) Date/time of start of the first OL maintenance treatment minus 1 minute. ii) Date of the end of last rescue treatment + REP [2] (112 days) at 23:59. iii) Date/time of the first treatment in OLE trial 1368.25 if the subject is rolled over, iv) last contact date on End of Study page at 23:59 if subject is not rolled over |
| OL maintenance phase (if applicable) | On OL maintenance treatment period | Date/time of start of the first OL maintenance treatment | Earliest of i) Date of the end of last OL maintenance treatment + REP [2] (112 days) at 23:59. ii) Date/time of the first treatment in OLE trial 1368.25 if the subject is rolled over, iii) last contact date on End of Study page at 23:59 if subject is note rolled over. |
| Off treatment phase[1] | Off-treatment period | Date of the end of last study treatment (including randomized treatment, flare treatment and OL maintenance treatment) + REP [2] (112 days) + 1 day at 0:00 | i) Date/time of the first treatment in OLE trial 1368.25 if subject is rolled over, ii) last contact date on End of Study page at 23:59 if subject is not rolled over. |

Dates are defined individually per subject. An analysis phase will not extend beyond the start date of the following phase.
[1] The off-treatment period only exists if the last contact date is after the date of end of last study treatment + 112 days.
[2] Per CTP Section 7.2.5, all adverse events occurring between start of treatment and end of the residual effect period will be considered 'treatment-emergent'; the residual effect period (REP) is defined as 16 weeks after the last dose of trial medication. Therefore, 112 days is included in the period

Efficacy analyses (Section 7.4, 7.5 and 7.6.1) that are on randomized maintenance treatment phase will take the intercurrent events into account under the concept of Estimand (see Section 5.1, 5.2, and 5.3)

Treatment groups for the randomized treatment period according to the randomized/actual treatment (see Table 6.1: 1) will be labelled as follows:

- **"Placebo"** (i.e., randomized to received placebo)
- **"Speso SC Low"** (i.e., randomized to spesolimab 150 mg s.c. q12w)
- **"Speso SC Medium"** (i.e., randomized to spesolimab 300 mg s.c. q12w)
- **"Speso SC High"** (i.e., randomized to spesolimab 300 mg s.c. q4w)
- **"Speso SC Total"**(across spesolimab randomized treatments)
- **"Overall Total"**(across randomized treatments), where appropriate**.**

"**Speso SC Total**" is applicable in disposition, demographics and baseline characteristics, compliance summaries, AE, clinically significant abnormal lab values and others as deemed necessary.

"**Overall Total**" is applicable in disposition, demographics and baseline characteristics, compliance summaries and others as deemed necessary.

- **"Overall Speso"**(across spesolimab treatments, regardless of i.v. or s.c. treatments), where appropriate.

"**Overall Speso**" is applicable in AE, clinically significant abnormal lab values and others when summarizing the safety outcomes post any spesolimab use.

Treatment groups for the loading dose received on Day 1 of the randomized treatment period according to the randomized treatment (see Table 6.1: 1) will be labelled as follows:

- **"Speso SC Loading Low "** (i.e., randomized to spesolimab 150 mg s.c. q12w)
- **"Speso SC Loading High"** (i.e., randomized to spesolimab 300 mg s.c. q4w or spesolimab 300 mg s.c. q12w)

Treatment groups for the flare treatment period will be labelled as follows:

- **"Speso IV Total"**(i.e., received at least one flare treatment spesolimab 900mg i.v.)
- **"Speso IV SD"**(i.e., received i.v. flare treatment at Day 1 of flare treatment period)
- **"Speso IV DD"**(i.e., received i.v. flare treatment at Day 1 and Day 8 of flare treatment period)

Treatment groups for OL maintenance treatment period will be labelled as follows:

- "**Speso OL SC**"(i.e., received at least one OL maintenance treatment)

When applicable, output columns should be arranged in the order as given above.

More details on the technical implementation of these analyses are provided in the ADS Plan of this TSAP.

## 6.2 IMPORTANT PROTOCOL DEVIATIONS

Listings of protocol deviations will be provided to be discussed at the MQRM, at the Trial Oversight Meeting prior to DBL or at the RPM. At these meetings, it will be determined whether a discrepant data value can be used in analyses or whether correction is needed. Each protocol deviation must be assessed to determine whether it is an important protocol deviation (iPD). Refer to the Integrated Quality and Risk Management Plan (IQRMP) Section 4.1 for the detailed specifications of PDs and iPDs (32). For the process of identification of iPDs, refer to "Identify and Manage Important Protocol Deviations (iPD) (3).

If any iPDs are identified, they are to be summarized into categories and will be captured in the MQRM/RPM minutes or the TOM minutes and additionally via an accompanying Excel spreadsheet. The iPDs may lead to exclusion of subjects from analysis sets (e.g., the Per Protocol Set), referring to IQRMP. The documentation of the iPD categories and how to handle iPDs in the analysis is included in the DV domain specifications and stored within the TMF in EDMS.

All COVID-19 related protocol deviations, regardless of important or non-important ones will be included in the DV domain as well. See *BI-KMED-COPS-HTG-0141 "*CTR writing guidance for trials impacted by the COVID-19 pandemic" (31) and *BI-KMED-COPS-HTG-0117* "IQRM and Centralized Monitoring during COVID-19 - Guidance for Trial Teams" (33) for details.

A summary of iPD decisions will be documented in the decision log.

## 6.3 SUBJECT SETS ANALYSED

The following analysis sets will be defined for the randomized maintenance treatment period of this trial:

- Enrolled Set (ES)
  This subject set includes all subjects who signed informed consent. It will be used to display the subject disposition.

- Randomized Set (RS):
  This subject set includes all randomized subjects. Treatment assignment will be used as randomized. It will be used for analyses of subject for baseline demographics and

disease characteristics and is the main set for the analyses of efficacy endpoints during the randomized maintenance treatment period.

- 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 analyzed according to the actual treatment received.

- 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 and key secondary endpoints.

For the flare treatment period, the following set is defined as below:

- Safety Analysis set for flare treatment period (SAF-FT):
  This subject set includes all subjects who took at least one flare treatment with OL i.v. dose of spesolimab. This is the main analysis set for efficacy and safety during the flare treatment period.

For the OL maintenance treatment period, the following set is defined as below:

- Safety Analysis set for OL maintenance treatment period (SAF-MT):
  This subject set includes all subjects who received at least one dose of OL s.c. maintenance treatment. This is the main analysis set for efficacy and safety during OL maintenance treatment period.

**Handling of Treatment Misallocations in the Analysis Sets**

If a subject is randomized but not treated, they will be reported under their randomized treatment group for efficacy analysis according to RS and PPS (per the intent-to-treatment principle). Such subjects are excluded from the safety analyses (SAF) since no randomized study medication was taken.

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

If a subject is randomized but took incorrect treatment during the study,

- For efficacy analyses according to the RS and PPS, subjects who took incorrect treatment will be reported under their randomized treatment group.
  - In the case of stratification error at randomisation, 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 randomisation and is therefore consistent with regulatory guidance.

- For the safety analysis based on SAF, the actual treatment will be used as below:
    - For subjects randomized to active spesolimab arms and are planned to receive multiple dose administrations of spesolimab, in the case of incorrect medication taken, the subjects will still be reported under their randomized treatment group for safety analysis, as the overall safety profile is expected to be driven by the amount of spesolimab received in totality over the entire treatment duration. If the subject receives only a few syringes of the incorrect medication at only some dosing visits, it is not expected that the safety profile will deviate from the planned treatment regimen.
    - For subjects randomized to placebo: if the subject receives ⩾1 syringe of randomized spesolimab s.c., they will be reported as treated under **Speso SC Low** dose group.

The discussion of all exceptional cases and the decisions on the allocation of subjects to populations will be made at the last the RPM/DBLM.

Table 6.3: 1 Subject sets analyzed

| | *Subject Set* | | | | | |
|---|---|---|---|---|---|---|
| *Class of endpoint* | ES | RS | PPS | SAF | SAF-FT | SAF-MT |
| Disposition | X | | | | | |
| iPDs | | X | | | | |
| Demographic | | X | | | | |
| [redacted] | | | | [redacted] | [redacted] | [redacted] |
| Baseline characteristics | | X | | | X | |
| Primary endpoint | | X [a] | X [b] | | | |
| Key secondary endpoint | | X [a] | X [b] | | | |
| Secondary endpoints | | X | | | | |
| [redacted] | | [redacted] | | | [redacted] | [redacted] |
| Adverse event | | | | X | X | X |
| Lab/other safety/ tolerability | | | | X | X | X |

[a] Primary analysis
[b] Sensitivity analysis

[redacted]

## 6.5 POOLING OF CENTRES

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

## 6.6 HANDLING OF MISSING DATA AND OUTLIERS

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

The original results (OR) approach implies the presentation of data exactly as observed (not using time windows and not setting values to missing).

OR analysis will be performed on parameters and endpoints, such as adverse event, concomitant medications, and the use of investigator-prescribed SoC, those are not collected based on visits and assignment to time windows will be not necessary. It is not meaningful to apply any imputation rule for the replacement of missing values either.

### 6.6.1 Withdrawals

The reasons for withdrawal from treatment will be reported as indicated on the eCRF.

### 6.6.2 Efficacy data

Based on the different reasons for subjects' data missing for different endpoints, various approaches will be used to assess the impact of missing data on the efficacy endpoints of this trial, depending upon the type of the endpoint and treatment period (See Table 6.6.2:1). Approaches to be applied are described below.

6.6.2.1 Randomized treatment period

**Time-to-event efficacy endpoints**

Per CTP Section 7.3,

*It is generally assumed that given the severity of a GPP flare, patients will always report to the investigator in a timely manner in order to ensure that proper treatment is received so that the developing flare can be rapidly treated. For the primary endpoint, only observed GPP flare events will be included in the primary analysis. No further imputation will be implemented on the missing values of GPPGA score and/or missing GPPGA pustule sub score. This will be the primary imputation method for the primary analysis. The same imputation strategy will be used for the two secondary endpoints, time to first worsening of PSS and time to first worsening of DLQI in the hierarchical testing procedure.*

The detailed rules as outlined in Table 6.6.2:1 will be used as the primary method for handling censoring (Primary Method, abbreviated to **PM**).

Note here, with no event confirmed, censoring will be made at the earliest of the date of End of Study, Day 351 and the occurrent date of intercurrent events which hypothetical approach applied (per Table 5.1:1). This will also be done even if a subject had an event afterwards. Day 351 is the last day of the analysis time window of week 48 per Table 6.7:1. The details about analysis time windows can be found in Section 6.7. Such specifications reflect the objective of the trial that the treatment comparison for randomized subjects is made within 48-week study period per CTP Section 2.1.1.

[redacted]

Table 6.6.2: 1 Primary Method (PM): Description of censoring rules for primary endpoint, and two secondary endpoints

| *Situation* | *Outcome (event or censored)* | *Date of outcome* |
|---|---|---|
| *Without post randomisation assessment* | | |
| No event led by an intercurrent event | Censored | Date of randomisation, or the date of first dose, whichever comes later. |
| The first event led by an intercurrent event | Event | Date of the first event led by an intercurrent event |
| *With post randomisation assessment* | | |
| No event* | Censored | Earliest of last contact date on End of Study page, Day 351, censor date specified by Estimand (if applicable) |
| The first event* | Event | Date of the first event* |

*The event includes the event defined by endpoint and the event led by an intercurrent event per Estimand definition

**Binary efficacy endpoints**

The multiple imputation method described below (abbreviated to **MI**) is applicable for the primary analysis of the key secondary endpoint and the secondary binary endpoint.

As stated in CTP, missing GPPGA or GPPGA pustulation sub scores will not be imputed and only observed values will be utilized. The imputation of binary endpoint will only be done to binary level, i.e., success or failure.

Considering the endpoint emphasizes on either the positive side (sustained remission) or negative side (occurrence of GPP flare) of disease outcome. The imputation method described here will focus on the imputation on the failure to avoid confusion. See Section 5.2 for the illustration of treatment failure and monotone increasing.

Prior to the occurrence of failure, if for any reason, one or more subjects have missing visit, e.g., due to loss of follow-up or early discontinuation from the study before reaching the time-point of Week 48, a sequential logistic regression multiple imputation method will be implemented to impute the missing outcome by each visit at a binary level (Yes as failure vs. No as success).

Before the imputation procedure, any non-monotone missing outcome (binary level) will be imputed by the next observed value. The achieved monotone missing data will be then imputed per the following steps:

1. *Multiple Imputation of Missing data:* A sequential logistic regression method is used to impute missing values of binary event (Yes vs. No) at each visit.

*a)* Identify the visit with the earliest missing assessment from all subjects, denoted as *n*
*b)* For the imputation of missing data at *Visit n*, the binary level (Yes vs. No) available at *visit n-1* as well as the corresponding randomized treatment, will be included as covariates in the logistic regression imputation model. The subjects with missing binary assessment at *Visit n* will be imputed by the imputation model. If the assessment of a subject at *Visit n* is observed or imputed as a failure, the assessments of all subsequent visits up to week 48 of this subject will be imputed as failure.
*c)* Using the same approach in step *b)*, all visits will be imputed sequentially up to Visit 14 (Week 48).

Note that, the random seed 136827 will be used at the start of the imputation. If a second seed is needed, 136828 will be used, and so on so forth as deemed necessary. The imputation will be repeated for 100 times.

2. *Analysis of Completed Datasets*: The imputed complete dataset will be used to perform the corresponding statistical analysis per imputation as specified in Section 7.5 and Section 7.6.1

3. *Combine Results*: Approaches below will be applied to pool the estimates of the response rate for each arm and the risk difference between active arms and placebo from each imputed dataset:
   a) For the response rate of each arm, the distributions are not expected to be approximately normal, so Rubin's rules (18) should not be used. Instead, the response rate for each arm will be estimated as the mean of individual imputations and the corresponding 95% confidence interval will be calculated using the MI Wilson (17) approach.
   b) The distribution of risk difference between two arms is approximately normal, therefore, Rubin's rules are applicable. Accordingly, PROC MIANALYZE is used to combine the analysis results from step 2 and generate valid statistical inferences by accounting for the variability introduced by the MI process.

Note here, imputing the treatment failure status above is equivalent to imputing the status of not achieving remission status for the secondary endpoint.

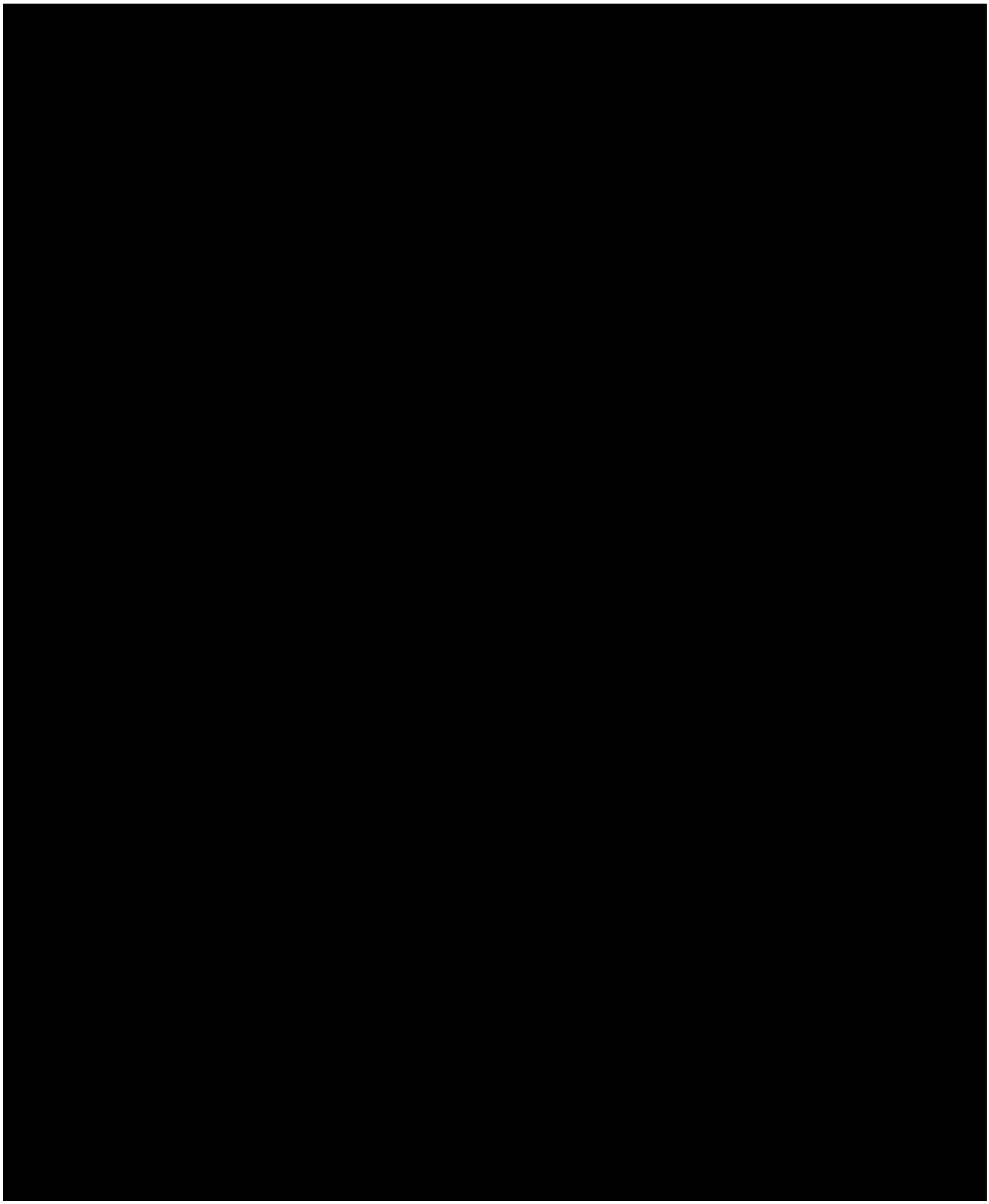


Table 6.6.2: 3 Summary of missing data handling approaches under corresponding Estimand

| *Class of endpoint* | *Randomized maintenance treatment period (RS)* |
|---|---|
| Primary endpoint | EM-PM* [redacted] |
| Key secondary endpoint | EM-MI* [redacted] |
| Secondary Endpoint | Binary: EM-MI* [redacted]<br><br>Time-to-event: EM-PM*, [redacted] |

[redacted]

*Indicates the approach used as primary analysis for this type of endpoint in the specific treatment period
EM=primary **E**stimand for randomized **M**aintenance treatment period. The use of rescue medication (iv spesolimab) use of investigator-prescribed SoC will be considered as on set of GPP flare /treatment failure

[redacted]

### 6.6.3 Safety data

It is not planned to impute missing values in safety evaluations.

For the descriptive reporting of safety data by visit, the data available on each visit will be summarized for the randomized maintenance treatment period, flare treatment period, and OL maintenance treatment period, respectively.

For safety data that is not collected by visit such as AE and possibly clinically significant laboratory abnormality, the original results (**OR**) to be used for the descriptive reporting for corresponding treatment periods.

The only exceptions where imputation might be necessary for safety evaluation are AE dates and, start and stop dates for concomitant medications. Missing or incomplete AE dates are imputed according to BI standards (see *BI-KMED-BDS-HTG-0035* (4)).

Partial start and stop dates for concomitant medications, and background, investigator-prescribed SoC, as well as historical medication for GPP will be imputed to enable subsequent calculation (but not for display) by the following "worst case" approach:

- If the day of the end date is missing, the end date is set to last day of the month (or to the subject's trial completion date, if it is earlier than the last day of the month).
- If the day and month of the end date are missing, the end date is set to 31st of December of the year (or to the subject's trial completion date, if it is earlier than the 31st of December of the year).
- If the day of the start date is missing, the start date is set to first day of the month (except for investigator-prescribed SoC, where the first dosing day will be used if first dosing happened in the same month).
- If the day and month of the start date are missing, the start date is set to 1st January of the year (except for investigator-prescribed SoC, where the first dosing day/month will be used if first dosing happened in the same year).
- All other cases need to be assessed by the trial team on an individual basis, using the above points as guidance.

If a concomitant medication was ticked to be ongoing, it is expected that the end date is missing and will not be imputed for display purposes.

Missing/incomplete start dates of flare treatment at R1/D1 for a GPP flare will be set to the date of occurrence of the applicable flare, the date being consistent with any specification on month and/or year of the flare treatment; other situations need to be assessed by the trial team on an individual basis. Missing/incomplete start dates of flare treatment at R3/D8 will be set to date of the Day 8 visit (if consistent with any specification on the month and/or year) of flare treatment period, otherwise it needs to be assessed by the trial team on an individual basis.

### 6.6.8 Time since first diagnosis

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 June 30th 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

For efficacy and safety analysis, baseline for randomized maintenance treatment period, flare treatment period or OL maintenance treatment period, unless otherwise specified, refers to the last measurement collected prior to the first dose administered during each treatment period separately.

For each treatment periods, measurements reported with date and time and taken prior to start of the first administration of that treatment period will be considered pre-treatment values of that treatment period. Measurements reported with a date only (and no time) and taken on the day of the first administration will also be considered pre-treatment values.

Measurements taken after the first study medication for each of treatment periods will be considered either on- or off-treatment values based on the definition in Section 6.1 for that period, and will be assigned to visits for statistical analysis, if applicable, as defined below.

Analysis of AE data, concomitant medications, and the use of investigator-prescribed SoC, will not be based on visits therefore, no assignment to time windows will be necessary.

The time windows for randomized maintenance treatment period are defined in Table 6.7: 1.

Table 6.7: 1 Time windows for assignment of efficacy, safety lab, vital signs, and biomarker to visits for the randomized maintenance treatment period

| *Visit number* | *Visit label* | *Planned day* | *Time window* | | |
|---|---|---|---|---|---|
| | | | *Window (per CTP)* | *Start (extended)* | *End (extended)* |
| 2 | Day 1 | Day 1[d] | 0 | Day 1 | Day 1 |
| 3 | Week 4 | Day 29 | +/- 7 days | Day 2 | Day 43 |
| 4 | Week 8 | Day 57 | +/- 7 days | Day 44 | Day 71 |
| 5 | Week 12 | Day 85 | +/- 7 days | Day 72 | Day 99 |
| 6 | Week 16 | Day 113 | +/- 7 days | Day 100 | Day 127 |
| 7 | Week 20 | Day 141 | +/- 7 days | Day 128 | Day 155 |
| 8 | Week 24 | Day 169 | +/- 7 days | Day 156 | Day 183 |
| 9 | Week 28 | Day 197 | +/- 7 days | Day 184 | Day 211 |
| 10 | Week 32 | Day 225 | +/- 7 days | Day 212 | Day 239 |
| 11 | Week 36 | Day 253 | +/- 7 days | Day 240 | Day 267 |
| 12 | Week 40 | Day 281 | +/- 7 days | Day 268 | Day 295 |
| 13 | Week 44 | Day 309 | +/- 7 days | Day 296 | Day 323 |
| 14 | Week 48 | Day 337 | +/- 7 days | Day 324 | Day 351 |
| Post week 48[a] | | | | Day 352 | EoT +112 days |
| Off treatment [b] | | | | EoT +113 days | |
| Post Week 48[c] | | | | Day 352 | |

All days are counted relative to the day of the first randomized maintenance treatment, which is defined as V2/D1.
[a] only applicable to safety lab and vital signs analysis for subjects without any flare treatment or OL maintenance treatment who are not rolled over to OLE trial and whose date of EoT is after Day 239.
[b] only applicable to safety lab and vital signs analysis for subjects without any flare treatment or OL maintenance treatment who are not rolled over to OLE trial and whose EoT is before Day 239
[c] only applicable to efficacy and biomarker analysis for subjects without any flare treatment or OL maintenance treatment.
[d] measurements post the first randomized maintenance treatment

All safety and efficacy measurements of the flare treatment period will be assigned to visits around the planned visit dates relative to R1/D1, i.e., the administration of the first i.v. flare treatment. These time windows are defined in Table 6.7: 2.

Table 6.7: 2 Time windows for assignment of efficacy, safety lab, vital signs, and biomarker to visits for the flare treatment period

| *Visit number* | *Visit label* [a] | *Planned day* | *Time window* | | |
|---|---|---|---|---|---|
| | | | *Window (per CTP Flow chart 2)* | *Start (extended)* | *End (extended)* |
| R1 | Week 1, Day 1 | Day 1 | exact day | Day 1 | Day 1 |
| R2 | Week 1, Day 4 | Day 4 | exact day | Day 2 | Day 6 |
| R3 | Week 1, Day 8 | Day 8 | exact day | Day 7 | Day 10 |
| R4 | Week 2 | Day 15 | +/- 3 days | Day 11 | Day 18 |
| R5 | Week 3 | Day 22 | +/- 3 days | Day 19 | Day 25 |
| R6 | Week 4 | Day 29 | +/- 3 days | Day 26 | Day 43 |
| R7 | Week 8 | Day 57 | +/- 7 days | Day 44 | Day 71 |
| Week 12 visit [b] | Week 12 | Day 85 | +/- 3 days | Day 72 | Earlier of Day 99 from first flare treatment at R1/D1 or the day/time before first OL maintenance treatment administration if applicable |

Days are counted relative to the day of first flare treatment received, which is defined as R1/D1 if not specified otherwise.
[a] For subjects who received the administration of the first flare treatment with i.v. spesolimab for the first GPP flare after Week 34 (Day 239) from randomisation, they may not need to attend all visits scheduled per Flow Chart 2 of CTP.
[b] Week 12 visit of flare treatment period could also be the first visit of the OL maintenance treatment period. The assessments before the first OL maintenance treatment could be used for both Week 12 visit of flare treatment period and the baseline for OL maintenance treatment.

The day of administration of the first OL s.c. maintenance treatment will be treated as V1 for OL maintenance treatment period. After V1, subject needs to attend the following visits per Flowchart 1 of CTP. In the table and figures for OL maintenance treatment period, all following visits should count even subject didn't receive the treatments in some of the visits. For example, when the first administration of OL s.c. maintenance dose was given on Day 186, Vx+4 will be treated as V1 (the first day and the planned date of V1 is Day 186), Vx+5 will be treated as V2, Vx+6 will be treated as V3 and etc. (per Table 6.7: 3).

Table 6.7: 3 Time windows for assignment of efficacy, safety lab, vital signs, and biomarker to visits for the OL maintenance treatment period

| *Visit* [a, c] | *Planned day*[*b] | *Time window* | | |
|---|---|---|---|---|
| | | *Window (per CTP)* | *Start (extended)*[b] | *End (extended)* |
| Vx | 85 | +/- 7 days | 72 | 99 |
| Vx+1 | 113 | +/- 7 days | 100 | 127 |
| Vx+2 | 141 | +/- 7 days | 128 | 155 |
| Vx+3 | 169 | +/- 7 days | 156 | 183 |
| Vx+4 | 197 | +/- 7 days | 184 | 211 |
| Vx+5 | 225 | +/- 7 days | 212 | 239 |
| Vx+6 | 253 | +/- 7 days | 240 | 267 |
| Vx+7 | 281 | +/- 7 days | 268 | 295 |
| Vx+8 | 309 | +/- 7 days | 296 | 323 |
| Vx+9 | 337 | +/- 7 days | 324 | 351 |
| | | | | |
| Post last OL visit [d] | | | 352 | EoT+112 days |
| Off treatment [e] | | | EoT + 113 days | |
| Post last OL visit [f] | | | 352 | |

[*]Days are counted relative to the day of first randomized treatment, which is defined as V2/D1.
[a] The visit of the first OL maintenance treatment will be treated as V1 and the following number of visits will be derived accordingly.
[b] For V1 of OL maintenance treatment period, the planned date of this visit is the day of the first administration of OL s.c. maintenance treatment.
[c] The visit label for OL maintenance starts with "OL M-".
[d] only applicable to safety lab and vital signs analysis for subjects with OL maintenance treatment who are not rolled over to OLE trial and whose date of EoT is after Day 239.
[e] only applicable to safety lab and vital signs analysis for subjects who have OL maintenance treatment and are not rolled over to OLE trial and whose EoT is before Day 239
[f] only applicable to efficacy and biomarker analysis and to subjects with OL maintenance treatment.

Repeated and unscheduled efficacy, safety and other measurements will be handled similarly to scheduled measurements and will also be assigned to a time window depending upon the date of measurement. For handling of laboratory measurements see also Section 7.8.2.

[redacted].

Tables and figures presenting results of the statistical analysis will only display visits at which the respective parameter was planned to be collected according to the CTP.

# 7. PLANNED ANALYSIS

The primary objective is to provide dose-ranging data for 3 dose regimens of spesolimab compared to placebo on the primary endpoint of the time to the first GPP flare onset up to week 48. If the primary objective regarding achievement of a non-flat dose response curve is successful, the secondary objective will be performed, which is to perform formal testing on the superiority of spesolimab s.c. treatment versus placebo, on the efficacy endpoints as defined in Section 7.1 of CTP.

Per CTP Section 7

*The primary analysis is planned to be performed once all randomized subjects have completed the 48-week treatment observation period. The final analysis is planned to be performed at the end of the study once all randomized subjects have completed the study (including any follow-up period), if applicable. The two analyses may be performed as a single analysis (at the time of trial completion), if, prior to the time of the primary analysis, the trial team agrees that the expected time interval between the planned analyses is insufficient to justify the performance of separate analyses.*

*To support a potential spesolimab GPP flare treatment submission, interim analysis of the open-label rescue treatment and subsequent maintenance treatment periods will be performed using all open-label data up to a cut-off date, which will be pre-specified in the data cleaning plan for the interim analysis. Randomized maintenance s.c. treatments will remain blinded and data from the randomized treatment period will not be analyzed in the interim analysis. The timing of the interim analysis is driven by the timing of the submission of the flare treatment when deemed necessary*

The detailed information of interim analysis is described in Section 7.9

The format of the listings and tables will follow the BI guideline "Standards for Reporting of Clinical Trials and Project Summaries " (*BI-KMED-BDS-HTG-0045*) (10).

The individual values of all subjects will be listed. Listings will generally be sorted by country, center number, patient number and visit (if visit is applicable in the respective listing). AE listings will be sorted by assigned treatment (see section 7.8.1 below for details). The listings will be contained in Appendix 16.2 (SDL) of the CTR.

The following standard descriptive statistical parameters will be displayed in summary tables of continuous variables:

| | |
|---|---|
| N | number of non-missing observations |
| Mean | arithmetic mean |
| SD | standard deviation |
| Min | minimum |
| Q1 | lower quartile |
| Median | median |
| Q3 | upper quartile |
| Max | maximum |

Statistical parameters will be displayed to a defined number of decimal places as specified in the BI guideline "Standards for Reporting of Clinical Trials and Project Summaries " (*BI-KMED-BDS-HTG-0045*) (10).

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. Percentages will be rounded to one decimal place. The category missing will be displayed if and only if missing values exist. Percentages will be displayed based on all subjects in the respective subject set regardless of the status of missingness.

Disposition of the patient population participating in the trial will be summarized by the frequency of subjects screened, randomized, screened but not randomized, randomized but not treated, randomized and treated, who completed randomized medication, who were prematurely discontinued from trial medication from randomized maintenance treatment, by reason, who received flare treatment at R1/D1 and at R3/D8 respectively, who completed flare treatment period, who were prematurely discontinued from flare treatment period, by reason, who received OL maintenance treatment, who completed the planned OL maintenance treatment and who were prematurely discontinued from OL maintenance treatment, by reason.

## 7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this Section of the CTR.

Descriptive statistics will be presented by treatment for demographic parameters and baseline characteristics, based on the RS. The systemic GPP medication use at randomisation will be presented by treatment for baseline characteristics as well.

The presence of mutations (yes or no) in the following genotypes will be descriptively presented by treatment for the RS: IL36RN, CARD14, or AP1S3 based on information collected via eCRF and the results for the DNA resequencing respectively.

Characteristics of the trial disease, including details on the past GPP flares prior to trial onset, will be displayed for randomized subjects based on the RS.

For the continuous variables described below, the following categories will be defined, and presented according to the number and percentage of subjects in each category.

Table 7.1: 1 Categories for summary of continuous variables

| *Variable* | *Categories* |
|---|---|
| Age | < 50 years<br>50 to < 65 years<br>≧ 65 years<br><br>Adolescent: age ≥12 years and <18 years<br>Adult: age ≥18 years<br><br>< 65 years<br>≧65 years |
| Weight | ≤70 kg<br>>70 to ≤80 kg<br>>80 to ≤ 90 kg<br>>90 kg<br><br>Weight related BE bound<br>< 53.8 kg<br>≧53.8 to < 91 kg<br>≧ 91 kg |
| BMI | < 25 kg/$m^2$<br>25 to < 30 kg/$m^2$<br>≧ 30 kg/$m^2$ |
| Time since first diagnosis | ≤ 1 year<br>> 1 to ≤ 5 years<br>> 5 to ≤ 10 years<br>> 10 years |

## 7.2 CONCOMITANT DISEASES AND MEDICATION

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

Analyses of concomitant diseases (i.e., baseline conditions) and concomitant medications for randomized treatment period will be based on RS. Analyses of concomitant medication for flare treatment period and OL maintenance treatment period will be based on the SAF-FT and SAF-MT respectively. The grouping should be aligned with the treatment arms specified in Section 6.1 of each treatment period, respectively.

Concomitant diseases and concomitant non-drug therapies will be coded according to the most recent version of MedDRA. Concomitant medications will be coded according to the most recent version of the World Health Organisation – Drug Dictionary.

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

- is ongoing at the start of that treatment period or

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

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 randomized trial treatment.

Concomitant medication use (excluding investigator-prescribed SoC as defined in the CTP) will be summarized with frequency and percentage of subjects by ATC3 class and preferred name.

Concomitant use of restricted medication for indications other than GPP will be summarized with frequency and percentage of subjects by ATC3 class and preferred name, based on RS.

The frequency and percentage of subjects with historical medication for GPP will be displayed, including presentation by type of historical medication (preferred name), by randomized treatment and in total, based on RS.

The frequency and percentage of subjects with concomitant use of systemic GPP medication at randomisation will be displayed, including presentation by type of systemic GPP medication (preferred name). In case there are discrepancies between the actual concomitant use of systemic GPP medication and the stratum assigned for randomisation from IRT, the stratification used for IRT may also be summarized by randomized treatment and in total, based on RS.

All the concomitant medication use from the eCRF will be reviewed by the sponsor medical team and the use of investigator-prescribed to treat GPP worsening will be identified and documented in the decision log before DBL. The use of investigator-prescribed SoC will be summarized separately (see Section 7.6.2).

Concomitant use of non-drug therapies will be summarized with frequency and percentage.

[redacted]

## 7.4 PRIMARY ENDPOINT(S)

### 7.4.1 Primary analysis of the primary endpoint(s)

The primary analysis will be implemented under **EM-PM** approach (primary **E**stimand for randomized **M**aintenance period using **P**rimary **M**ethod for censoring rules) defined in Section 5.1 and Section 6.6.2.

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

**Primary Objective: Dose Finding**

The Multiple Comparison Procedures and Modeling (MCP-Mod) approach (19, 20) is implemented in two main steps: (1) trial design stage; (2) trial analysis stage. The procedures for the trial design stage, including the selection of candidate models covering a suitable range of dose-response shapes and sample size and power calculations, are provided in the CTP Section 7.2.2. The procedures for the trial analysis stage are specified below.

For the primary analysis, the dose-response relationship will be modeled using the total planned dose. In this trial, the total is the sum of all planned randomized maintenance doses administered to the subject prior to week 48, including both loading and maintenance phase. Therefore, it is assumed that the cumulative concentration over time (AUC) and thus the cumulative total dose is the key driver of the efficacy response in the modeling part of MCP-Mod. Table 7.4:1 shows the calculated total doses per treatment arm.

Table 7.4:1 Total dose per treatment arm during randomized maintenance treatment period

| *Treatment arm* | *Total dose* |
|---|---|
| Speso SC Low: 300 mg day 1<br>150mg q12w | 300mg at Day 1, 150mg at week 12, week 24 and week 36,<br>Total dose:750 mg spesolimab |
| Speso SC Medium: 600 mg day 1<br>300mg q12w | 600mg at Day 1, 300mg at week 12, week 24 and week 36,<br>Total dose:1500 mg spesolimab |
| Speso SC High: 600 mg day 1<br>300mg q4w | 600mg at Day 1, 300mg at week 4, week 8, week 12, week 36, week 20, week 24, week 28, w32, w36, week 40, week 44<br>Total dose: 3900 mg spesolimab |
| Placebo | Placebo at Day 1, week 4, week 8, week 12, week 16, week 20, week 24, week 28, w32, w36, week 40, week 44,<br>Total dose 0 mg spesolimab |

The responses for treatment difference estimate over placebo for each active dose group, which is based on the log hazard ratio of the active doses versus placebo, as well as their estimated variance-covariance matrix estimate for the primary endpoint are estimated by stratified Cox regression model on the time to the first GPP flare. The subsequent MCP-Mod analysis are based on the log hazard ratio from the stratified Cox regression model. In the case

of zero event in one/some of the arms by stratum, the stratified Cox regression model will be conducted using Firth's penalization (21, 22, 23)

*Sample code*

```
PROC PHREG DATA=adtte;
 CLASS treatment stratification (REF='placebo');
 MODEL aval*cnsr (list)=treatment/ TIES=BRESLOW FIRTH;
 STRATA stratification;
 HAZARDRATIO treatment / DIFF=REF CL=WALD ALPHA=0.05;
 ODS OUTPUT HAZARDRATIOS=hazard;
RUN;
```

The multiple comparison procedure will be implemented using optimal contrast tests which control the 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 7.2.2:1 of CTP. For the final evaluation, these optimal contrasts will be updated using the estimated variance-covariance matrix from the collected data. The updated contrast coefficients will be reported 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 dose-response model is derived as a weighted average over all significant model shapes. The weights for each significant model ($M_k$) are given by

$$w(M_k) = \frac{exp(-0.5AIC(M_k))}{\sum_{i=1}^{K} \exp\left(-0.5AIC(M_i)\right)},$$

where $AIC(M_k)$ is the Akaike Information Criterion (AIC) of model $M_k$

Estimates for each dose group will be calculated and the final dose-response curve will be based on the final model.

The following displays are planned,

- Table of the updated contrast coefficients per dose group and candidate model, together with the MCP-Mod test statistics and p-values for each model and the critical values;
- For averaging model, figure of the dose-response curve;
- For all significant model shapes, figures of the dose-response curve plus 95% confidence band (of the predicted shape) and 95% CI per dose (estimated from stratified Cox model).

**Secondary Objective: Formal Statistical Testing**

The primary analysis for the secondary objective on the superiority of spesolimab over placebo. Time to first GPP flare up to week 48 for **Speso SC High** and **Speso SC Medium** versus placebo will be tested using **EM-PM** approach, i.e., primary Estimand using the

primary censoring rule, and via the stratified log-rank test stratified by the factor of the systemic concomitant use of GPP medications at randomisation (yes or no), based on the **RS**.

The estimated hazard ratios based on the same stratified Cox regression model as for the primary objective will be displayed for active spesolimab treatment arm versus placebo. In the case of zero event in one/some of the arms by stratum, the stratified Cox regression model will be conducted using Firth's penalization (21, 22, 23). A hazard ratio of less than one favors spesolimab. The treatment comparison will be made regardless of the treatment adherence or early discontinuation up to Week 48.

Kaplan-Meier (KM) estimates of the survival/failure probabilities at 4-week intervals, as well as the median survival time will be provided by treatment arm. $10^{th}$ and $25^{th}$ survival time percentile will be provided as deemed necessary. KM estimates of the event probability does not take the stratification factor, use of systemic GPP medication at baseline, into account.

As more flare events are expected within the first 3 months after randomisation (per CTP Section 7.5), the KM estimates are shown at a 1-week interval for the first 12 weeks of observation. Confidence intervals will be based on two-sided $\alpha = 0.05$ using complementary log(-log) transformation (*conftype=loglog*). A KM curve will also be provided by treatment.

*Sample SAS Code*

```
PROC LIFETEST DATA=adtte;
 TIME aval*cnsr (list);
  STRATA stratification / GROUP=treatment TEST=logrank;
RUN;
```

The primary method for handling of missing data and censoring rules on the time to the first GPP flare is described in Section 6.6.2.

[redacted]

## 7.5 SECONDARY ENDPOINT(S)

### 7.5.1 Key secondary endpoint(s)

7.5.1.1 Primary analysis of the key secondary endpoint(s)

The key secondary endpoint serves the secondary objective of the trial through formal statistical testing procedure.

The primary analysis for the key secondary endpoint will be tested using **EM-MI** approach, i.e., primary Estimand after applying multiple imputation. The stratified Cochran-Mantel-Haenszel (CMH) test based on the RS will be used. If a subject discontinues the treatment early but continues in the study, the primary analysis will include subjects' on- and off-treatment data up to Week 48.

The stratified Cochran-Mantel-Haenszel (CMH) test will be performed for each dose level of spesolimab versus placebo stratified by the concomitant use of systemic GPP medications at randomisation (yes or no) based on the RS. The difference in the proportion of subjects who have at least one GPP flare up to week 48, will be presented for each active group versus the placebo group using the Mantel-Haenszel type weighted average of risk differences. The averaged risk difference will use weights as proposed by Greenland & Robins (24). The associated confidence intervals of the averaged risk difference will use Sato's method (25).

*Sample code for CMH test*

```
PROC FREQ DATA=data;
 TABLES stratification*treatment*response / CMH  commonriskdiff nopercent
RISKDIFF(COMMON COLUMN=2);
```

RUN;

The primary method for handling of missing data on the occurrence of at least one GPP flare is described in Section 6.6.2.

In addition to the risk difference up to week 48, as a monotone binary endpoint, the proportion of subjects who have at least one GPP flare for each arm up to certain time points may also be provided using data handled by **EM-MI** approach. The certain time points are specified as each visit at a 4-week interval up to week 48. 95% confidence interval (CI) of the proportion will be calculated using the method of Wilson.

### 7.5.2 Secondary endpoint(s)

The secondary endpoints defined below, for the secondary objective of the trial only, are included into the statistical testing strategy.

*Time to first worsening of Psoriasis Symptom Scale (PSS) up to week 48 defined as a 4-point increase in total score from baseline. Intake of rescue medication, or investigator-prescribed SoC, will be considered as onset of a worsening.*

*Time to first worsening of Dermatology Quality of Life Index (DLQI) up to week 48 defined as a 4-point increase in total score from baseline. Intake of rescue medication, or investigator-prescribed SoC, will be considered as onset of a worsening.*

The primary analyses of the two secondary endpoints are as same as that of the primary endpoint using **EM-PM** approach based on RS.

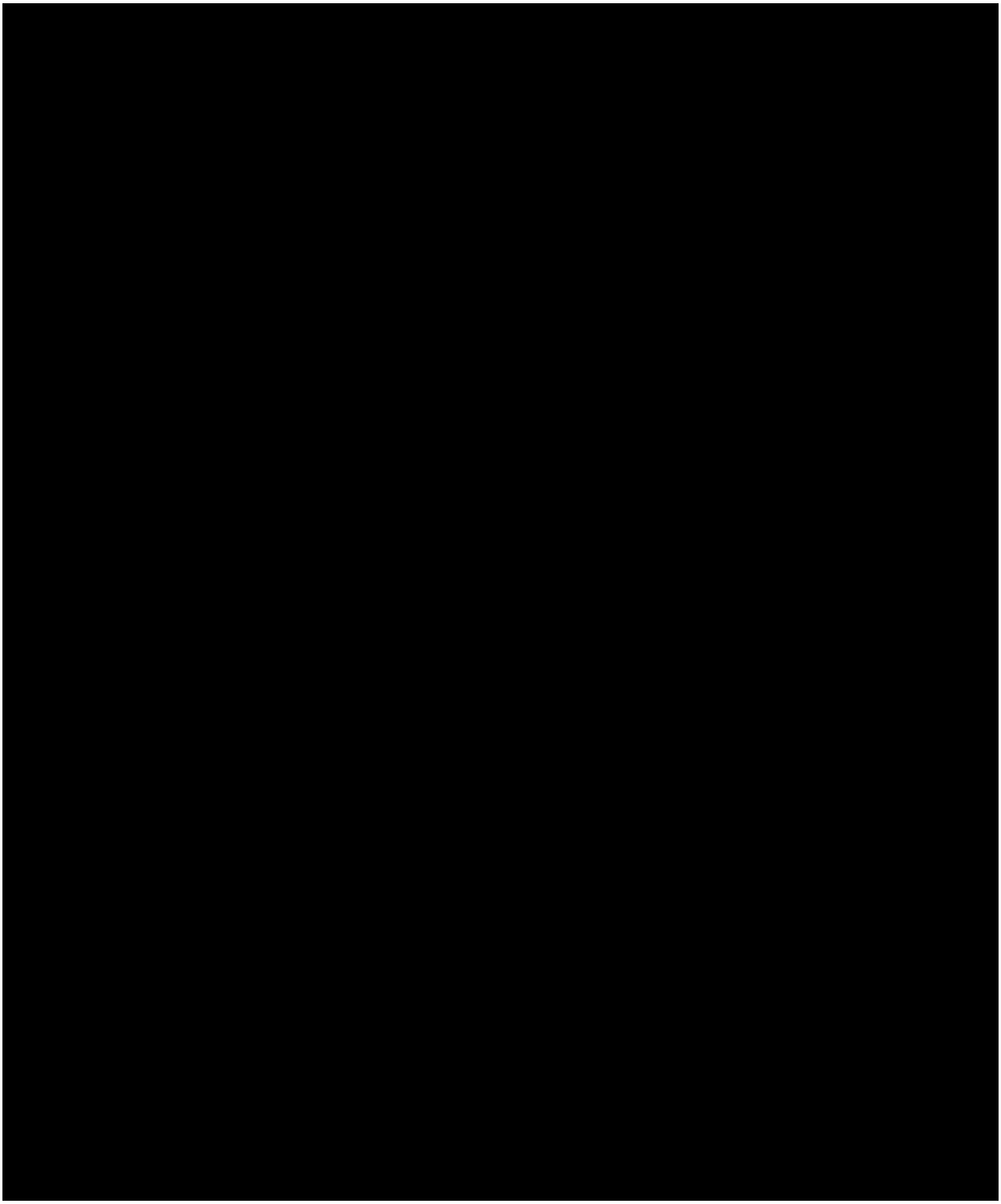
Subjects with the following situation/s will be censored at Day 1 in all corresponding time-to-event analyses

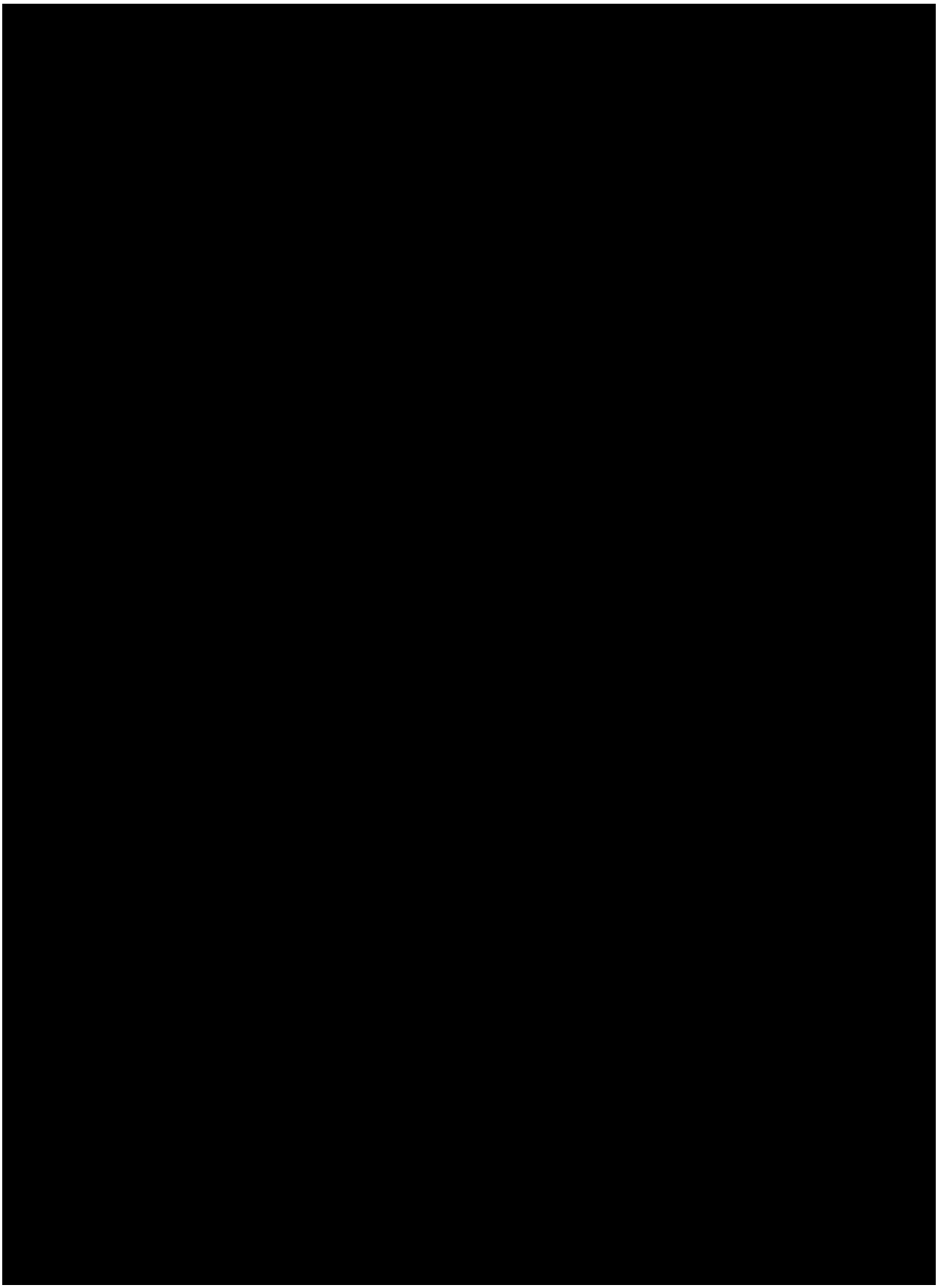
- Without a baseline evaluation in PSS/DLQI
- Do not eligible for the evaluation of worsening
    - PSS baseline >12;
    - DLQI baseline >26;
    - DLQI questionnaire for subject whose age is under 16.

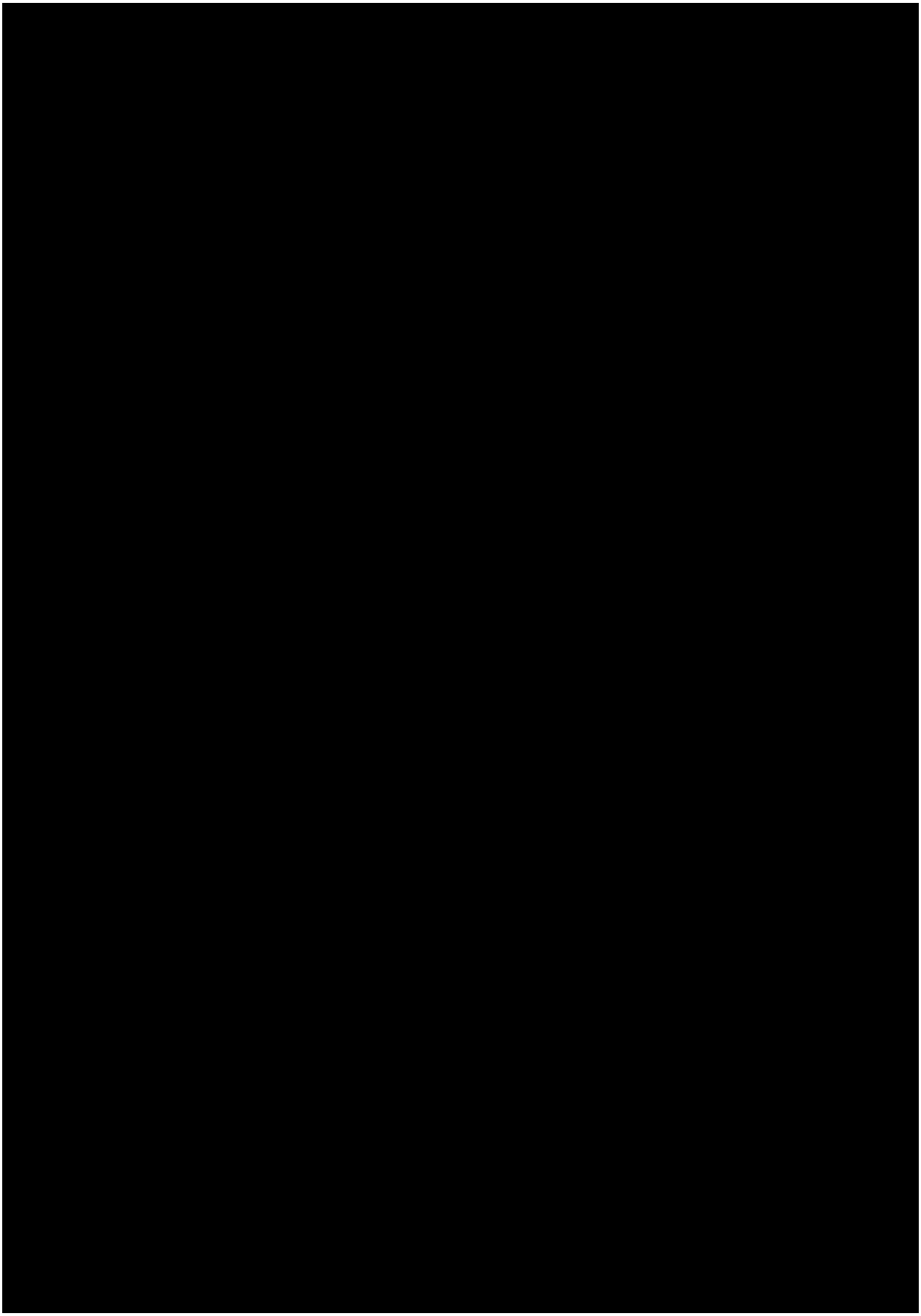
The below-defined secondary endpoint is not included into the statistical testing strategy of the secondary objective.

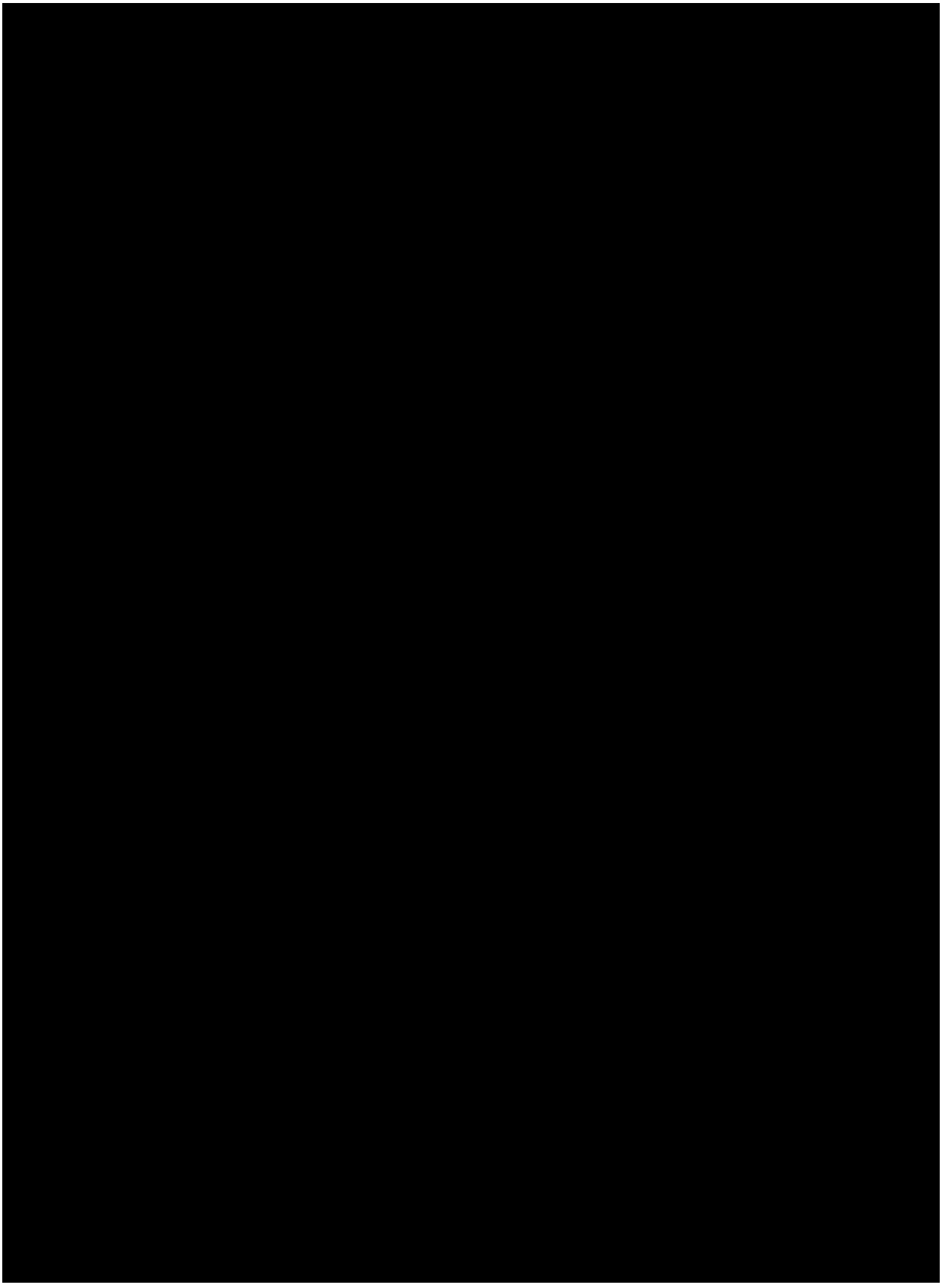
*Sustained remission, defined as a subject with a GPPGA score of 0 or 1 (clear or almost clear) at all visits up to week 48, without intake of rescue medication, or investigator-prescribed SoC.*

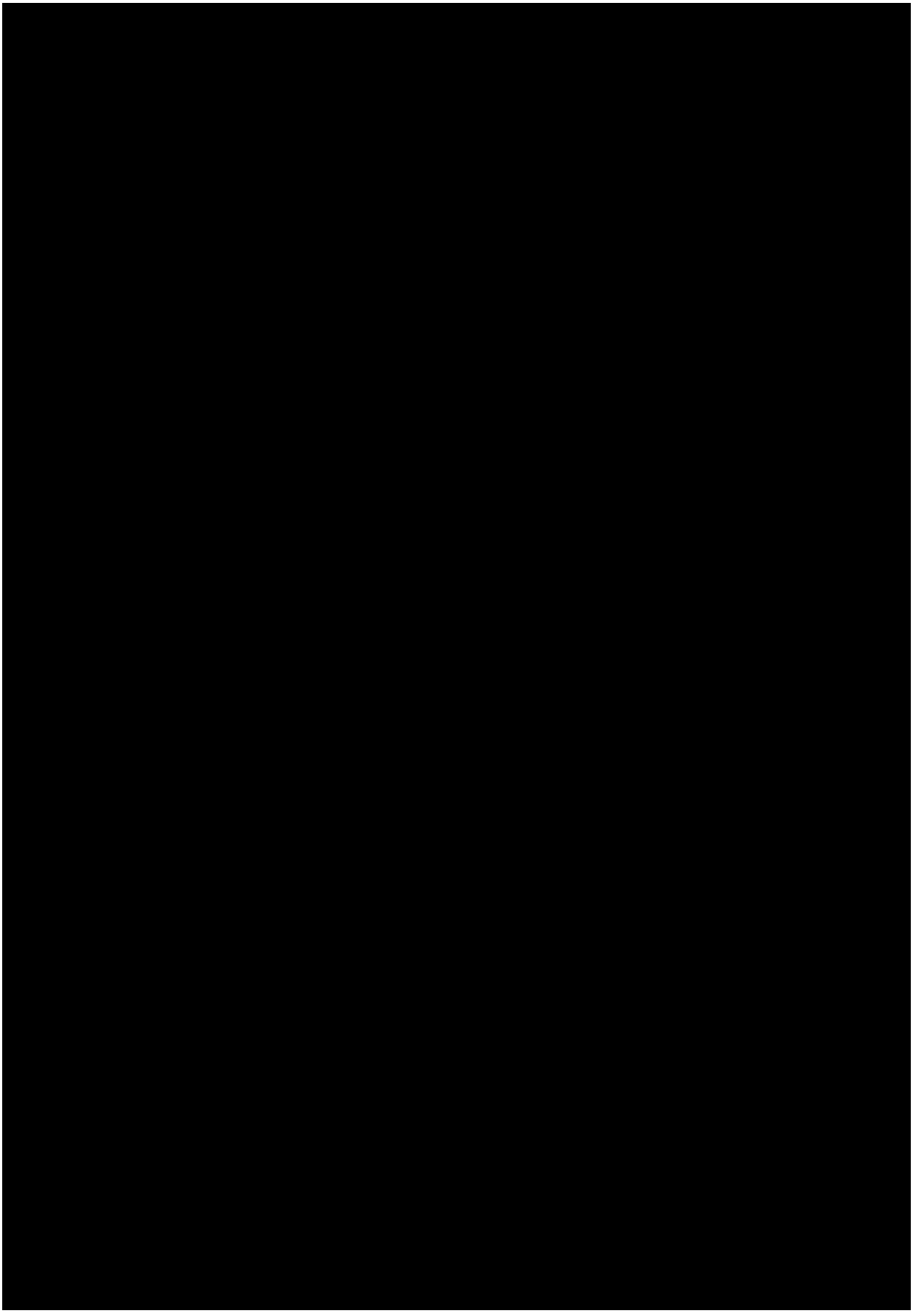
The primary analysis of the above secondary endpoints is consistent with that of the key secondary endpoint using **EM-MI** approach.

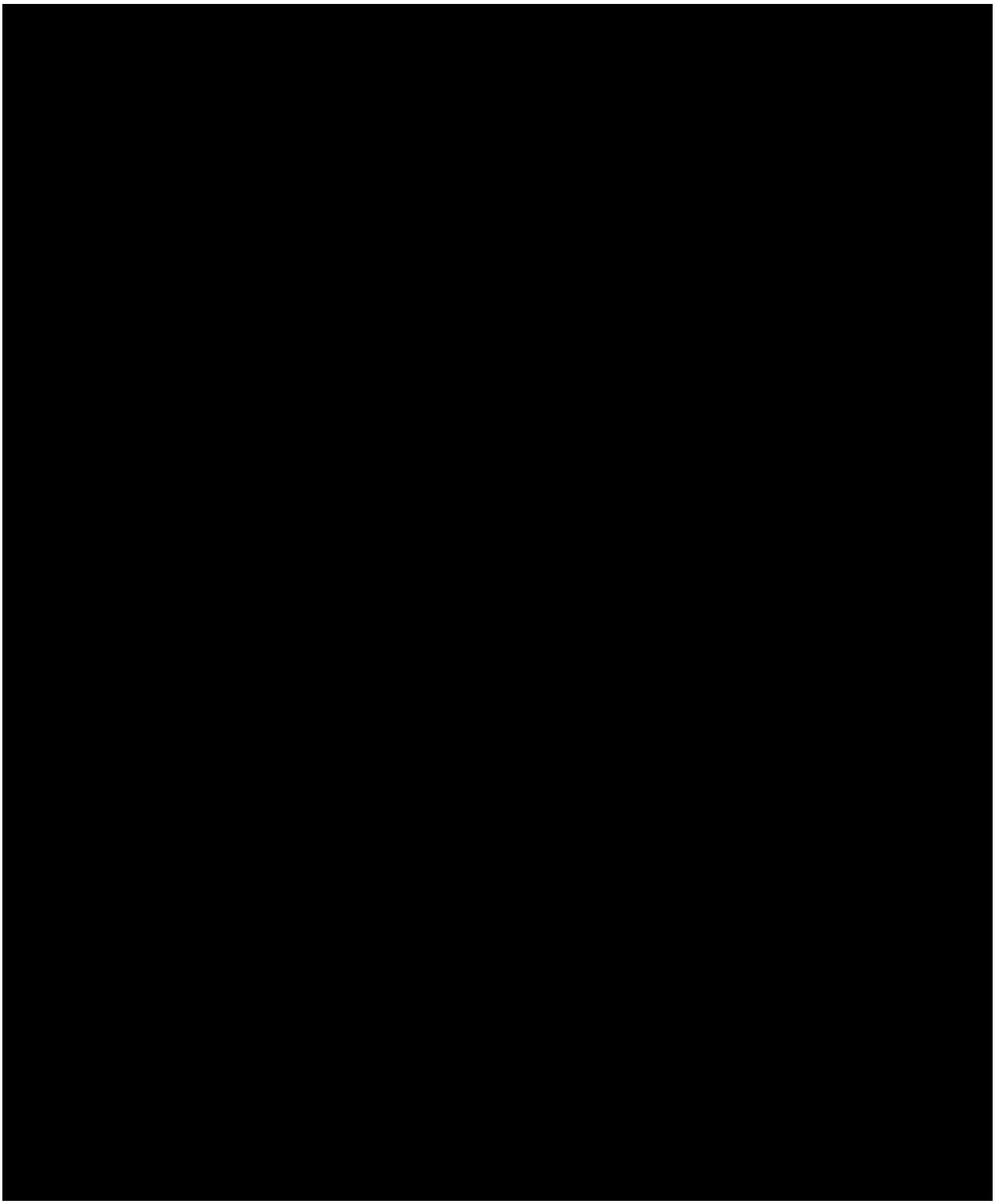












## 7.8 SAFETY ANALYSIS

Safety analyses for randomized maintenance treatment period, flare treatment period and OL maintenance treatment period will be performed based on the SAF, SAF-FT and SAF-MT respectively following BI standards. Data will be summarized descriptively without any imputation based on data available of each corresponding treatment period. In addition, AEs post any spesolimab (i.v. or s.c.) will be summarized. No hypothesis testing is planned. Since the onset time of an AE will not be collected in the trial, any AE which occurs on the same day as the first dose of each treatment period will be assigned to that treatment period.

### 7.8.1 Adverse Events

AEs will be coded with the most recent version of MedDRA. Subjects will be analyzed according to the actual treatment received in each treatment period, i.e., randomized maintenance period, flare treatment period and OL maintenance period, respectively. In addition, the analysis for overall period post use of any spesolimab (s.c. or i.v.) will be performed for all subjects received at least one dose of spesolimab (s.c. or i.v.).

The exposure adjusted incidence rate (per 100 subject years) of a treatment emergent adverse event (TEAE) is defined as the number of subjects experiencing the adverse event per treatment group during time at risk divided by the total time of subjects at risk in that treatment group to contribute the event to the analysis multiplied by 100 (per 100 subject years), where:

Time at risk [subject years] = (date of onset of TEAE – the first dose of treatment in the applicable treatment period + 1) / 365.25 for subjects with onset of TEAE

During randomized maintenance treatment period, if the selected treatment emergent adverse event did not occur, the time at risk will be censored at the end of the treatment period as defined in Section 6.1.

To distinguish the GPP flare symptoms from treatment emergent adverse event, sensitivity analysis for the safety during randomized maintenance treatment period will be done by censoring the time at risk to 7 days prior to first spesolimab iv treatment for subject who received the rescue spesolimab i.v. treatment. For subjects without the flare treatment, the time at risk will be censored at the end of the randomized treatment period as specified in Section 6.1.

For the randomized maintenance treatment period, analysis of the time to the first specific AE, which will be pre-defined in the ISS SAP, may also be provided. Kaplan-Meier (KM) estimates of the survival/failure probabilities, as well as the median time-to-event, will be displayed by randomized treatment arm. Confidence intervals will be based on two-sided $\alpha$= 0.05 using complementary log(-log) transformation (conftype=loglog). A Kaplan-Meier curve will also be produced. For subjects who do not experience the defined the event, the time at risk will be censored at the end of the treatment period as defined in Section 6.1.

For flare treatment period, if the selected treatment emergent adverse event did not occur, the time at risk will be censored at the end of the treatment period as defined in Section 6.1.

For OL maintenance treatment period or overall period post any spesolimab use (i.e., i.v. or s.c.), if the selected treatment emergent adverse event did not occur, the time at risk will be censored at the end of the treatment period as defined in Section 6.1 for OL maintenance phase.

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

Incidence rate [1/100 Subject years (pt-yrs)] = 100 * number of subjects with AE / Total AE-specific time at risk [subject years].

The analyses of AEs will be descriptive in nature. All analyses of AEs will be based on the exposure adjusted incidence rates (per 100 subject years), as well as the number of subjects with AEs and not on the number of AEs. System organ classes (if applicable) will be sorted according to the standard sort order specified by the EMA. Preferred terms (if applicable) will be sorted by total frequency (within system organ class) across all treatment columns.

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" (7) [*001-MCG-156*] and "Handling of missing and incomplete AE dates" (4) [*BI-KMED-BDS-HTG-0035*].

The analysis of AEs will be based on the concept of treatment emergent AEs. This means that all AEs will be assigned to the screening phase, applicable treatment phase or follow-up phase as defined in Section 6.1.

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):

- Hepatic injury
- Systemic hypersensitivity reactions including infusion reactions and anaphylactic reaction
- Severe infections (according to RCTC grading in the ISF, selected laboratory parameters will be assessed by CTCAE in addition to RCTC grades, where possible)
- Opportunistic and mycobacterium tuberculosis infections

The investigator identified AESI will be captured from the eCRF and reported as "Investigator reported AESI" table.

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

Table 7.8.1: 1 Project MedDRA search criteria for User Defined Adverse Event Concepts

| *User-defined AE category* | | |
|---|---|---|
| *Label* | | *Description* |
| Infections (serious/severe, opportunistic) | Infections ALL | Combined search strategy based on the individual UDAECs described below; the UDAEC "severe infections (investigator-defined) will be disregarded for this search |
| | Opportunistic infections | Narrow SMQ "Opportunistic infections" |
| | Tuberculosis infections | BIcMQ "Infections":<br>Narrow sub-search 8.2 "Tuberculosis related terms" |
| | Serious infections | all serious events in SOC "Infections and infestations" |
| | Severe infections | all events in SOC "Infections and infestations" of at least severe RCTC grade, by HLGT |
| Hypersensitivity | Hypersensitivity ALL | Combined search strategy based on the individual UDAECs for hypersensitivity described below |
| | Anaphylactic reaction | Narrow SMQ "Anaphylactic reaction" |
| | Angioedema | Narrow SMQ "Angioedema" |
| | Hypersensitivity | Narrow SMQ "Hypersensitivity" |
| | DRESS, algorithmic | Based on broad SMQ "Drug reaction with eosinophilia and systemic symptoms" (SMQ code 20000225), defined using algorithm as follows:<br>A or (B and C and D) or (B and C and E) or (B and D and E) where the categories A, B, C, D and E are defined categorisations of the PTs of the SMQ. For PTs of category A only narrow scope is used, for all other categories broad scope is used.<br>For identification of potential DRESS through the combination of adverse event occurrences within each of the categories B, C, D and E, adverse event start and end dates will be used. For the latter, potential DRESS is then identified if, within a 7-day period after occurrence of a relevant contributing event (assessed on each day between start and end date [inclusive] of the initiating event), there is at least one adverse event reported (based on start date only) from each of the other applicable categories within a specific combination of categories as described above (in parentheses). |
| | DRESS, narrow | Narrow SMQ "Drug reaction with eosinophilia and systemic symptoms", any event within category A only |
| Malignancies | Malignant tumours | Narrow Sub-SMQ "Malignant tumours"<br>Narrow Sub-SMQ "Haematological malignant tumours"<br>Narrow Sub-SMQ "Non-Haematological 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 NMSC | Sub-SMQ "Malignant tumours" excluding NMSC, whereas NMSC is defined above |

| *User-defined AE category* | | |
|---|---|---|
| *Label* | | *Description* |
| 3-point MACE | 3-point MACE | BIcMQ "Major Adverse Cardiovascular Events" with<br>Narrow sub-search 1.1 "3-Point MACE (part 1/2)"<br>Narrow sub-search 1.2 "3-Point MACE (part 2/2)" * |
| Torsade de Pointes | Torsade de Pointes | Broad sub-SMQ "Torsade de pointes/QT prolongation" |
| Peripheral neuropathy | Peripheral neuropathy | SMQ "Demyelination, narrow;<br>SMQ "Guillain-Barre syndrome", narrow;<br>SMQ "Peripheral neuropathy", narrow |

* 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)

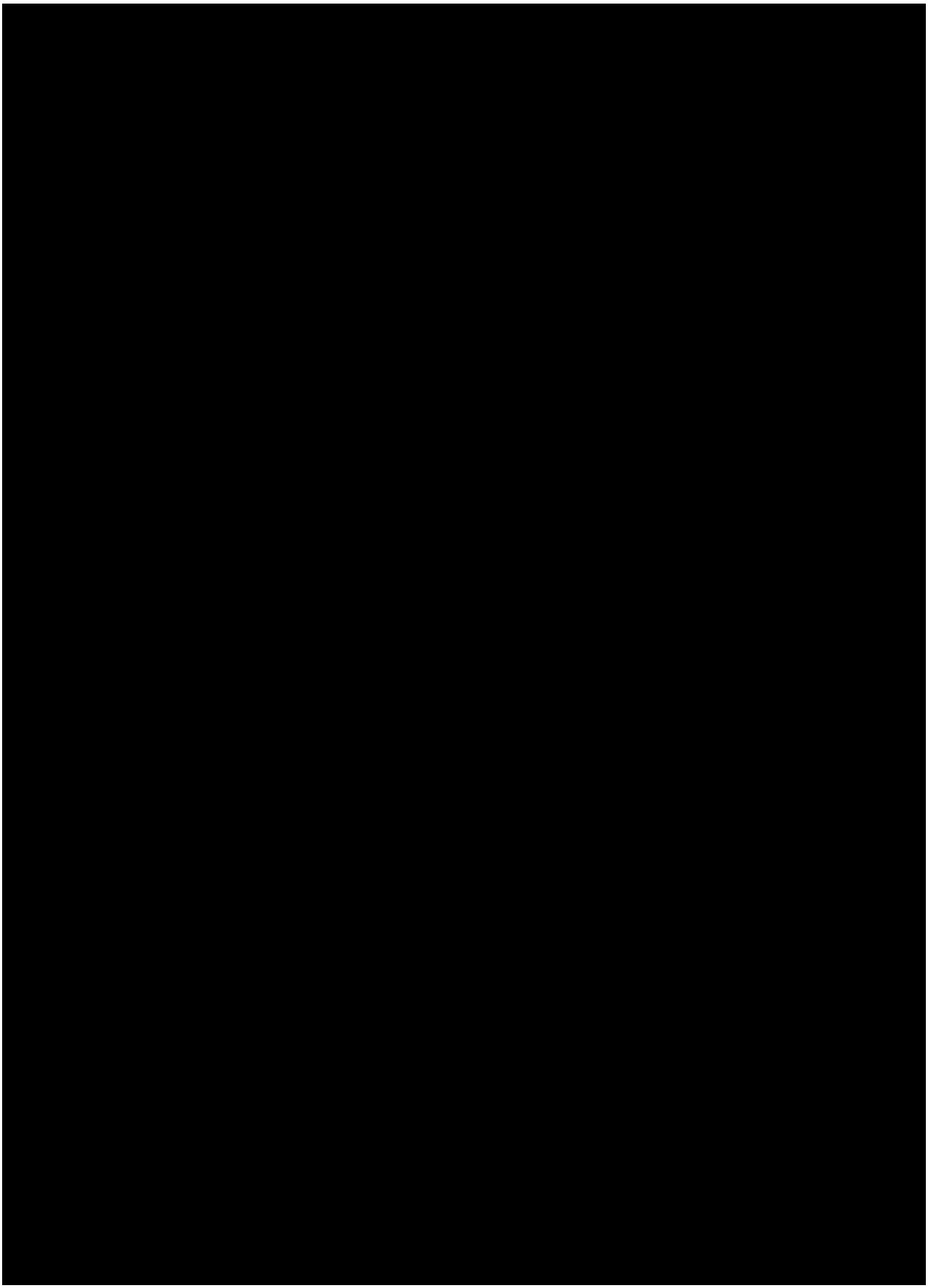
According to ICH E3 (10), in addition to Deaths and serious adverse events, 'other significant' AEs need to be listed in the clinical trial report. These will be any non-serious adverse event that led to an action taken with study drug (e.g., discontinuation or dose reduced or interrupted). An overall summary of adverse events will be presented.

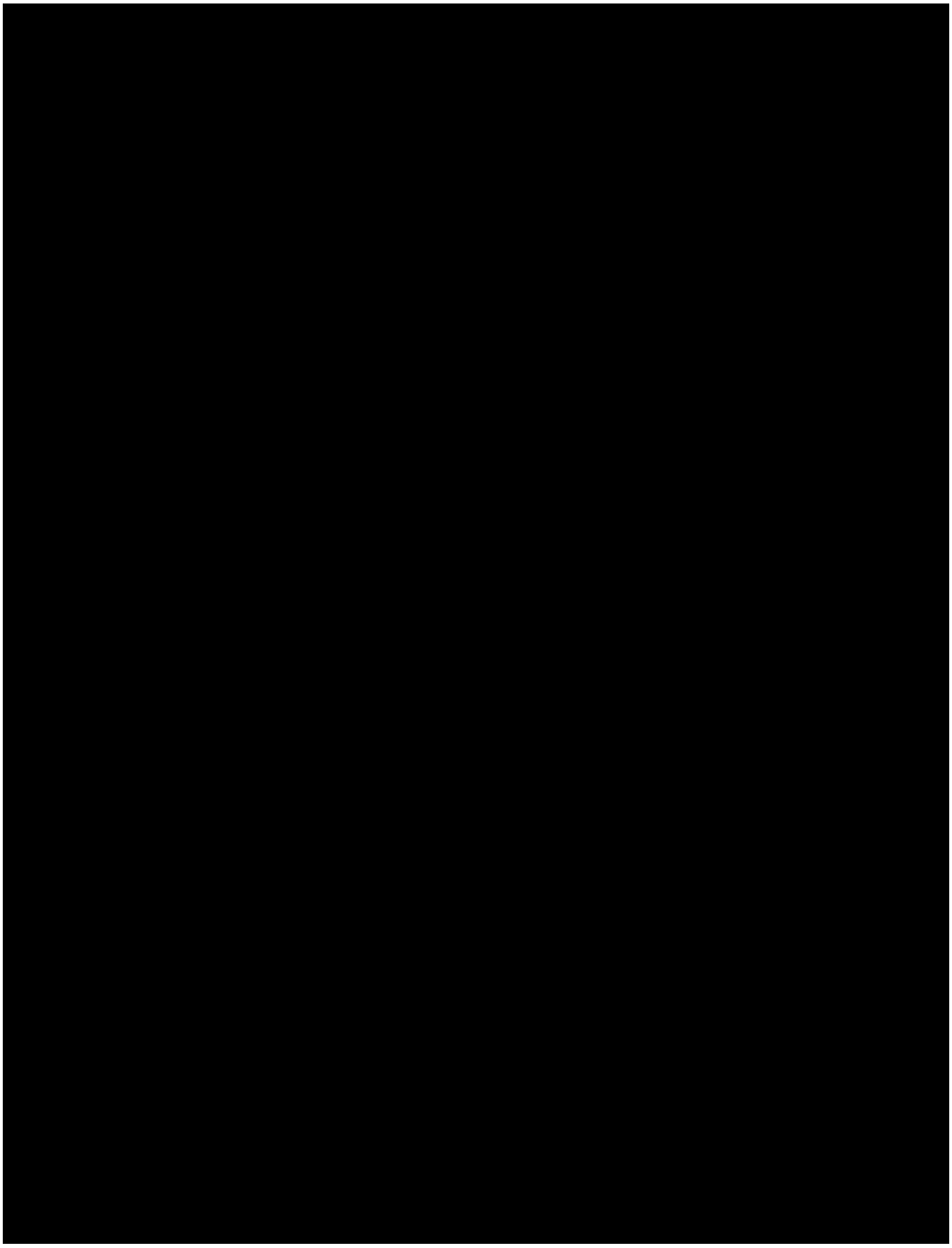
The exposure-adjusted incidence rate and frequency of subjects with AEs will be summarized by treatment, primary system organ class and preferred term. AEs which were considered by the investigator to be drug related will be summarized separately. Separate tables will also be provided for subjects with SAEs, subjects with AEs leading to study drug discontinuation, subjects with AESIs, subjects with other significant AEs (derived based upon ICH E3 (9)), User-defined Adverse Event Concepts (UDAEC) (Table 7.8.1:1) and serious UDAEC. AEs will also be summarized by maximum intensity.

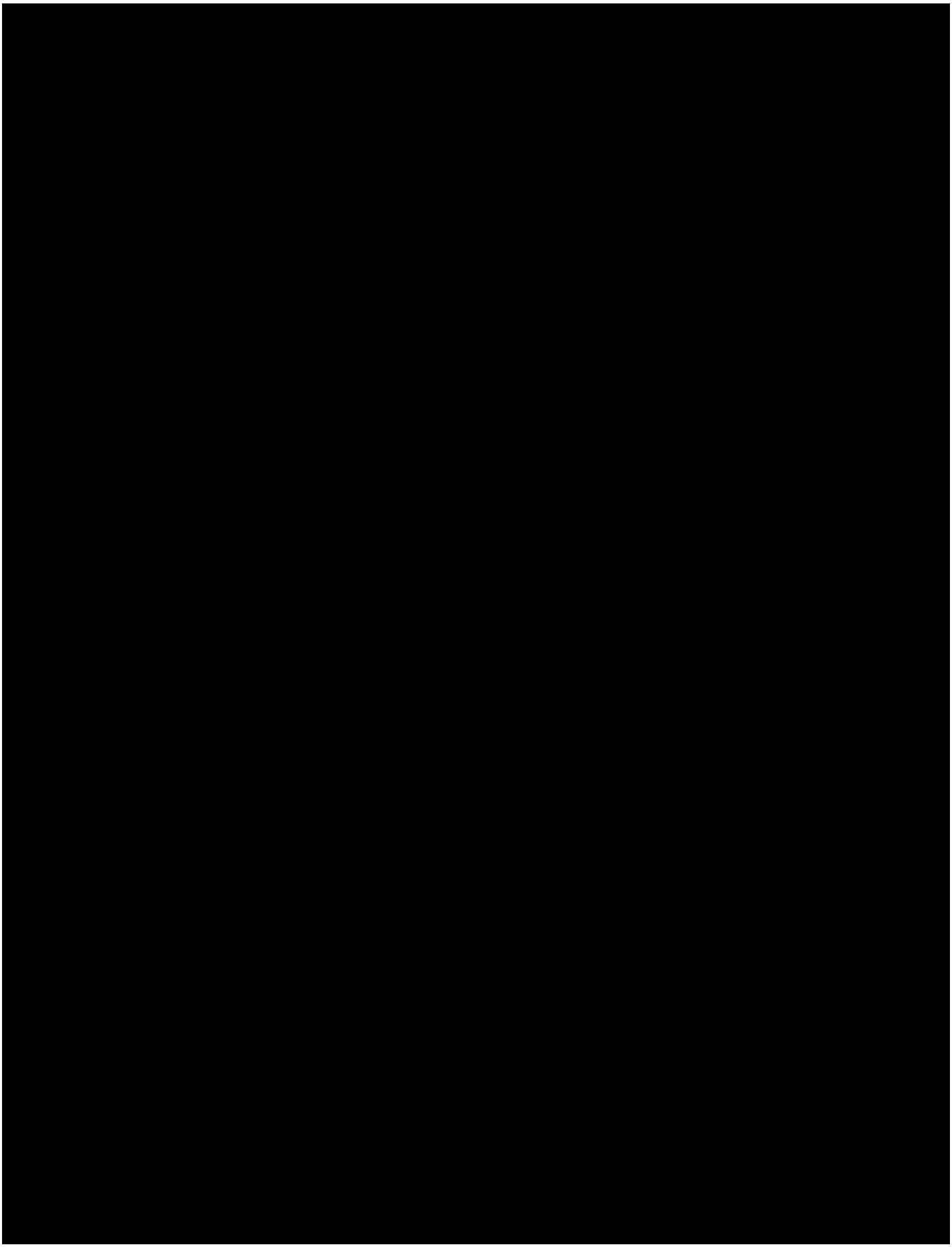
For disclosure of AE data on ClinicalTrials.gov, the frequency of subjects with non-serious AEs occurring with an incidence of greater than 5 % (in preferred terms) will be summarized by treatment, primary system organ class and preferred term. The frequency of subjects with SAEs and drug related SAEs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

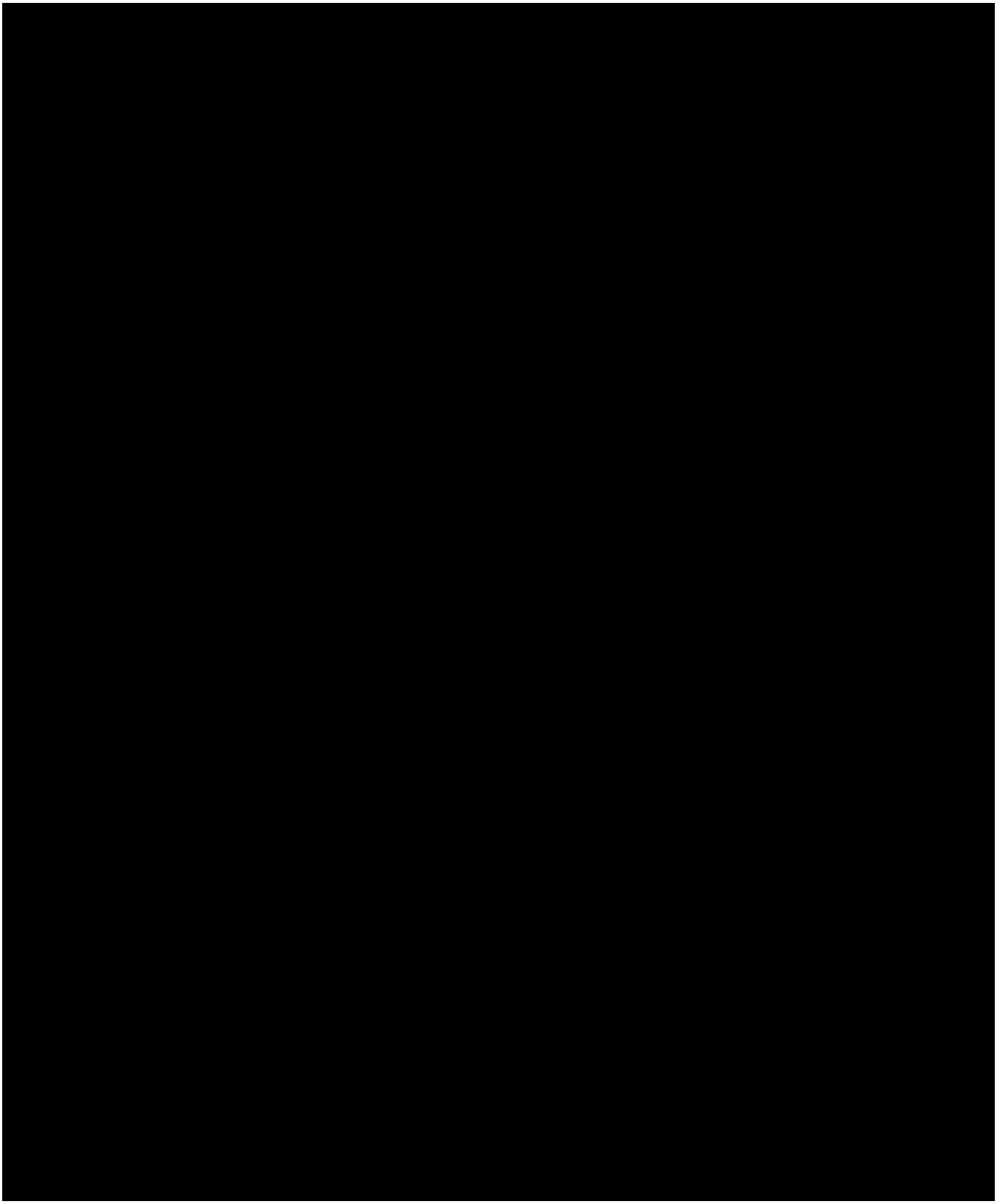
For disclosure of AE data in the EudraCT register, the frequency of non-serious AEs with an incidence of greater than 5 % (in preferred terms) and the frequency of SAEs will be summarized.

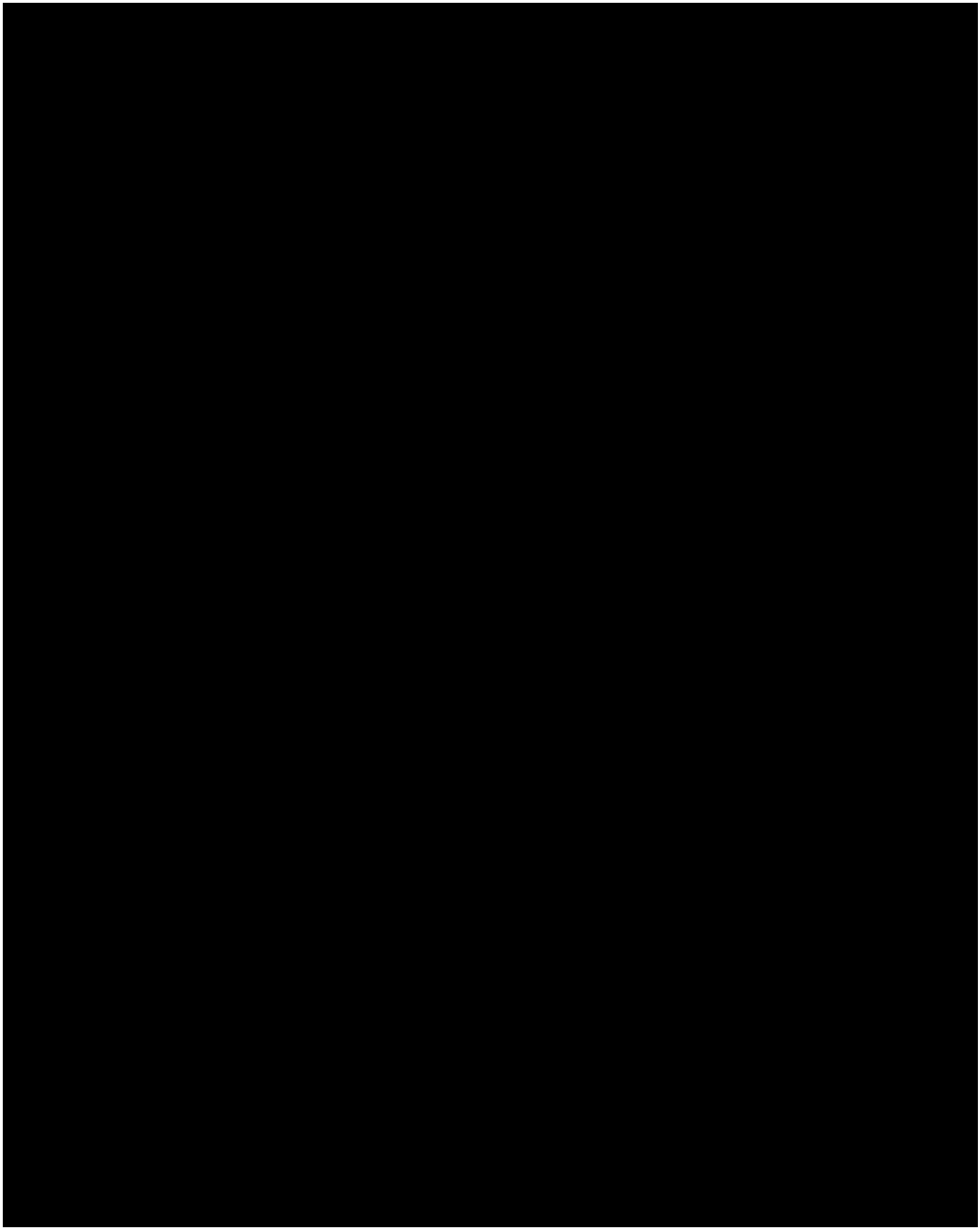
[redacted]











*To support a potential spesolimab GPP flare treatment submission, interim analyses of the open-label rescue treatment and subsequent maintenance treatment periods will be performed using all open-label data up to a cut-off date, which will be pre-specified in the data cleaning plan for the interim analysis. Randomized maintenance s.c. treatments will remain blinded and data from the randomized treatment period will not be analyzed in the interim analysis. The timing of the interim analysis is driven by the timing of the submission of the flare treatment when deemed necessary*

Further, at the cut-off time point of the interim analysis, if applicable, only data up to its cut-off date will be included, and some subjects may not have completed all their scheduled visits in Flow Chart 2 (see Section 3.1 of CTP). Similarly, for summary tables and figures of the interim analysis, these subjects will not be accounted in the planned visits which they haven't yet completed.

PK analysis, biomarker analysis, and ADA related immunogenicity analysis are not planned in the interim analysis

Missing data imputations will be performed using all available data for each treatment period separately up to the respective analysis cut-off date.

# 8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

As discussed in Section 7, if the primary analysis and the final analysis are planned to be performed separately, a database lock for the primary analysis will be done and treatment will be unblinded to trial and project team members.

The Fast-track approach will be followed:
*Once the last patient has completed their End-of-Treatment (EOT) visit and all corresponding data up to week 48 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 collection for the off-treatment residual effect period until 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.*

If, prior to the time of the primary analysis, the trial team are in alignment to perform a single analysis due to insufficient time to justify the performance of separate analyses, we will follow Standard approach:
*The treatment information will be released to unblind the trial database after the last patient has completed their End-of-Study/Follow-up visit and all data has been entered and cleaned as defined in the "Data Ready to be Unblinded and/or Final Trial Closure Notification" (RUN) form.*

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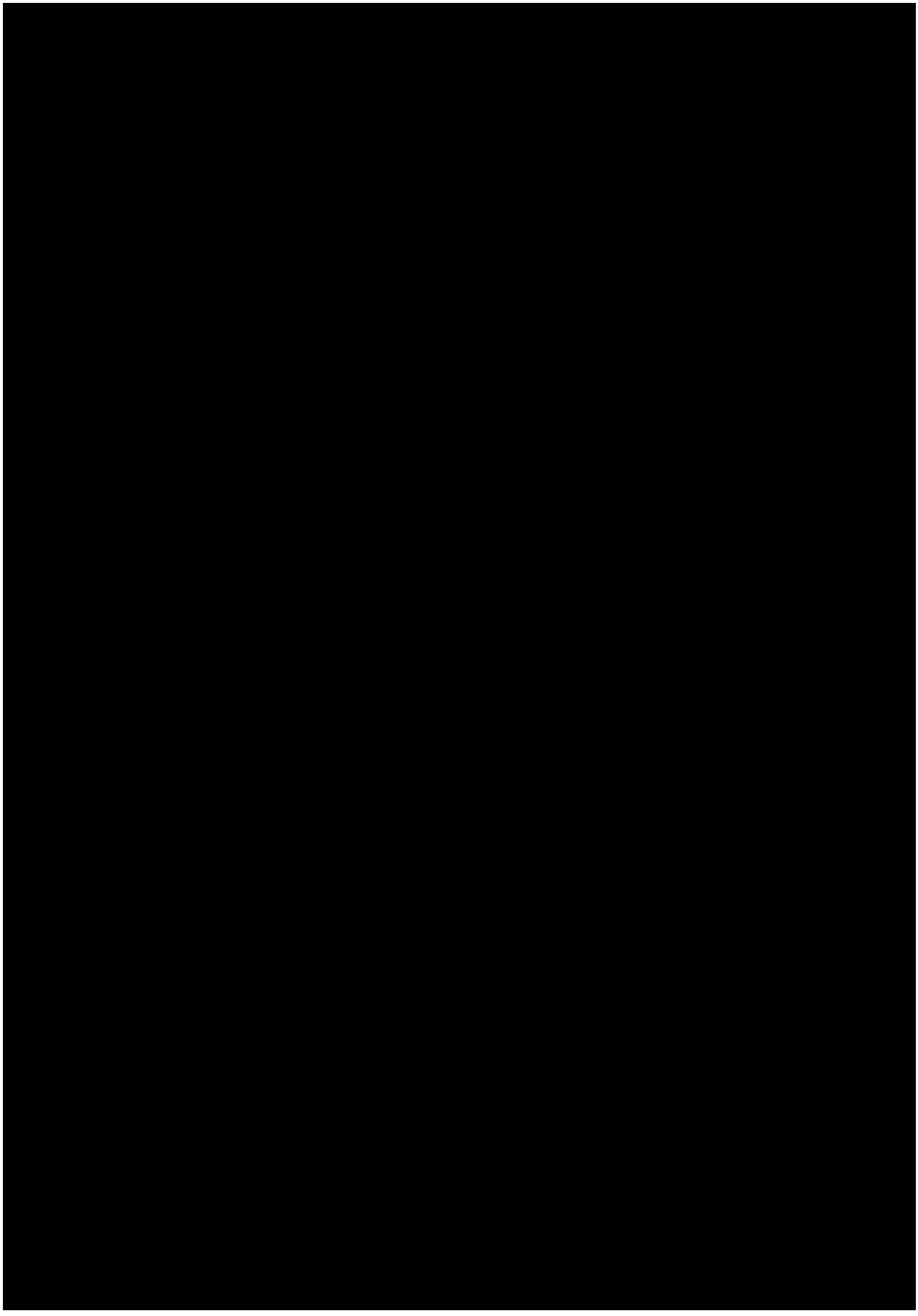

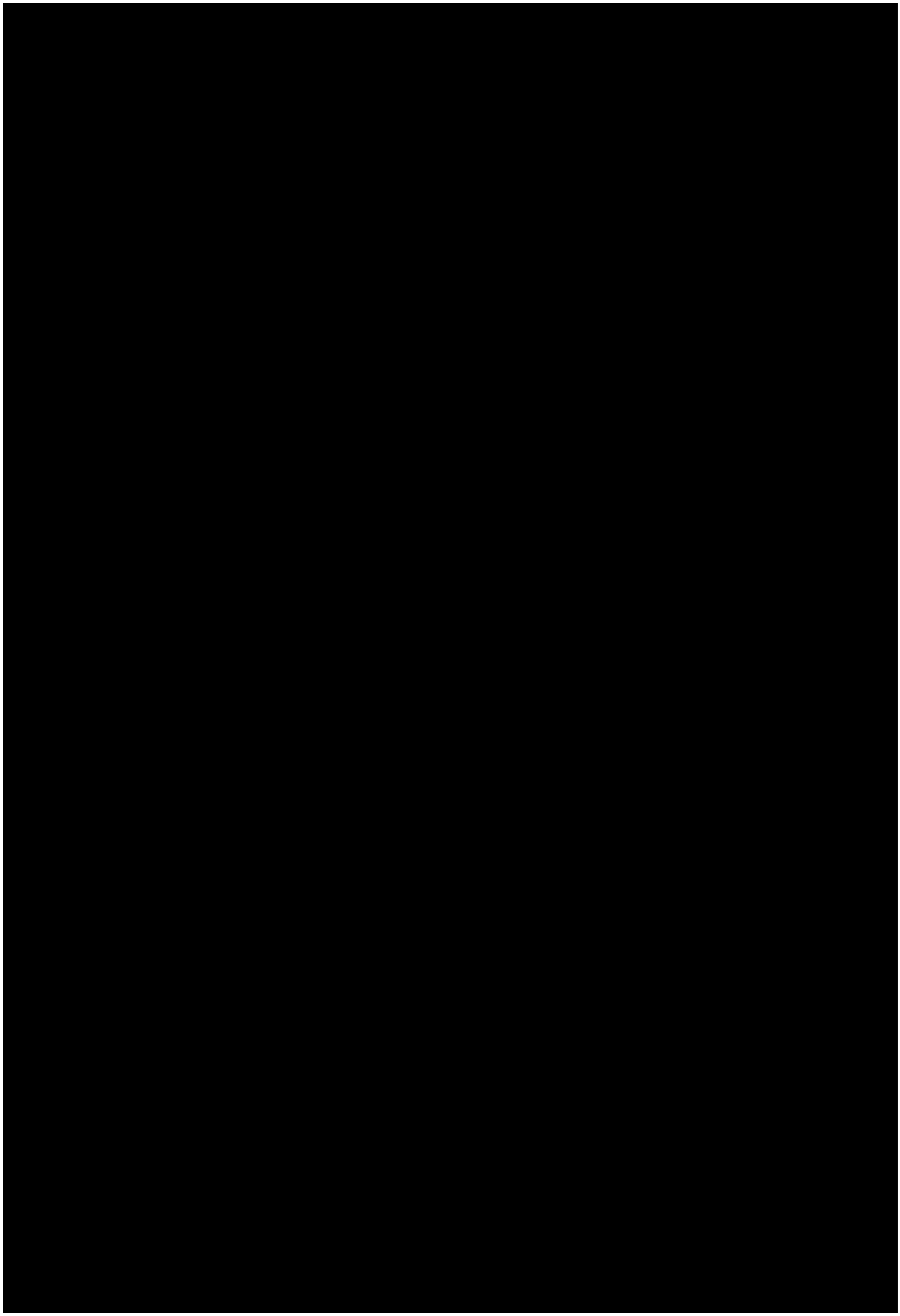

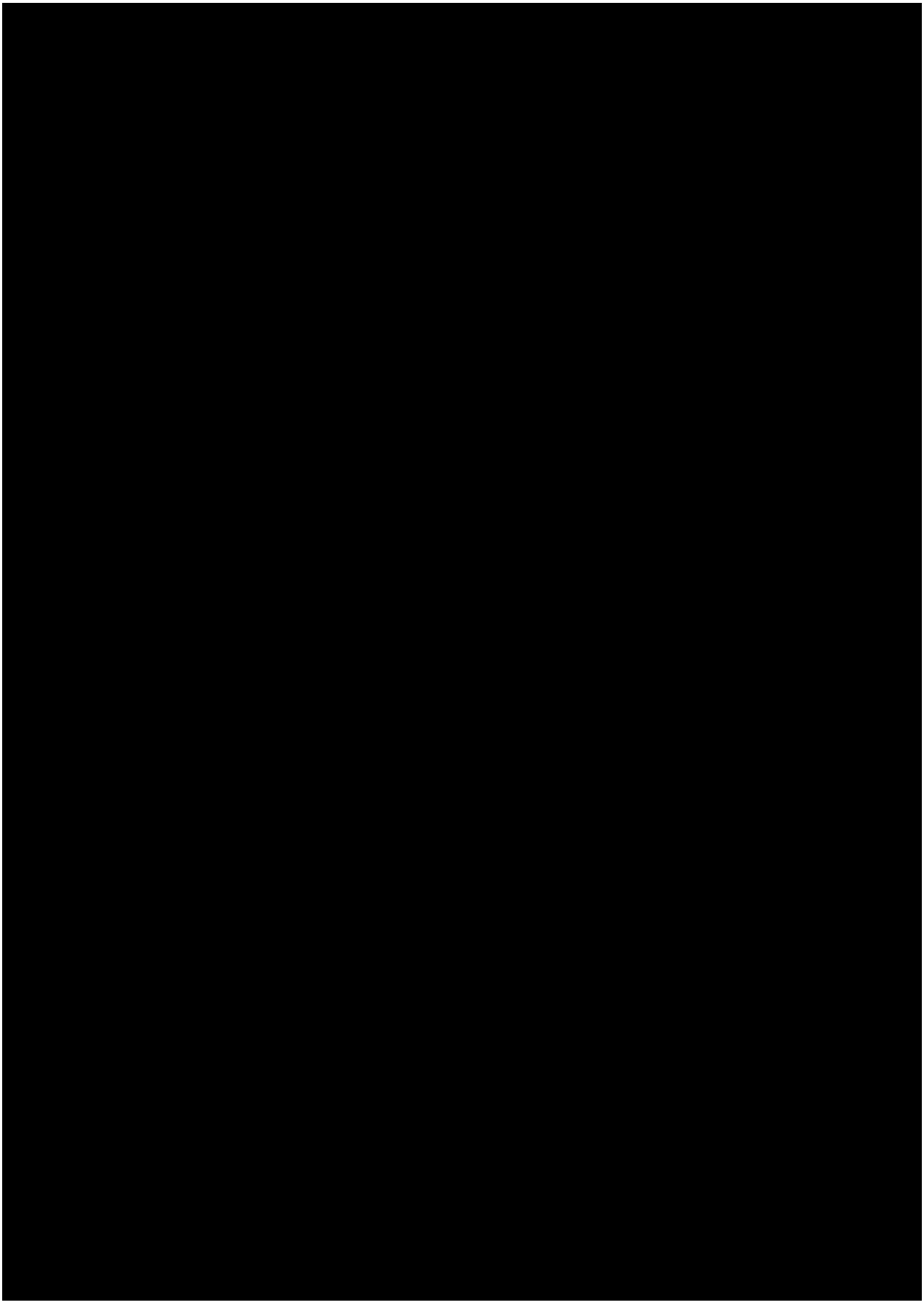

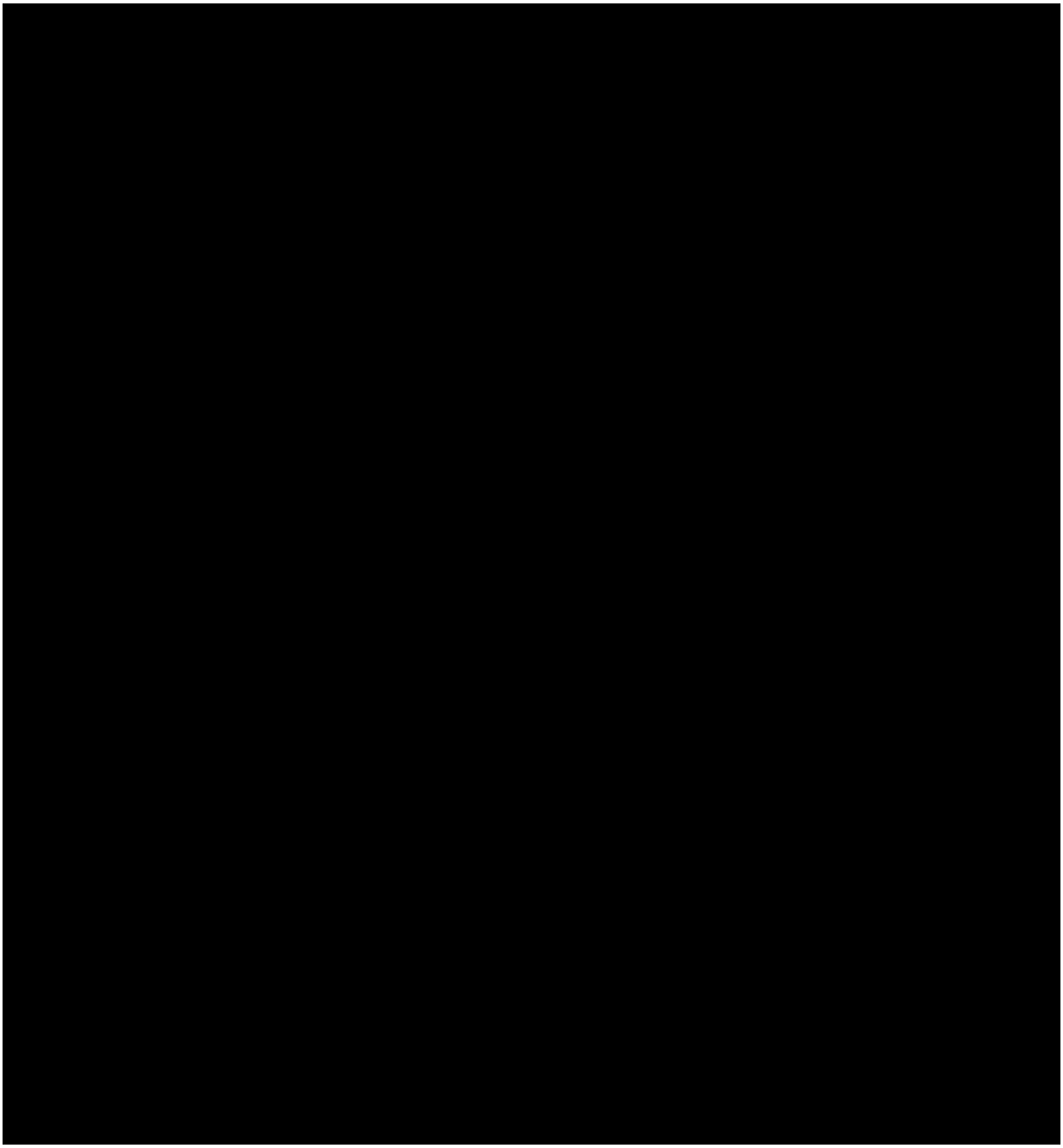

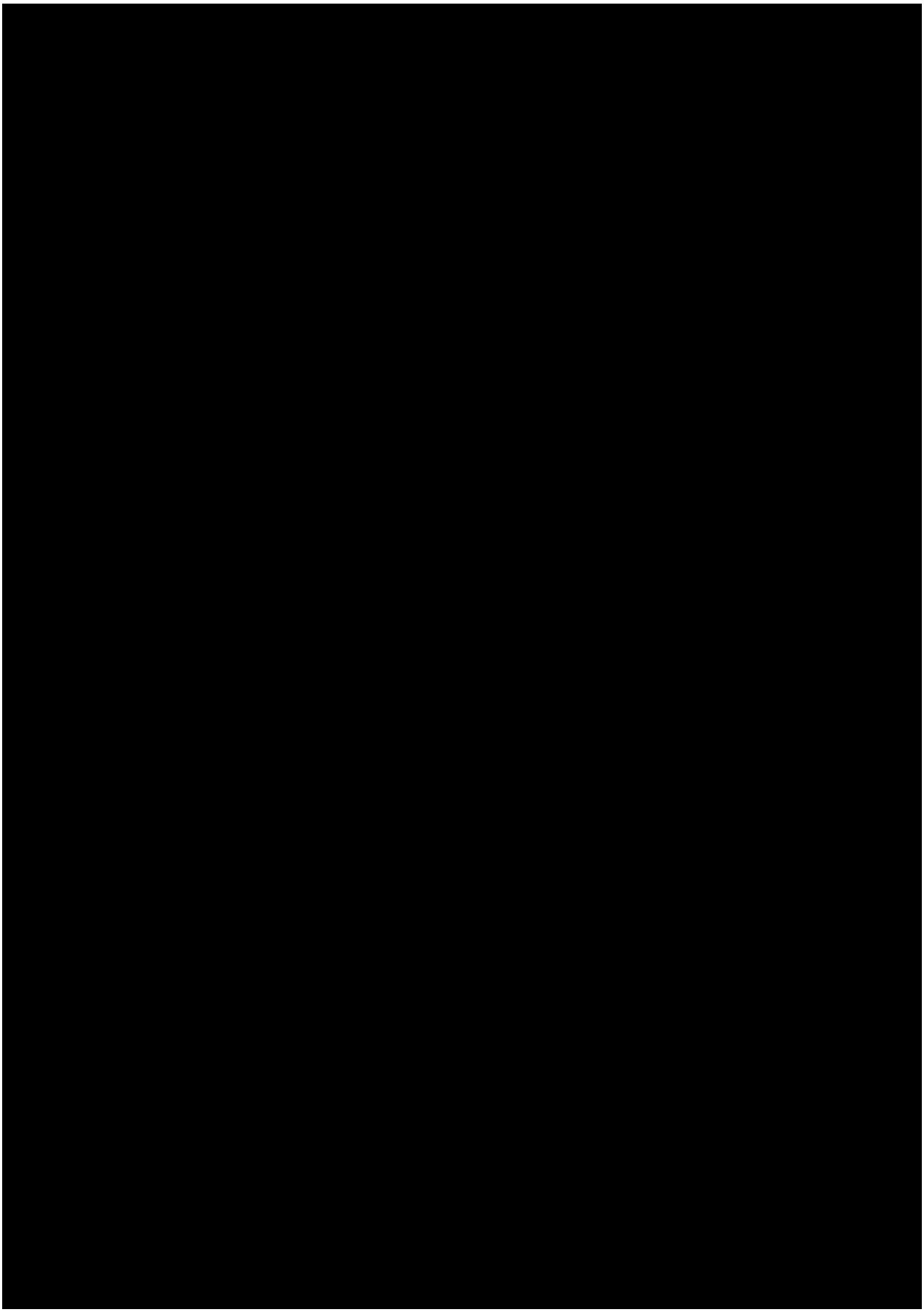

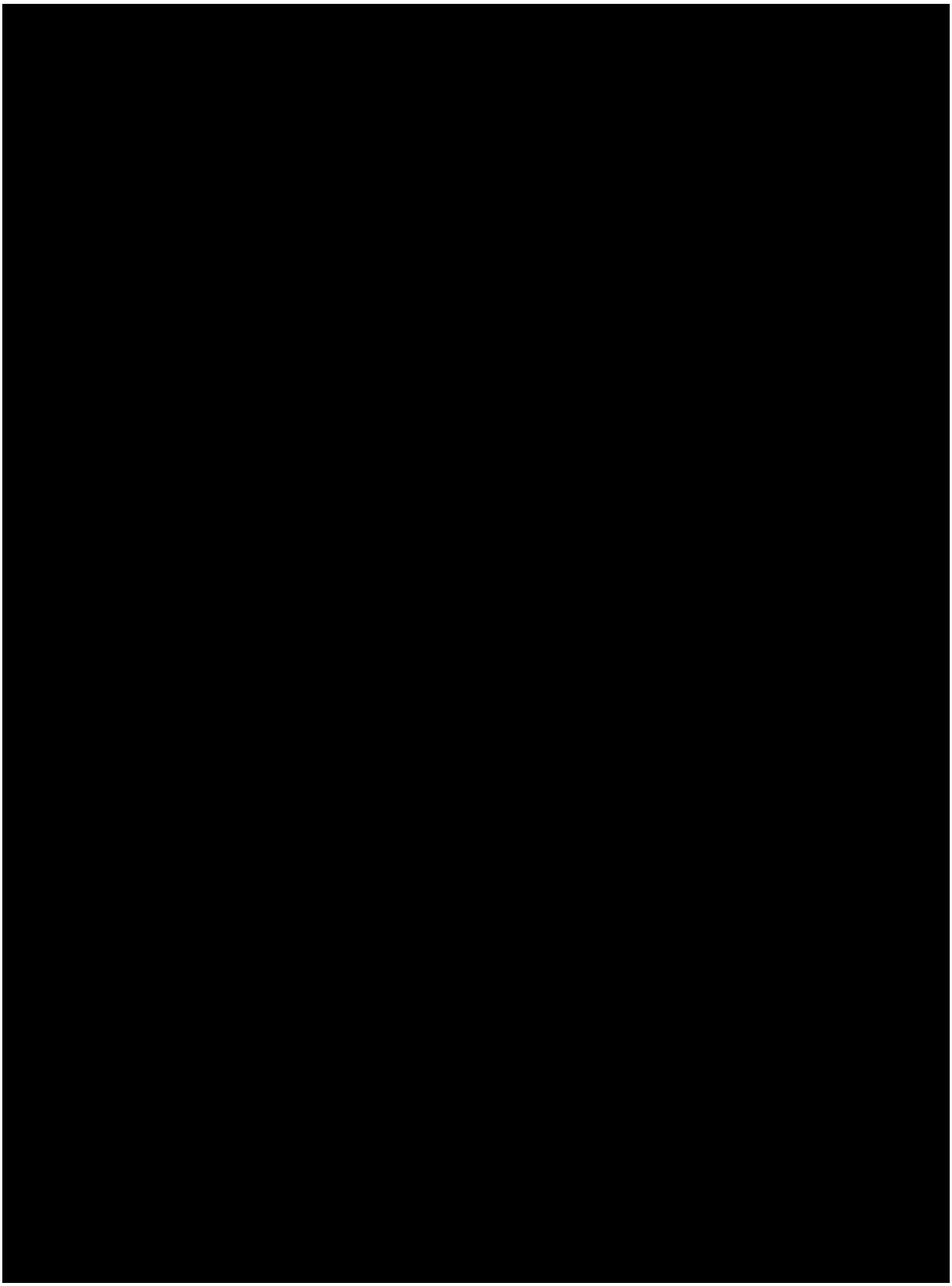

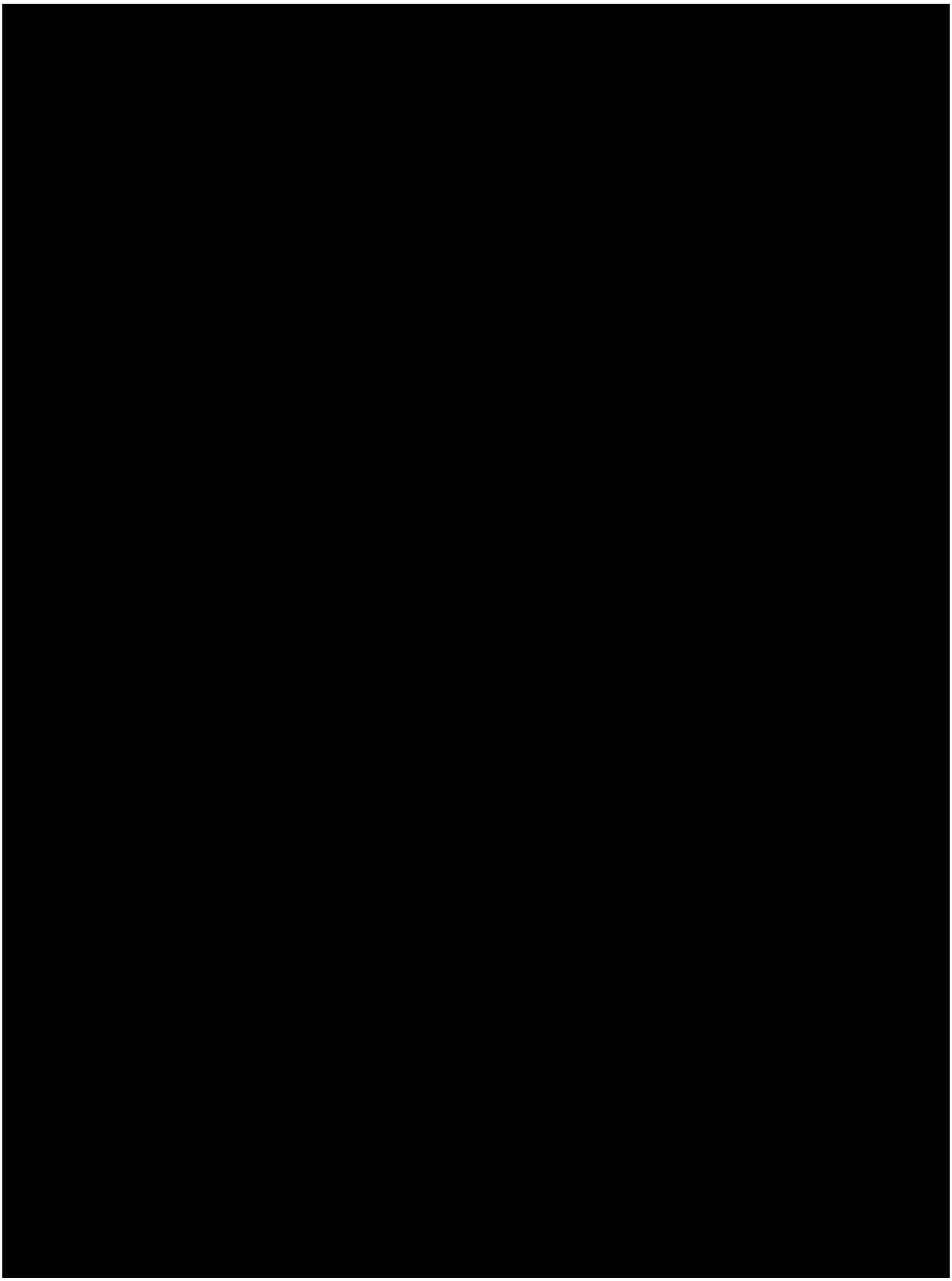

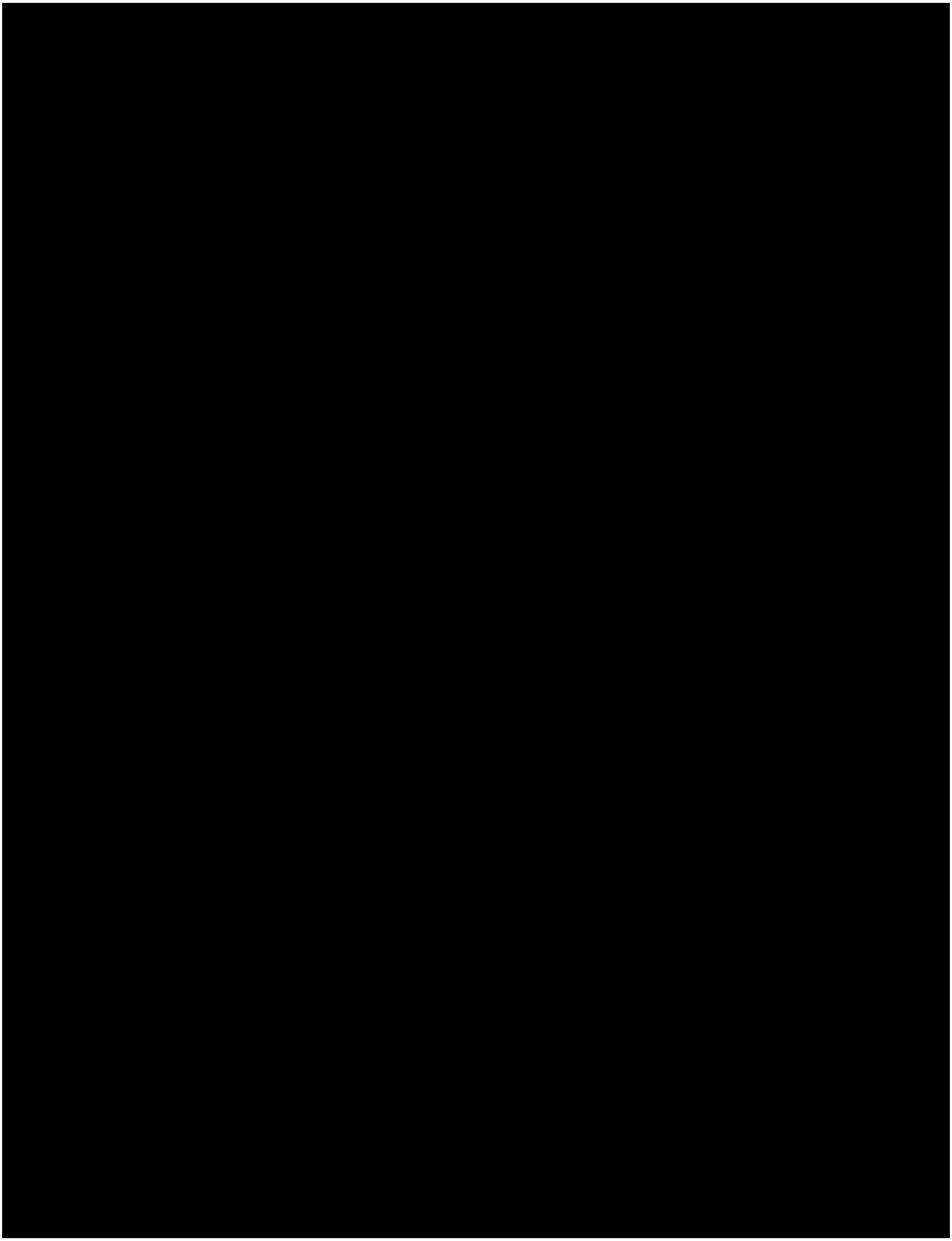

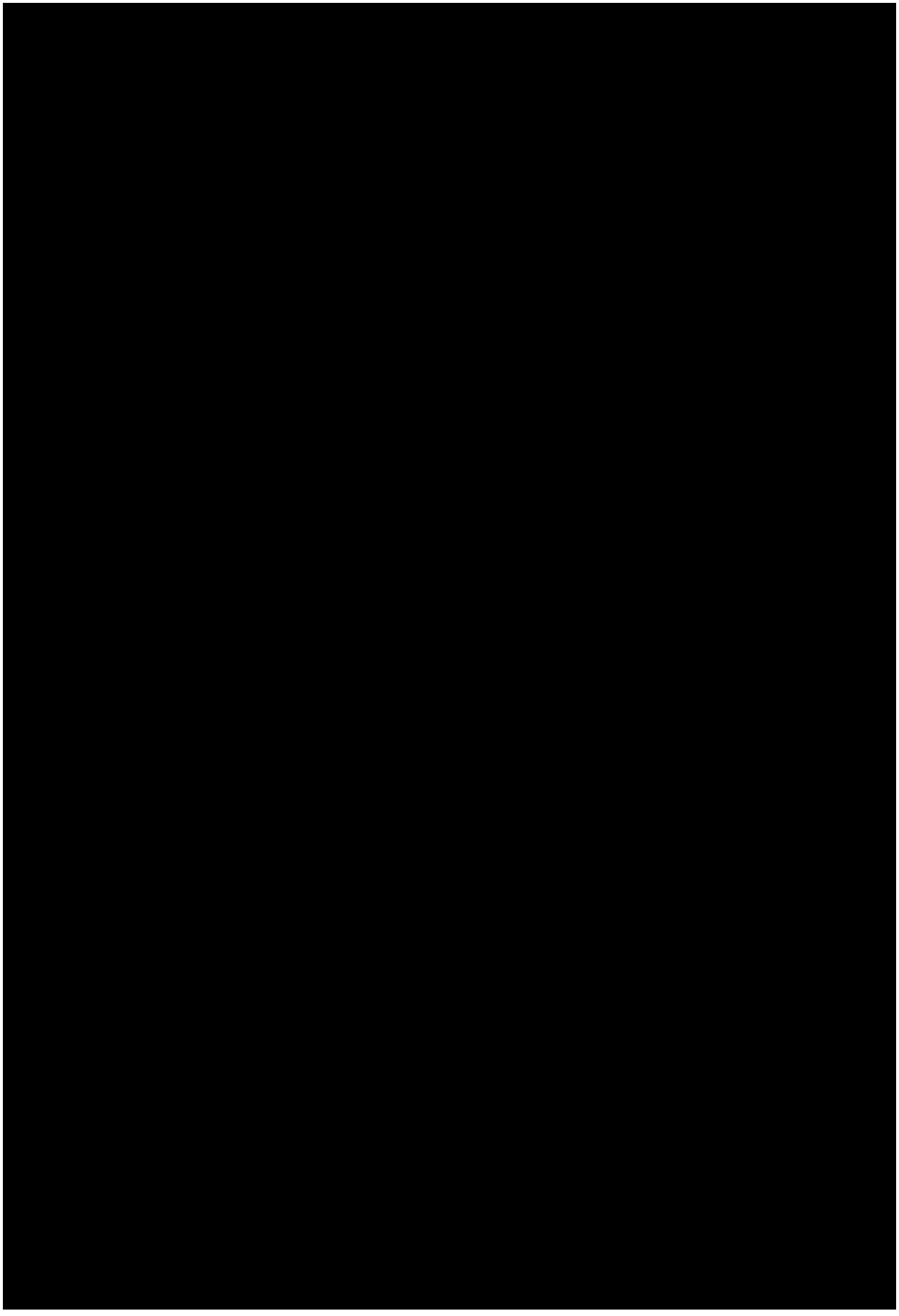

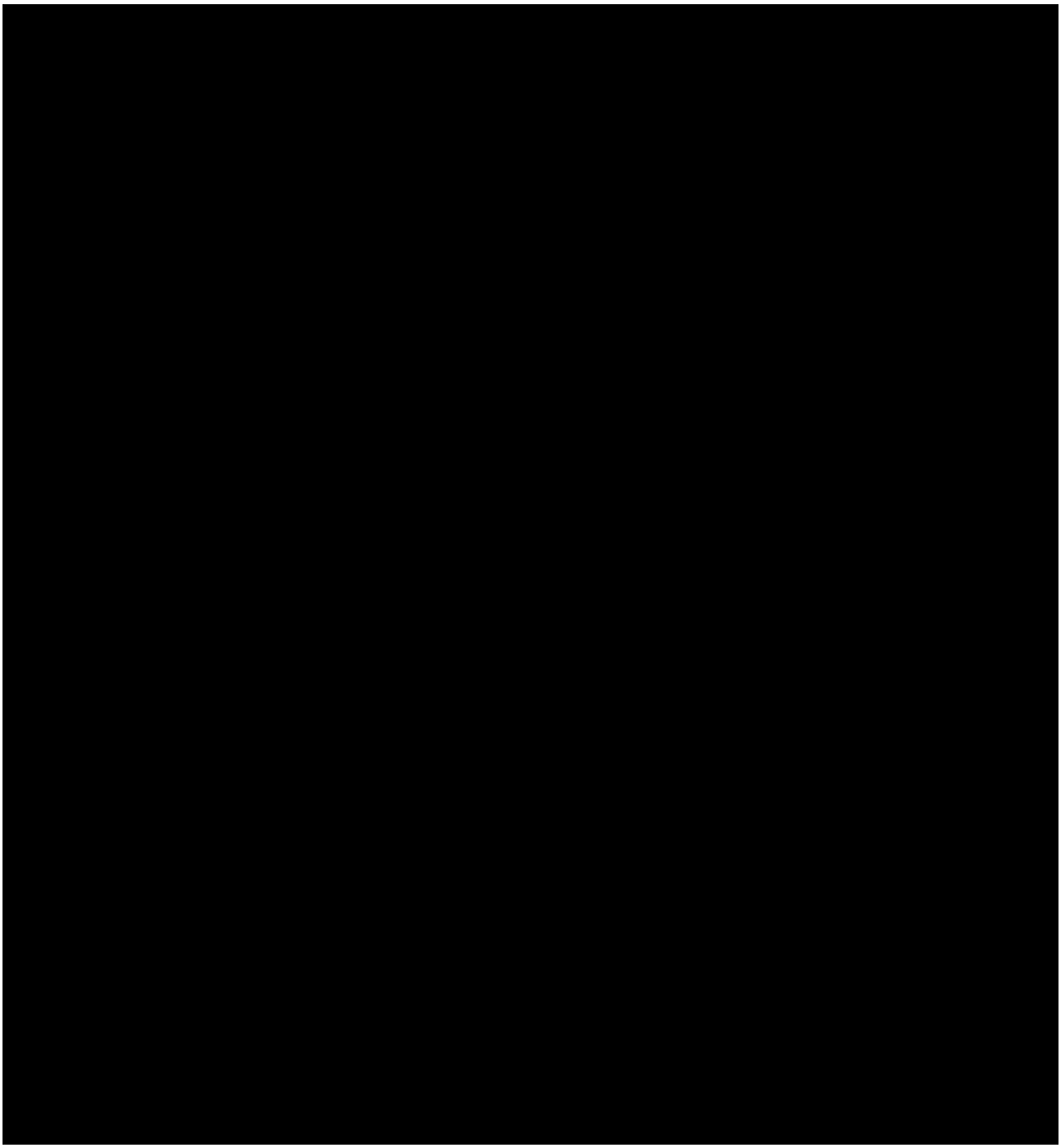

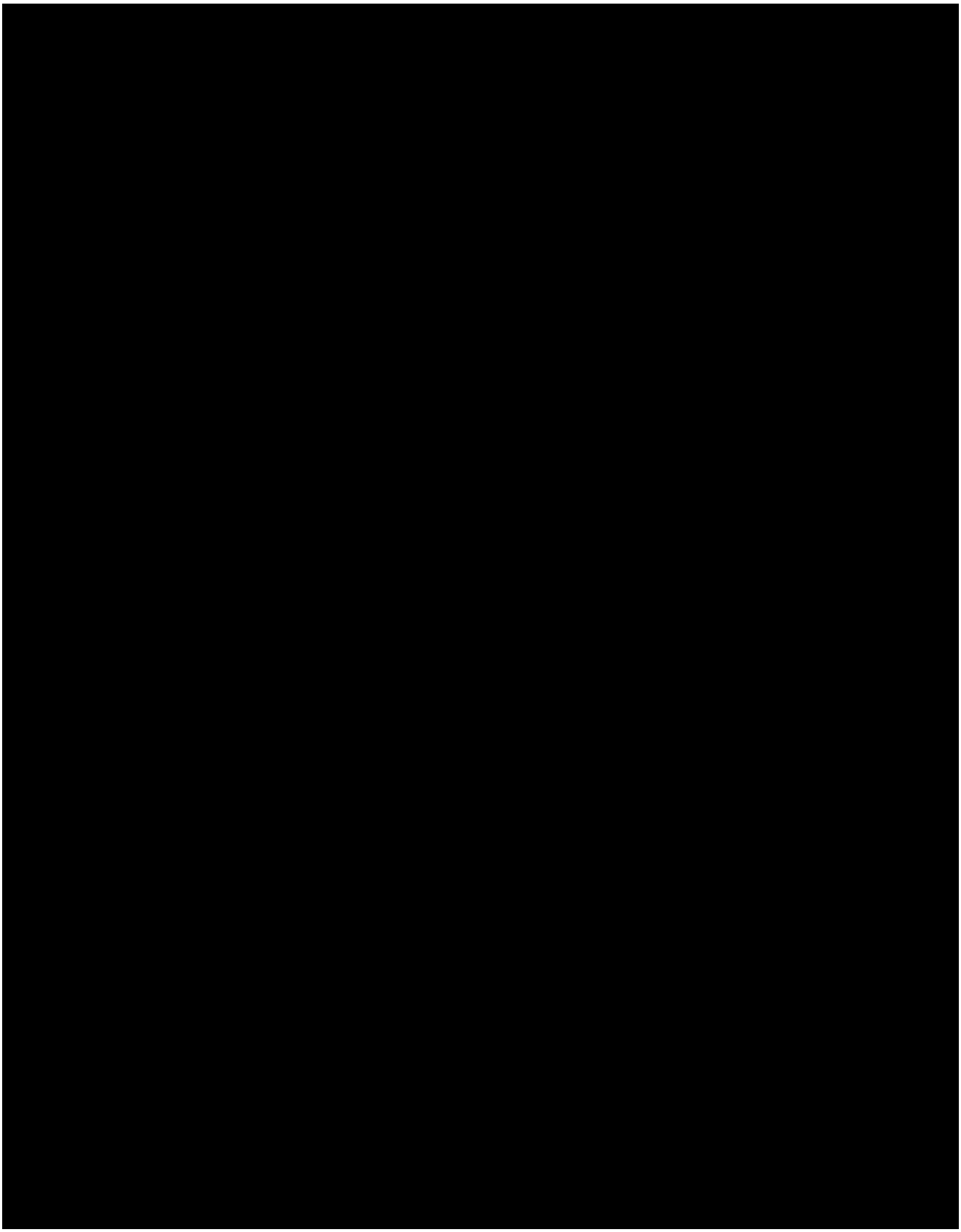

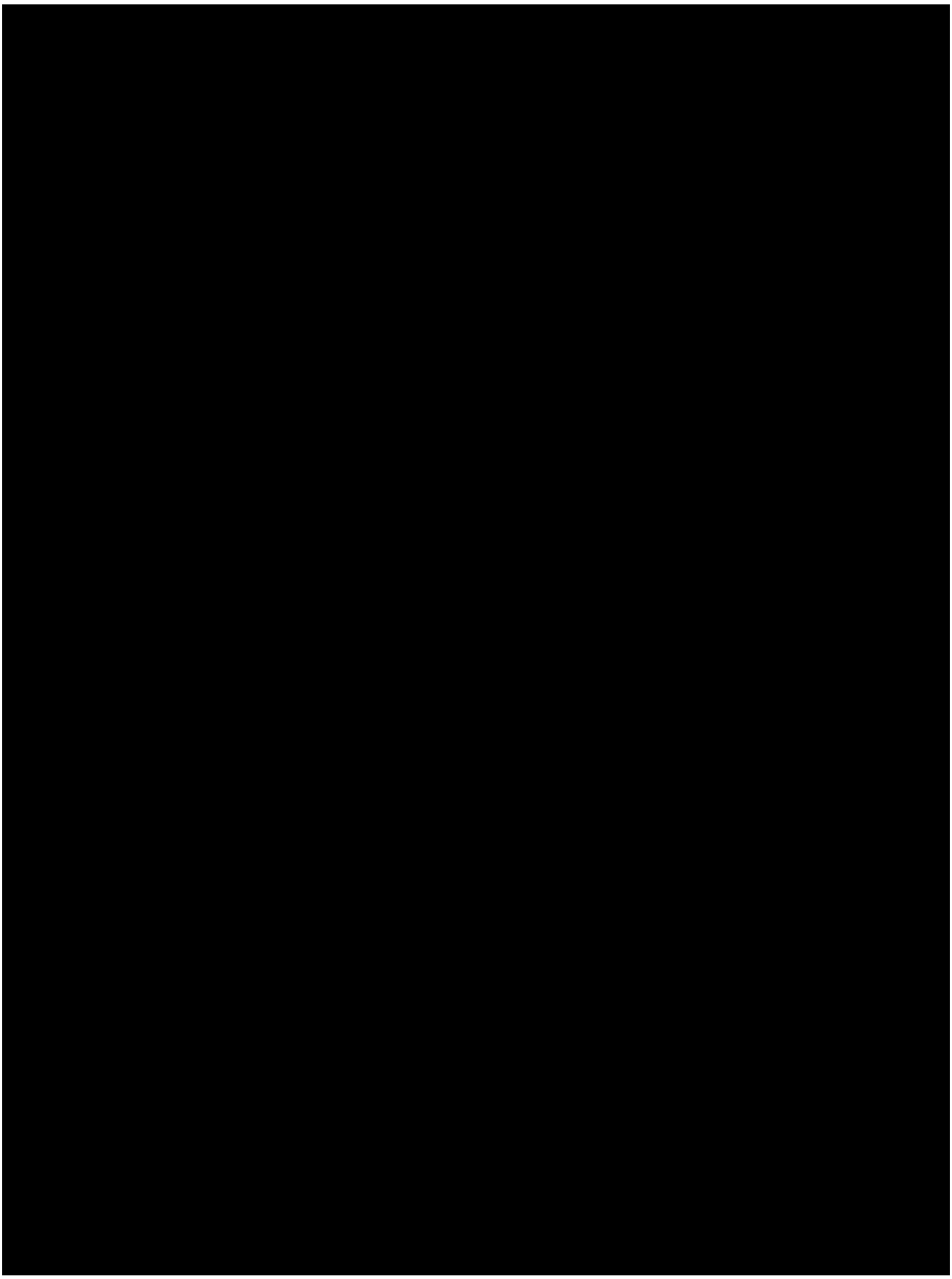

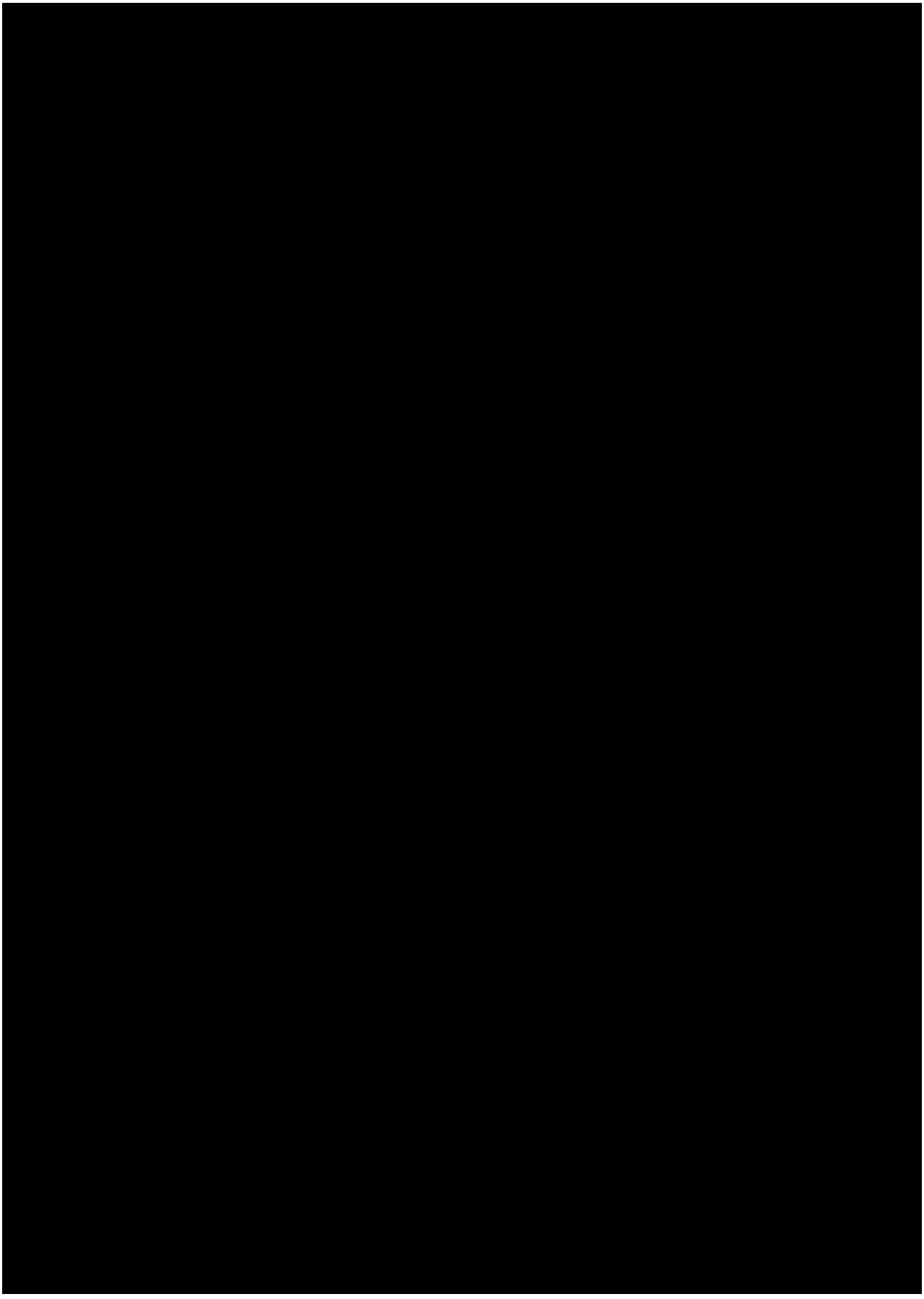

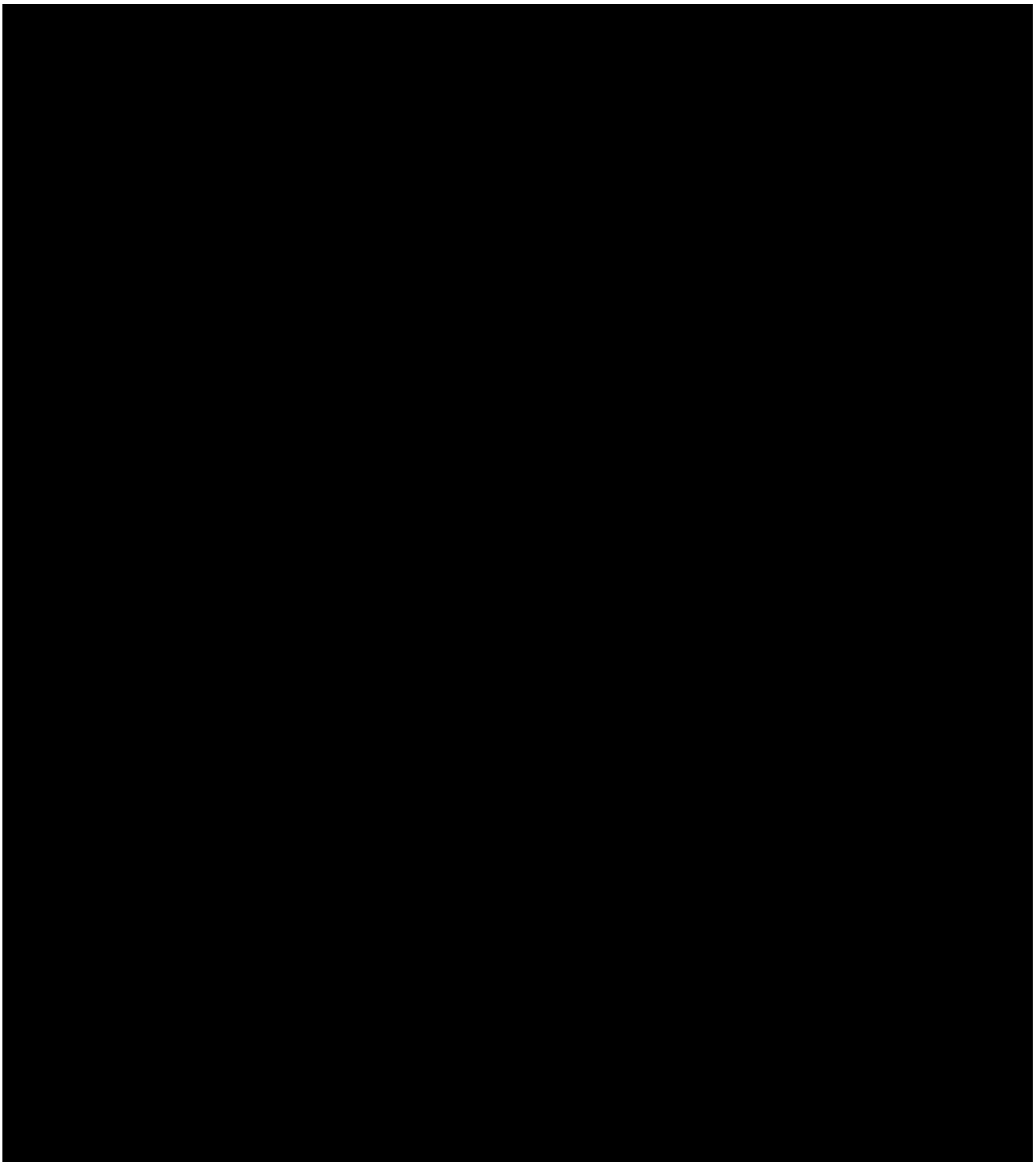

# 11. HISTORY TABLE

Table 11: 1 History table

| Version | Date (DD-MMM-YY) | Author | Sections changed | Brief description of change |
|---|---|---|---|---|
| 1 | **1-Jul-22** | [redacted] | None | This is the final TSAP |
| 2 | **2-Dec-22** | [redacted] | Section 6.6.2 | Multiple imputation algorithm is elaborated for clarity |
| | | | [redacted] | |
| | | | [redacted] | |
| | | | [redacted] | |
| | | | Section 7.5.2 | Eligibility of time-to-event analysis for DLQI worsening/ PSS worsening is elaborated for subjects without a baseline or with a high baseline |
| | | | [redacted] | |
| | | | [redacted] | |
| | | | [redacted] | |
| | | | [redacted] | |
| | | | Section 6.7 | Analysis time window of randomized maintenance treatment period is updated to capture the status of early-onset flare |
| | | | Section 7.4<br>Section 7.5 | Primary method to estimate the treatment effect i.e., hazard ratio, for secondary objective is changed to be consistent with treatment effect estimation in primary objective. |
| | | | Section 7.8.1 | UDAEC is modified to align with project-level standard |
| | | | [redacted] | |
| | | | Section 3 | Version of R software is updated |