STATISTICAL ANALYSIS PLAN

Study: SL0043

Product: Dapirolizumab pegol

A multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of dapirolizumab pegol in study participants with moderately to severely active systemic lupus erythematosus.

SAP/Amendment Number	Date
Final SAP	16DEC2020
Amendment 1	14JAN2022
Amendment 2	18DEC2023
Amendment 3	19Jul2024

Confidentiality Statement

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LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
[redacted]	
aPL	Antiphospholipid antibody
APS	Antiphospholipid syndrome
[redacted]	
AST	Aspartate aminotransferase
BICLA	BILAG 2004-based Composite Lupus Assessment
BILAG 2004	British Isles Lupus Assessment Group Disease Activity Index 2004
[redacted]	
CI	Confidence interval
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
CMH	Cochran-Mantel-Haenszel
CSR	Clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DBP	Diastolic blood pressure
DEM	Data Evaluation Meeting
DNA	Deoxyribonucleic acid
DORIS	Definitions of Remission in SLE
DZP	Dapirolizumab pegol
[redacted]	
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtration rate
eCOA	Electronic clinical outcomes assessment form
eLAS	Electronic Lupus assessment suite
ES	Enrolled Set
ESR	Erythrocyte Sedimentation Rate
EULAR/ACR	European League Against Rheumatism/American College of Rheumatology
EOT	End of Treatment
EQ-5D-5L	Euro Quality of life 5-Dimensions 5-Level
FAS	Full Analysis Set

FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue Scale
FCS	Fully conditional specification
FDA	Food and Drug Administration
GCP	Good clinical practice
GGT	Gamma-glutamyltransferase
HIV	Human immunodeficiency virus
HR	Heart Rate
HRQoL	Health-related quality of life
[redacted]	
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
Ig	Immunoglobulin
IMP	Investigational medicinal product
IPD	Important Protocol Deviation
Iv	Intravenous(ly)
KSE	Key Secondary Endpoint
[redacted]	
LLDAS	Lupus Low Disease Activity State
LLN	Lower limit of normal
LOE	Lack of efficacy
Lupus QoL	Lupus Quality of Life Questionnaire
MAR	Missing at random
MACE	Major Adverse Cardiovascular Event
MCAR	Missing completely at random
MedDRA	Medical Dictionary for Regulatory Activities coding dictionary
MI	Multiple imputation
MNAR	Missing not at random
mNRI	Modified non-responder imputation
MMRM	Mixed Model for Repeated Measurement
MSR	Minimum Significant Ratio
Nab	Neutralizing antibodies
NRI	Non-responder imputation
OLE	Open label extension
OR	Odds ratio
PBO	Placebo
PD	Pharmacodynamics(s)
PEG	Polyethylene glycol
PGA	Physician's Global Assessment of Disease
PHQ-9	Patient Health Questionnaire-9
PI	Principal investigator
PK	Pharmacokinetic(s)
PK-PPS	Pharmacokinetic Per Protocol Set
PPS	Per Protocol Set
PR	Pulse rate
PRO	Patient-reported outcome
Q4W	Every 4 weeks
QRS	QRS complex (Ventricular depolarization)

QTcF	QT Interval Corrected for Heart Rate (Fridericia's Formula)
RBC	Red blood cell
[redacted]	
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard deviation
SFI	SELENA (Safety of Estrogens in Lupus National Assessment) Flare Index
SFU	Safety Follow-up
SJC	Swollen joint count
SLE	Systemic lupus erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
SLICC	Systemic Lupus International Collaborating Clinics
SMQ	Standardized MedDRA Queries
SRI	The Systemic Lupus Erythematosus Responder Index
S2K RI-50	SLEDAI-2K Responder Index-50
SOC	Standard of care
SS	Safety Set
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TJC	Tender joint count
ULN	Upper limit of normal
uPCR	Urine protein-creatinine ratio
VAS	Visual analog scale
WBC	White blood cell
WHO-DD	World Health Organization Drug dictionary

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide all information necessary to perform the final statistical analysis of SL0043 supporting the final clinical study report (CSR). It also defines the summary tables, listings and figures to be included in the CSR according to protocol. The SAP is based on the following study document: Protocol amendment 4.0 dated 16 March 2023. The content of this SAP is compatible with the International Conference on Harmonization (ICH)/ Food and Drug Administration (FDA) E9 Guidance documents. UCB is the Sponsor and PAREXEL is the Contract Research Organization (CRO) for this study.

In this document, the following estimands' attributes will be considered:

(1) Treatment condition is standard of care (SOC) medication + dapirolizumab pegol (DZP) intravenous (iv) every 4 weeks (q4w) 24mg/kg and the alternative treatment condition is SOC medication + Placebo (PBO) iv q4w.

(2) Population: The population includes participants with moderately to severely active SLE despite stable nonbiological SOC medications (standard SLE therapy) and a persistent active or frequently relapsing remitting disease course or risk factors for relapsing remitting disease course. As defined in the protocol-specified inclusion/exclusion criteria reflecting the target study participant population for approval.

(3) Endpoints (Variables) are described in Section 2.2.

(4) Intercurrent events and specifications of how they will be handled for analysis purposes will be detailed in the sections related to the analysis of each endpoint.

(5) Population-level summaries for each endpoint will be detailed in the sections related to the analysis of each endpoint.

2 PROTOCOL SUMMARY

2.1 Study objectives

2.1.1 Primary objective

To evaluate the ability of DZP as an add-on treatment to SOC medication to achieve clinically relevant long-term improvement of moderate to severe disease activity

2.1.2 Secondary objectives

2.1.2.1 Key Secondary objectives

The key secondary objectives of the study are:

- To evaluate the ability of DZP as an add-on treatment to SOC medication to achieve fast, clinically relevant improvement of moderate to severe disease activity
- To evaluate the ability of DZP as an add-on treatment to SOC medication to achieve long-term control of disease activity
- To evaluate the ability of DZP as an add-on treatment to SOC medication to achieve and maintain the treat-to-target goal: low disease activity with low/acceptable corticosteroid dose over time

- To evaluate the ability of DZP as an add-on treatment to SOC medication to achieve improvement of disease activity as measured by numerical disease state score commonly used in clinical practice

2.1.2.2 Secondary objectives

The secondary objectives of the study are:

- To evaluate the ability of DZP as an add-on treatment to SOC medication to achieve components of the composite primary endpoint
- To evaluate the ability of DZP as an add-on treatment to SOC medication to achieve alternative responder endpoint
- To evaluate the ability of DZP as an add-on treatment to SOC medication to achieve endpoints supporting other key secondary endpoints
- To evaluate the safety and tolerability of DZP as add-on treatment to SOC medication

2.1.3 Tertiary objectives

The tertiary objectives of the study are:

- To evaluate the ability of DZP as add-on treatment to SOC to achieve endpoints which support the primary and secondary objectives and/or support the interpretation of the primary and secondary endpoints
- To evaluate the ability of DZP as an add-on treatment to SOC medication to achieve organ specific endpoints
- To evaluate the ability of DZP as an add-on treatment to SOC medication to achieve important patient reported outcomes (PRO)
- To evaluate the Pharmacokinetic (PK)
- To evaluate immunogenicity of DZP as an add-on treatment to SOC medication
- To evaluate the Pharmacodynamic (PD) and immunological parameters of DZP as an add-on treatment to SOC medication
- To evaluate the safety and tolerability of DZP as an add-on treatment to SOC medication
- To evaluate changes in exploratory biomarkers
- To evaluate risk for anti-phospholipid associated events

2.2 Endpoints

2.2.1 Primary Endpoint

Achievement of BILAG (British Isles Lupus Assessment Group Disease Activity Index) 2004-based Composite Lupus Assessment (BICLA) response at Week 48

2.2.2 Key Secondary Endpoints

- Achievement of BICLA response at Week 24
- Achievement of BICLA response at Week 12

- Achievement of prevention of severe BILAG flares (severe BILAG flare-free) through Week 48
- Achievement of Lupus Low Disease Activity State (LLDAS) in ≥50% of post Baseline visits through Week 48
- Change from Baseline in Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K) at Week 48

2.2.3 Secondary Endpoints

- Achievement of BILAG improvement without worsening at Week 48
- Change from Baseline in Physician's Global Assessment of Disease (PGA) at Week 48
- Achievement of SRI-4 response at Week 48
- Achievement of prevention of moderate/severe BILAG flares (moderate/severe BILAG flare-free) through Week 48
- Time to severe BILAG Flare through Week 48
- Time to moderate/severe BILAG flare through Week 48
- Treatment Emergent Adverse Events (TEAEs), serious TEAEs, TEAEs of special interest, and TEAEs of special monitoring

2.2.4 Tertiary Endpoints

- Achievement of reduction of corticosteroid dose from >7.5mg/day prednisone equivalent dose at start of study to ≤7.5mg/day prednisone equivalent by visit
- Achievement of reduction of corticosteroid dose from >7.5mg/day prednisone equivalent dose at start of study to ≤7.5mg/day prednisone equivalent at Week 24 and maintaining low corticosteroid dose afterwards and achievement of BICLA response at Week 48
- Achievement of reduction of corticosteroid dose from >7.5mg/day prednisone equivalent dose at start of study to ≤7.5mg/day prednisone equivalent at Week 24 and maintaining low corticosteroid dose and achievement of prevention of moderate/severe BILAG flares (moderate/severe BILAG flare-free) through Week 48
- Achievement of reduction in corticosteroid dose from >5mg/day prednisone equivalent dose at start of study to ≤5mg/day prednisone equivalent at Week 24 and maintaining low corticosteroid dose and achievement of BICLA response at Week 48
- Achievement of reduction of corticosteroid dose from >5mg/day prednisone equivalent dose to ≤5mg/day prednisone equivalent at Week 24 and maintaining low corticosteroid dose and achievement of prevention of moderate/severe BILAG flares (moderate/severe BILAG flare-free) through Week 48
- Total corticosteroid dose through Week 24, through Week 48, and from Week 24 through Week 48
- Achievement of BICLA response by visit
- Achievement of BILAG 2004 improvement without worsening by visit

- Change from Baseline in BILAG 2004 score by visit
- Achievement of BILAG 2004 shifts by visit
- Achievement of BILAG 2004 improvement by organ system by visit
- Achievement of maintained BICLA response by visit
- Achievement of persistent BICLA response between Week 24 and Week 48
- Worsening of any organ system with a BILAG 2004 B, C, D, E at Baseline to BILAG 2004 A or worsening of >1 organ system with a BILAG 2004 C, D, E at Baseline to BILAG 2004 B by visit
- Achievement of BILAG 2004 C, D, E in all organ systems by visit
- Change from Baseline in SLEDAI-2K by visit
- Change from Baseline in Clinical SLEDAI-2K by visit
- Achievement of SRI 4, 6, 8 response by visit
- Change from prior visits in S2K RI50 by visit
- Change from Baseline in PGA by visit
- Achievement of LLDAS status by visit
- Cumulative number of visits in LLDAS through Week 48
- Achievement of LLDAS Variant (demand for ≤5mg/day prednisone equivalent) in >50% of post-Baseline visits through Week 48
- Achievement of prednisone equivalent dose ≤7.5mg/day by visit
- Prednisone equivalent dose by visit
- Occurrence of severe BILAG 2004 flares by visit
- Occurrence of moderate BILAG flares by visit
- Occurrence of severe SFI flares by visit
- Occurrence of moderate SFI flares by visit
- Time to severe SFI flare
- Time to moderate SFI flare
- Change from Baseline in American College of Rheumatology (ACR)/ Systemic Lupus International Collaborating Clinics (SLICC) damage score by visit
- Achievement of Definitions of Remission in SLE (DORIS) remission by visit
- Change from Baseline in Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) activity score by visit for all study participants and for subset of study participants with high CLASI score

- Achievement of a meaningful improvement in CLASI activity score by visit for all study participants and for subset of study participants with high CLASI score
- Change from Baseline in tender joint count (TJC) and swollen joint count (SJC) and tender and swollen joint count (T&SJC) by visit for all study participants and for subset of participants with moderate to severe [redacted]
- Achievement of a meaningful decrease in TJC/SJC by visit for all participants and for a subset of participants with moderate to severe [redacted]
- Change from Baseline in Lupus [redacted] and Musculoskeletal Disease Activity (LAMDA) score and it's components by visit
- Change from Baseline in Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F) by visit
- Change from Baseline in Patient Health Questionnaire-9 (PHQ-9) score by visit
- Change from Baseline in FATIGUE-PRO 'Physical Fatigue', 'Mental Fatigue' and 'Fatigability' scores by visit
- Change from Baseline in Lupus QoL by visit
- Change from Baseline in EQ-5D-5L by visit
- [redacted]
- [redacted]
- Incidence of anti-drug antibodies (ADA): [redacted]
- Observed values and change from Baseline in [redacted] in all study participants by visit and in study participants 'positive' at Baseline by visit
- Seroconversion of [redacted] status by visit
- TEAEs leading to study withdrawal, TEAEs leading to permanent study medication discontinuation, TEAEs with start day on day or up to 1 day after infusion, other identified TEAE clusters
- Summary of participants withdrawn from the study due to TEAEs
- Summary of participants who permanently discontinued study medication
- Change from Baseline in vital sign parameters by visit
- Observed values and change from Baseline in safety laboratory tests (hematology, serum chemistry, urinalysis) by visit, % study participants achieving critical threshold for selected lab parameters by visits
- Change from Baseline in biomarkers selected for analysis

- [redacted]
- [redacted]
- Achievement of a meaningful improvement in CLASI activity sub score – erythema by visit for all study participants and for subset of study participants with high CLASI
- Achievement of a meaningful improvement in CLASI activity sub score – scaling by visit for all study participants and for subset of study participants with high CLASI
- Achievement of a meaningful improvement in CLASI activity sub score – alopecia by visit for all study participants and for subset of study participants with high CLASI

2.3 Study design and conduct

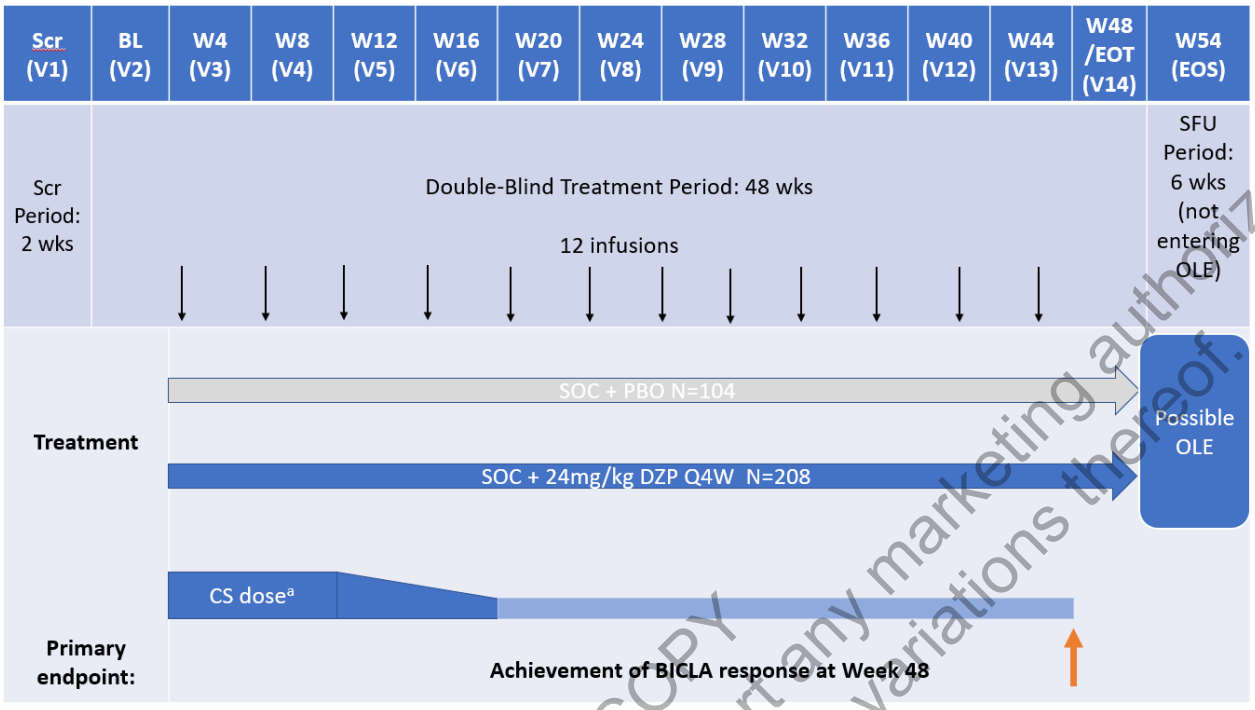
2.3.1 Study description

The study will be conducted to demonstrate efficacy, safety and tolerability of DZP in study participants with moderately to severely active SLE despite stable nonbiological SOC medications (standard SLE therapy) and a persistent active or frequently relapsing remitting disease course or risk factors for relapsing remitting disease course to support regulatory filing.

The study is a randomized, double-blind, placebo-controlled, parallel group, Phase 3 study in study participants 16 years of age and older with moderately to severely active SLE who are receiving stable SOC medication (ie, antimalarials, corticosteroids, and/or immunosuppressants) in line with local and international guidance at Screening Visit (V1).

The study consists of a 2-week Screening Period, 48-week Treatment Period, and 6-week Safety Follow-up (SFU) Period (if the participant completes the study but decides not to enter the open-label extension (OLE) study SL0046). Due to the required moderate to severe disease activity at Screening visit (V1) and limited allowed treatment possibilities during the Screening phase, a short Screening Period is planned, see Figure 2-1 below. At the start of the study, eligible study participants will be randomized (2:1) to DZP 24mg/kg or to placebo administered by iv infusion Q4W. The initial dose will be administered as a 2-hour infusion while each subsequent dose will be administered as a 1-hour infusion. Study participants who complete the 48-week Treatment Period may be eligible to participate in an OLE study (SL0046). Study participants who withdraw early from the 48-week Treatment Period will be followed up for at least 10 weeks after their final dose of study medication. Study participants who complete the study but choose not to enter the OLE will be followed up for at least 10 weeks after their final dose of study medication (ie, 10 weeks after last infusion at Week 44 which includes a 6-week SFU period).

Figure 2-1: Schema



BICLA=BILAG 2004-based Composite Lupus Assessment; BILAG=British Isles Lupus Assessment Group Disease Activity Index; BL=Baseline; CS=corticosteroid; DZP=dapirolizumab; EOS=End of Study; EOT=End of Treatment; N=number of study participants planned; OLE=open-label extension; PBO=placebo; Q4W=every 4 weeks; Scr=Screening; SFU=Safety Follow-up; SOC=standard of care; V=Visit; W/wk=week

[a] The CS tapering should start no later than the Week 8 Visit (V4) with a targeted prednisone equivalent dose ≤7.5mg/day (in line with current treatment guidelines), guidance on how to taper will be provided but dynamic of dose-reduction is finally in the discretion of the investigators to be adapted to the patient's individual needs.

Please see the schedule of activities in Section 1.3, Table 1-2 in the SL0043 protocol for details.

2.4 Determination of sample size

The statistical power and sample size consideration is based on the objective to detect a meaningful improvement in BICLA responder rate compared with SOC+PBO at Week 48. Given 104 study participants in SOC+PBO and 208 study participants in SOC+DZP 24mg/kg groups and an assumed SOC+PBO responder rate of 0.32, there will be 90% power to confirm an SOC+DZP 24mg/kg responder rate of 0.52 (ie, a 0.20 improvement), to achieve statistical significance using a 2-sided 0.05 significance level test (SAS® version 9.4 POWER procedure, Fisher's exact). The sample size assumptions for SOC+PBO and SOC+DZP are based on the Phase 2b study SL0023 responder data at Week 24 in the population fulfilling SL0043 eligibility criteria.

Participants who withdraw from the study prior to the Week 48 Visit will be included in the primary efficacy analysis as non-responders (see Section 4.3.2 for additional details about the non-responder imputation). Therefore, no additional participants are planned to be randomized in order to make up for early withdrawers.

3 DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

Statistical analysis and generation of tables, figures, study participant data listings, and statistical outputs will be performed using SAS® Version 9.4 (SAS Institute, Cary, NC, USA).

For continuous parameters, number of participants with available measurements, mean, standard deviation (SD), median, minimum and maximum, and for categorical parameters, number of participants and percentages (to one decimal place) in each category will be presented in the summary tables. Changes from Baseline and/or percentage changes from Baseline will be presented where required.

All descriptive statistics will be presented by treatment group where applicable. All tabulations will be sorted by treatment, parameter and visit (including time relative to dosing if applicable, unless otherwise stated). Only scheduled visits and times relative to dosing will be included in the tabulation. The number of decimal places for continuous summary statistics should be based on level of precision captured in the source (eg, case report form (CRF), lab transfer, etc.) for non-derived variables. In general, for derived variables, min/max will be presented as collected in the source, and mean, SD, median have 1 additional decimal place with respect to the source.

Categorical data will be summarized by visit and treatment group, including column for all study participants in certain outputs (see Section 3.7 for details). Percentages will be based on the corresponding population size (ie, the denominator of percentages should match the sample size in the column header), unless otherwise noted via footnote in the applicable summary table. Percentages will be presented to 1 decimal place. For data points with n=0 (ie, no participants in the applicable category), no value for percentage of participants will be displayed.
Missing observations will be counted and described in the reports unless otherwise specified. For the shift tables, the percentages will be based on non-missing records at Baseline and the related post Baseline time points.

Statistical tests of efficacy variables will be presented as 2-sided p-values. P-values will be rounded to 4 decimal places. P-values less than 0.0001 will be presented as "<0.0001" and p-values greater than 0.9999 will be presented as ">0.9999."

Handling of multiplicity for the primary and key secondary efficacy variables is discussed in Section 4.8. All other efficacy variables will be considered exploratory in nature, hence inferential analysis will be assessed at 0.05 alpha level.

Unless otherwise noted, each table will be supported by a corresponding participant data listing and each figure will be supported by a corresponding table or listing. Participant data listings should use the largest logical analysis set in which the data is captured, in most cases this will be Enrolled Set for items collected in all study participants, the Full Analysis Set or Safety Set for all assessments collected only for randomized study participants.

3.2 Analysis time points

The timeframe encompasses the entire study duration, which extends from Screening to 10 weeks after the final dose, ie, 48 weeks of the Double-Blind Treatment Period and 6 weeks of the SFU Period.

The following study periods will be included in the analysis (see Section 3.3 for the definition of Relative day):

- Screening Period: up to 14 days (Day -14 through Day -1).
- Double-Blind Treatment Period: 48 weeks, starts with the randomization (1:2) of eligible participants to 1 of 2 treatment arms (SOC + placebo [PBO] or SOC + DZP 24mg/kg), stratified in accordance with the 3 stratification factors (see Section 4.1). Study medication will be administered by iv infusion every 4 weeks, starting on Day 1.
- Safety Follow-up Period (SFU):
  - Participants who withdraw from the study prematurely will be followed up for at least 10 weeks after the last infusion.
  - Participants who complete the 48-week Double-Blind Treatment Period, but do not enter the OLE study will continue into a 6-week SFU Period (10 weeks after last infusion at Week 44). During this period, study participants will not receive study medication, but will be able to receive SOC treatment, as indicated.

The time points for individual assessments are provided in the schedule of activities in Section 1.3, Table 1-2 in the SL0043 protocol.

Analyses conducted by visit will include each planned study visit at which the assessment was scheduled. Data for planned study visits will be based on the nominal time point and will not include any unplanned visits. Usually, efficacy data will not be obtained at unscheduled visits, with the exception of lab data used in the BILAG grading process and for SLEDAI-2K. Here, labs that are obtained prior to the visit or up to 2 weeks after the original visit could be used to replace missing lab data (see separate Central BILAG Grading and Adjudication Plan for details on the BILAG grading process).

All data collected, including assessments (planned or unplanned) will be reported in participant data listings. Data from participants withdrawing from the study early at end of treatment (EOT) visits will be mapped to the next scheduled visit per assessment for purpose of analyses and inclusion in summary tables but will be presented in terms of nominal visit in listings.

3.3 Relative day

Relative days for an event or measurement occurring before a reference date (generally the date of the first dose of study drug) are calculated as follows:

- Relative Day = (Event Date-Reference Date)

Relative days for an event or measurement occurring on or after the reference date to the last day of dose administration are calculated as follows:

- Relative Day = (Event Date-Reference Date) + 1

For events or measurements occurring after the date of last dose of study drug the relative day will be calculated with the date of last dose administration as reference. Relative day in this case will be prefixed with '+' in the data listings and will be calculated as follows:

- Relative Day = + (Event Date-Reference Date)

Note: relative day will be computed for fully reported dates only (for imputed dates it will not be computed)

3.4 Definition of Baseline values

Unless otherwise specified, the last value collected prior to the first infusion of study medication (Visit 2) will be used as the Baseline value. If a Baseline measurement is missing, and a Screening value is available, then the available Screening value will be utilized as Baseline. If a Baseline measurement is missing and there are multiple Screening lab values, then the most recent lab value prior to Baseline will be considered as the Baseline value. Unscheduled lab measurements taken before Baseline will be labelled as Screen Re-test values.

- For vital signs, a measurement prior to, or at the moment of, the start of the first infusion will be available for each visit. The last measurement prior to, or at the moment of, the start of the first infusion of study medication will be used as the Baseline value. An additional analysis will be performed using the pre-infusion values as Baseline values to determine the changes from pre infusion to post-infusion for each infusion visit. At each post-Baseline visit, the pre-infusion value will be one taken prior to, or at the moment of, the start of the infusion of study medication.
- For BILAG 2004 assessments, if the assessment is completed at Baseline, but the Grade for 1 or more individual system(s) is missing, the Grade for the system will be imputed as the Grade observed at the Screening visit. If there is no Grade available for the individual system at the Screening visit, then the Grade for that system at Baseline will be set to a Grade of BILAG 2004 D or E (in case no organ involvement ever before is documented).
- For SLEDAI-2K assessments, if a lab component for SLEDAI is missing at Baseline, the following methods will be applied.
  - If the last observation is present the last observation will be carried forward.
  - If there is no last observation the next observation will be carried backwards when there is one within the next 2 weeks.
  - If there are no observations under above two conditions the Baseline value will be set to ‘not present’.
  - Missing lab values that determine hematuria, pyuria or proteinuria at Baseline and at Screening will be imputed to 0.

3.5 Protocol deviations

Important protocol deviations (IPDs) are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a participant’s rights, safety, or well-being.

The criteria for identifying IPDs will be defined within the Protocol Deviation Specification Form. IPDs will be reviewed as part of the ongoing data cleaning process and data evaluation. All IPDs will be identified and documented prior to unblinding to confirm exclusion from analysis sets.

Sources for identifying protocol deviations will include the clinical database and a cumulative protocol deviation log from the clinical sites. Protocol deviations will be classified at blinded

data cleaning and data evaluation meetings. Any exclusion of participants from analysis sets or individual data from summary outputs will be documented in the meeting minutes.

For participants enrolled under different versions of the protocol, the programming of protocol deviations should be performed according to the version of the Protocol Deviation Specification Form relevant to the specific protocol version. The Protocol Deviation Specification Form will provide further details with regards to which version of the protocol the specific Protocol Deviation Specification Form version is applicable to. The version of the protocol to be followed for each participant will be provided by the Project Manager.

3.6 Analysis sets

The population of interest defined in Section 1, will be managed for statistical/reporting purposes using the following analysis datasets:

3.6.1 Enrolled Set

The Enrolled Set (ES) will consist of all study participants who have given informed consent.

3.6.2 Randomized Set

The Randomized Set (RS) will consist of all randomized study participants.

3.6.3 Full Analysis Set

The Full Analysis Set (FAS) will consist of all study participants randomized into the study following the intent to treat principle. The FAS is the primary analysis set for efficacy analyses and will be based on the planned treatment (assigned during randomization).

Based on concerns pertaining to persistent GCP non-compliance related to primary investigator (PI) oversight and study conduct, site 50273 was closed on 08 August 2023. It was discussed and agreed by the study team at the final Data Evaluation Meeting prior to database lock that efficacy data collected at site 50273 is not reliable and will be excluded from efficacy analyses by excluding participants randomized at this site from the FAS. There were 6 participants randomized at site 50273. Five of the participants completed the study at site 50273. One of the participants, 1327, had the Baseline visit and subsequent visits through Visit 6 at site 50273, but then transferred to site 50339 and completed the study at site 50339. All 6 participants will be excluded from the FAS.

3.6.4 Safety Set

The Safety Set (SS) will consist of all study participants who are randomized and have received at least 1 dose (any amount) of study medication. Safety endpoints will be analyzed using the SS. In the case of any mistreated participants, participants will be analyzed 'as randomized' unless there is evidence the participant consistently received incorrect treatment, in which case an 'as treated' approach will be followed (which will consider the actual treatment received).

Note that site 50273 is included in the SS.

3.6.5 Per-Protocol Set

The Per-Protocol Set (PPS) will consist of study participants in the FAS who have received at least 1 full dose of study medication and have no important protocol deviations during the Treatment Period that may influence the validity of the data for the primary efficacy variable.

3.6.6 The Pharmacokinetic Per-Protocol Set

The Pharmacokinetic Per-Protocol Set (PK-PPS) consists of all study participants who received at least 1 dose of study medication and provided at least one quantifiable plasma concentration post-dose without important protocol deviations that would affect the concentration.
Note that site 50273 is included in the PK-PPS.

3.7 Treatment assignment and treatment groups

For all analyses (where applicable) the results will be presented by treatment group:

- SOC + PBO iv q4w
- SOC + DZP 24mg/kg iv q4w

Selected parameters (where stated in the following sections) may be summarized also by subgroup (definition of subgroups, Section 4.9.1). A column for 'All Participants' will be added to group all participants regardless of treatment group, in the disposition, demographics, Baseline characteristics, prior and concomitant medications, corticosteroid dose at Screening and Baseline, exposure and Adverse Events (AEs) summary tables.

3.8 Center pooling strategy

There is no pooling strategy (by sites) defined for this study. Results will be combined across all sites, or by region according to the specified analysis.

3.9 Coding dictionaries

All AEs, concomitant diseases, and medical history will be coded for analysis according to the Medical Dictionary for Regulatory Activities (MedDRA)® coding dictionary, version 24.0 Prior and concomitant medications will be coded for analysis using the World Health Organization Drug dictionary (WHO-DD), Sep/2020 B3. The version number of coding dictionary will be displayed within the table. The coding dictionaries used to code adverse events (AEs), medical history, concomitant medications and concomitant diseases will be specified.

3.10 Changes to protocol-defined analyses

Table 3-1: Changes to the protocol defined analyses

Current in the protocol	Change
Tertiary endpoints: Observed values and change from Baseline in [redacted] levels in all	Observed values and change from Baseline in [redacted] levels in all study

Table 3-1: Changes to the protocol defined analyses

study participants by visit and in study participants 'positive' at Baseline by visit	participants by visit and in study participants 'positive' at Baseline by visit.
Tertiary endpoints: Achievement of a meaningful improvement in CLASI Index by visit for all study participants and for subset of study participants with high CLASI	Achievement of a meaningful improvement in CLASI activity score by visit for all study participants, for subset of study participants with high CLASI, and study participants with a CLASI ≥10
Tertiary endpoints: Observed values and change from Baseline in [redacted] levels in all study participants by visit and in study participants 'positive' at Baseline by visit	Added [redacted] conversion to the immunological parameters of DZP that will be evaluated
Tertiary endpoints: Achievement of reduction in corticosteroid dose from ≥7.5mg/day prednisone equivalent dose at start of study to ≤5mg/day prednisone equivalent at Week 24 and maintaining low corticosteroid dose and achievement of BICLA response at Week 48	Achievement of reduction in corticosteroid dose from >5mg/day prednisone equivalent dose at start of study to ≤5mg/day prednisone equivalent at Week 24 and maintaining low corticosteroid dose and achievement of BICLA response at Week 48
Tertiary endpoints: Achievement of reduction of corticosteroid dose from >7.5mg/day prednisone equivalent dose at start of study to ≤7.5mg/day prednisone equivalent at Week 24 and maintaining low corticosteroid dose and achievement of prevention of moderate/severe BILAG flares (moderate/severe BILAG flare-free) at Week 48	Achievement of reduction of corticosteroid dose from >7.5mg/day prednisone equivalent dose at start of study to ≤7.5mg/day prednisone equivalent at Week 24 and maintaining low corticosteroid dose and achievement of prevention of moderate/severe BILAG flares (moderate/severe BILAG flare-free) through Week 48
Tertiary endpoints: Achievement of reduction in corticosteroid dose from >5mg/day prednisone equivalent dose at start of study to ≤5mg/day prednisone	Achievement of reduction in corticosteroid dose from >5mg/day prednisone equivalent dose at start of study to ≤5mg/day prednisone equivalent at Week 24 and maintaining low

Table 3-1: Changes to the protocol defined analyses

equivalent at Week 24 and maintaining low corticosteroid dose and achievement of BICLA response at Week 48	corticosteroid dose and achievement of BICLA response at Week 48
Tertiary endpoints: Achievement of reduction of corticosteroid dose from ≥7.5mg/day prednisone equivalent dose to ≤5mg/day prednisone equivalent at Week 24 and maintaining low corticosteroid dose and achievement of prevention of moderate/severe BILAG flares (moderate/severe BILAG flare-free) at Week 48	Achievement of reduction of corticosteroid dose from >5mg/day prednisone equivalent dose to ≤5mg/day prednisone equivalent at Week 24 and maintaining low corticosteroid dose and achievement of prevention of moderate/severe BILAG flares (moderate/severe BILAG flare-free) through Week 48
To the current tertiary endpoints:	Added: • Achievement of a meaningful improvement in CLASI activity sub score – erythema by visit for all study participants and for subset of study participants with high CLASI • Achievement of a meaningful improvement in CLASI activity sub score – scaling by visit for all study participants and for subset of study participants with high CLASI • Achievement of a meaningful improvement in CLASI activity sub score – alopecia by visit for all study participants and for subset of study participants with high CLASI • Change from Baseline in Clinical SLEDAI-2K by visit Revised definition of DORIS: - Clinical SLEDAI-2K score =0 (SLEDAI-2K without serology: [redacted] - PGA ≤16mm - Prednisone equivalent systemic dose for a SLE indication ≤5mg per day at >50% of the last 28 days (>14 of the last 28 days) and the prednisone dose is

Table 3-1: Changes to the protocol defined analyses

	≤5mg/day at all days in the 7 days before a visit, at the day of the visit and at the day after the visit - [redacted] ≤ULN - [redacted] ≥LLN
To the current primary efficacy subgroup analyses:	[redacted]

4 STATISTICAL/ANALYTICAL ISSUES

4.1 Adjustments for covariates

[redacted]

[redacted]

4.2 Handling and definition of the corticosteroid prednisone equivalent dose

[redacted]

[redacted]

4.3 Handling of Missing Data

4.3.1 Missing data strategy for missing items within scales and missing components of composite endpoints such as BICLA response

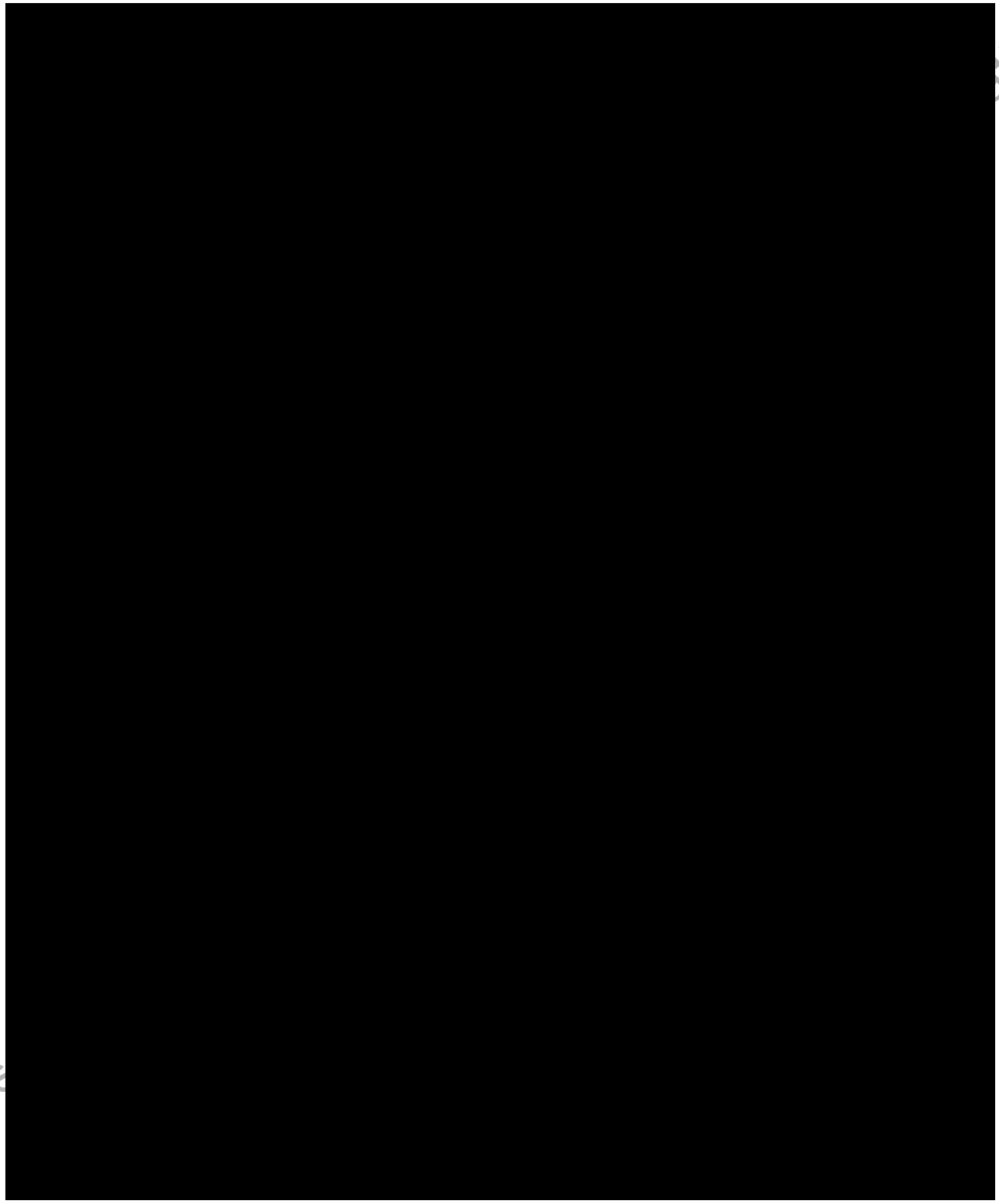
[redacted]

[redacted]

4.3.2 Non-Responder Imputation (NRI)

[redacted]

4.3.3 Multiple imputation (MI) assuming Missing at Random (MAR) – (MI-MAR) of BICLA, No Worsening in PGA, SLEDAI and BILAG Improvement at Week 48



[redacted]

4.3.4 Multiple imputation (MI) assuming Missing at Random (MAR) – (MI-MAR) of SLEDAI-2K at Week 48

[redacted]

[redacted]

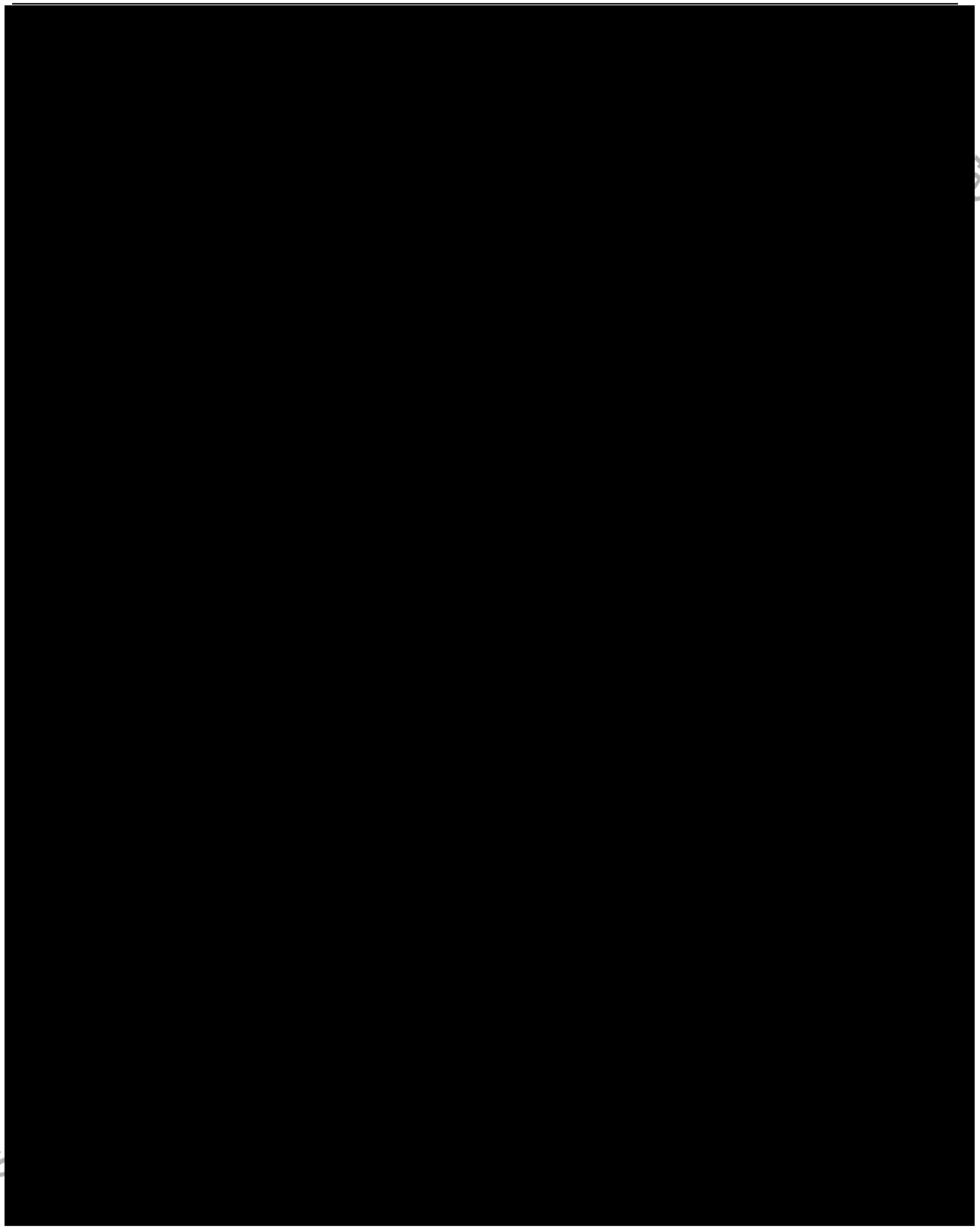
4.3.5 Multiple imputation (MI) assuming Missing at Random (MAR) – (MI-MAR) of Severe BILAG Flares Through week 48

[redacted]

[redacted]

4.3.6 Dates and times

[redacted]



4.4 COVID-19

[redacted]

4.5 Escape Treatment Interventions – Definitions

[redacted]

4.5.1 Escape Treatment Intervention 1 (Landmark endpoints, Flare endpoints)

[redacted]

4.6 Interim analyses and data monitoring

4.6.1 Data Monitoring

4.6.1.1 Independent Data Monitoring Committee (IDMC)

An IDMC will be established to monitor safety and the benefit-risk profile of study participants. The composition and operation of the IDMC will be defined in the IDMC Charter. The presentation and analysis of data for the IDMC meetings will focus on safety data, but efficacy data will be provided to support benefit-risk assessment, and is described within the Appendix of this SAP in Section 13.19. The IDMC data review will occur at least every six months, with the first data cut (for the IDMC meeting) scheduled at the latest after the first participant in SL0043 has completed 6 months on treatment. The last data review meeting will be scheduled after all participants have finished treatment, and the data have been appropriately prepared for final IDMC review. At each meeting, the IDMC will provide a recommendation as to whether the study should be stopped, should be adapted, or can proceed as planned.

4.6.1.2 Data Evaluation Meetings (DEMs)

Four DEMs are planned for assessment of blinded aggregate data throughout the study:

(1) DEM-1 will take place after approximately 15 to 20% of the enrolled participants have completed the Week 12 assessment. Objectives: Evaluation of aggregate data in order to identify systemic data errors and potential trends in important protocol deviations, and review of aggregate data to detect outliers and to evaluate relevant data distributions.

(2) DEM-2a will take place after approximately 25% - 30% of randomized participants have completed the Week 24 assessments or have withdrawn from study medication in the study. Objectives: Evaluation of aggregate data in order to identify systemic data errors and potential trends in important protocol deviations, discussion of dry-run tables, listings and figures, and finalization of the content of outputs defined in the SAP.

(3) DEM-2b will take place after approximately 30 to 60% of the enrolled participants have complete data of the primary variable. Objectives: Evaluation of aggregate data in order to identify systemic data errors and potential trends in important protocol deviations, discussion of dry-run tables, listings and figures, and finalization of the content of outputs defined in the SAP.

(4) DEM-3 will take place after 100% of the enrolled participants have complete data of the primary variable, all data are entered and approximately 95% to 100% of the data are clean. Objectives: confirmation of statistical assumptions, discussion of any outstanding analysis topics and finalization of rules for exclusion from analysis set.

4.6.2 Interim Analyses

An interim analysis to assess futility was specified within the original protocol and was removed for protocol Amendment 4. Therefore, an interim analysis is no longer planned.

4.7 Multicenter studies

This is a multicenter study with participation of approximately 230 sites in approximately 31 countries.

4.8 Multiple comparisons/testing strategy

[redacted]

4.9 Examination of subgroups

4.9.1 Subgroup analyses on the primary efficacy endpoint

Summary tables on the primary efficacy endpoint variable (BICLA) by visit using descriptive statistics in the FAS, will be presented in the following subgroups:

- Prior use of biological response modifier (Yes/No)
- Pooled regions (North America vs. Western Europe/Asia-Pacific vs. Latin America/Eastern Europe)
- Chronic active vs. acute flaring at Screening
- SLEDAI-2K Total Score (<10 vs. ≥10) at Screening
- [redacted] antibody positive (yes/no) at Baseline
- [redacted] antibody positive AND low complement (yes/no) at Baseline
- Region

- Ethnicity
- Age group 2 at Baseline
  - <median age
  - ≥median age
- Antimalarial use at Baseline (yes/no)
- Immunosuppressant use at Baseline (yes/no)
- Corticosteroid dose at Baseline >7.5mg/day (yes/no)
- Low complement at Baseline
  - Low [redacted] (yes/no)
  - Low [redacted] (yes/no)
  - Low [redacted] and/or [redacted] (yes/no)

5 STUDY POPULATION CHARACTERISTICS

5.1 Participant disposition

The following summary tables using descriptive statistics will be created:

(1) Disposition of participants screened (using the ES)

(2) Disposition and discontinuation reasons (using the RS)

(3) Reasons for Screen Failures (using the ES)

(4) Discontinuation Due to AE (using the RS)

Note:

The number of screened participants, as well as screening events (to account for rescreened participants), will be presented, as well as the number of re-screened participants, the number of participants randomized after first screening and the number of participants randomized after re-screening.

The time to permanent study drug discontinuation or premature withdrawal, whichever event occurs first will be plotted using Kaplan-Meier methods by treatment group in RS. Time until permanent discontinuation of study drug or premature withdrawal from the study will be calculated using the date at which a participant is considered a non-responder in efficacy analyses due to study withdrawal or permanent study treatment discontinuation determined as per the algorithm in Section 4.3.

If a participant has not prematurely withdrawn from the study nor discontinued study drug permanently by Week 48, she/he should be censored on the day of the Week 48 visit date (or final visit date if Week 48 visit was missed).

The following listings will be also created:

(1) Study Participants Disposition (using the ES)

(2) Study Participants Eligibility Criteria Text (using the ES)

(3) Study Participants Who Did Not Meet Study Eligibility Criteria (using the ES)

(4) Participants Completions and Discontinuations during the Study (using the RS)

(5) Visit Dates (RS)

(6) Study Participants Analysis Sets

(7) Study Participants Who Were Re-Screened (using the ES)

(8) Randomization Scheme and Codes (using the RS)

A listing of the actual treatment received for each participant will be produced separately for each participating study site. This listing will not be produced as part of the listings for the CSR and is instead generated to support external reporting obligations.

5.2 Protocol deviations

A summary of IPDs (described in Section 3.5) will be provided on the FAS by treatment group and overall to tabulate the number study participants excluded from the PPS and the PK-PPS due to IPD by categories (eg, inclusion criteria, exclusion criteria and all other categories included in the Protocol Deviation Specification document).

5.3 2019 EULAR/ACR Classification Criteria for SLE

A summary of past or present fulfillment of 2019 EULAR/ACR classification criteria for SLE (single items) will be provided on the FAS by treatment group and overall. Information on fulfillment of 2019 EULAR/ACR classification criteria (single items and overall score) for SLE will be listed by participant.

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

6.1 Demographics

Demographics information below, will be summarized (using descriptive) for the FAS (and the SS should these analysis sets differ) by treatment and overall. The demographic summary will include country information grouped into pooled regions, which are defined as North America, Western Europe/Asia-Pacific, and Latin America/Eastern Europe. Demographics information will also be listed for the ES. Please see below for additional information about categories that will be reported:

Age (years)
Age Category 1:
<65 years
≥65 to <75 years
≥75 years.
Age Category 2 (clinicaltrials.gov age categories):
≤18 years
19 to <65 years
≥65 years
Age Category 3 (EudraCT age categories)
12 to <18 years
18 to <65 years

65 to <85 years
≥85 years
Gender
Race Group
Ethnicity
Weight (Kg)
Height (cm)
BMI (kg/m2)
BMI (kg/m2)
<25
≥25
BMI (kg/m2)
<25
25 to <30
≥30
Missing
Country
Region
North America
Eastern Europe
Western Europe
Asia-Pacific
Latin America
Pooled Region
North America
Western Europe/Asia-Pacific
Latin America/Eastern Europe
For patients randomized in the USA:
Race group
Ethnicity.

6.2 Baseline characteristics

Baseline (BL) Characteristics summary using the FAS will display the following (by treatment group):

Disease history

1) Time since first diagnosis of SLE (years)
2) Number of Flares in the 6 Months Prior to Screening (0,1,2,>2, missing)
3) The number of participants with a thromboembolic event in the medical history (based on Thromboembolic Standardized MedDRA Queries (SMQs) and tabulated overall)
4) The number of participants with Urine Protein-Creatinine Ratio (uPCR) >113mg/mmol at Baseline
5) The number of participants with antiphospholipid antibodies (aPLs) in central lab:

- Any aPLs: any participant with >0 aPLs (as documented in Section 9.3) >ULN OR [redacted] >ULN
- Triple positivity (any): as defined in Section 9.3
- Double positivity: as defined in Section 9.3
- Single positivity: as defined in Section 9.3
- [redacted] >ULN

6) The number of participants with renal dysfunction (defined as estimated GFR<60mL/min/1.73m^2)

Disease Activity

1) BILAG 2004 total score at baseline
2) BILAG total score <20 vs. >=20 at baseline
3) Number of participants with BILAG A, B, C, D or E by Body/Organ system
4) Number of participants with
   - Moderate to severe disease activity as defined per protocol: BILAG 2004 Grades either >=1 BILAG Grade A and/or >=2 BILAG Grade Bs
   - One organ with moderate disease activity: 1 BILAG Grade B Only, No BILAG Grade A
   - No moderate or severe disease activity: No BILAG Grade A, No BILAG Grade B
   - At least 1 organ system severely active: ≥1 BILAG Grade A
   - Only 1 (severely) involved organ system: 1 BILAG Grade A and no other organ system with BILAG Grade A, Grade B
   - Multi-organ involvement: ≥2 organ systems with BILAG Grade A or Grade B
   - Multiple severely active organs: ≥2 organ systems with BILAG Grade A
   - Multiple organ involvement but no severely active: ≥2 organ systems with BILAG Grade B, no organ system with BILAG Grade A
5) Summaries of SLEDAI-2K scores at baseline as follows:
   - SLEDAI-2K total score at baseline
   - SLEDAI-2K total score (<10 vs. ≥10) at baseline
   - Clinical SLEDAI-2K (SLEDAI-2K without serology: [redacted] items) at baseline
   - Clinical SLEDAI-2K total score (≥6 vs. <6) at baseline
   - SLEDAI-2K without laboratory dependent descriptors (urinary casts, hematuria, proteinuria, pyuria, low complement, increased DNA binding, thrombocytopenia, leucopenia) (>=4 vs. <4)
6) Physician Global Assessment score

7) SELENA (Safety of Estrogens in Lupus National Assessment) Flare Index (SFI)
   - Baseline SFI (No flare, Mild flare, Moderate flare and Severe flare)
8) Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI)
   - CLASI: Disease activity score (continuous)
   - CLASI: Damage scores score (continuous)
   - CLASI disease activity score >0
   - CLASI disease activity score ≥8
9) Cutaneous SLE Manifestations: Percent Body Surface Skin Eruption (<5% vs. ≥5%)
10) Tender Joint Count/Swollen Joint Count (TJC/SJC)
   - Swollen joints count
   - Tender joint count
   - Count of joints that are both swollen and tender at the same time
   - >=4 joints that are both swollen and tender at the same time
11) Lupus [redacted] and Musculoskeletal Disease Activity (LAMDA) Physician Assessment
12) Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index
   - Total score (continuous)
   - SLICC/ACR =0
   - SLICC/ACR =1
   - SLICC/ACR >1

SLE Serology

1) The number of participants with [redacted]
2) The number of participants with [redacted] antibody
   a) ELISA (<30 IU (negative), 30 – 75 IU (indeterminate) and >75 IU (positive)) at Screening
   b) CLIFT (negative vs. positive) at Screening
   c) EliA (negative vs. positive) at Baseline
3) The number of participants with low complement
   a) [redacted] <LLN
   b) [redacted] <LLN
   c) [redacted] >ULN
   d) [redacted] <LLN

e) [redacted] <LLN

Baseline Patient-Reported Outcome Characteristics

1) FATIGUE-PRO
   a) Physical Fatigue Score
   b) Mental Fatigue Score
   c) Fatigability Score
2) FACIT Fatigue Scale Version 4 Total Score
3) PGI-S by Symptoms Over the Past Week (None, Mild, Moderate, Severe, Very Severe)
4) PGI-S – Fatigue by Severity Over the Past Week (None, Mild, Moderate, Severe, Very Severe)
5) Lupus QOL
   a) Physical Health Score
   b) Pain Score
   c) Planning Score
   d) Intimate Relationships Score
   e) Burden to Others Score
   f) Emotional Health Score
   g) Body Image Score
   h) Fatigue Score
6) PHQ-9
7) EQ-5D UK Tariff
8) EQ-5D-5L Scores by Domain (Mobility, Self-Care, Usual Activities, Pain/Discomfort, Anxiety/Depression) and Visual Analog Scale

Stratification Factors at Screening

Note that below are the stratification factors reported to IXRS for randomization.

9) Pooled region (North America vs. Western Europe/Asia-Pacific vs. Latin America/Eastern Europe).
10) Screening disease activity pattern (chronic active vs. acute flaring, as collected in the stratification electronic case report form (eCRF)).
11) Screening SLEDAI score (<10 vs. ≥10),

6.3 Procedure History and Concomitant Medical procedures

Procedure history and concomitant medical procedures will be listed chronologically for all participants in the SS including the reported term for the procedure, the date of the procedure and, for concomitant medical procedures only, what the procedure is primarily related to. Concomitant medical procedures will also be summarized for the SS.

6.4 Medical history conditions

Medical history will be listed for all participants in the SS including the reported term, start date, end date (or ongoing if applicable).

A glossary of all medical conditions will also be presented including the reported term, the preferred term and the system organ class. The classification of medical history and concomitant medical conditions will be done according to the MedDRA coding system using system organ class, high level term and preferred term. This data will be summarized for the SS using

frequency tables for participant count by MedDRA system organ class, high level term and preferred term.

6.5 Prior and concomitant medications

Prior medications include any medications with an end date prior to the start date of study medication. Concomitant medications are medications taken at least 1 day in common with the study medication dosing period up to 10 weeks after the last infusion.

Details of imputation methods for missing or partial dates are described in Section 4.3.5.

Prior and concomitant medications that are SLE-related will be summarized for participants in the SS and FAS. In addition, SLE-related concomitant medications taken at the Baseline visit will be summarized in the FAS. SLE-related prior and concomitant medications taken at the Baseline visit will also be summarized in a single table in the FAS. Prior and concomitant medications that are not SLE-related will be summarized for participants in the SS only. All prior and concomitant medications will be listed for the SS.

The number and percentage of participants taking prior medications will be summarized by treatment group, overall and by ATC class, presenting Anatomical Main Group (ATC Level 1), Pharmacological Subgroup (ATC level 3), and preferred term. Prior corticosteroid medications will be summarized similarly.

The number and percentage of participants taking concomitant medications will be summarized similarly for the Treatment Period.

The prednisone equivalent dose at Baseline and Week 48 as well as the Change from Baseline in prednisone equivalent dose will be presented as a cumulative distribution function plot by dose level. Further the mean prednisone dose will be plotted by visit. Note that all analyses on corticosteroid (prednisone equivalent) doses will be restricted to those for a SLE indication only.

The classification of the medication will be done according to the WHO-DD ATC classification, version Sep/2020 B3. The data will be classified by SLE-related/not SLE-related (information about (no) SLE-relation will be provided by investigator using specified tick box in CRF). The number and percentage will be summarized separately by treatment group, overall, and by ATC class, presenting Anatomical Main Group (ATC Level 1), Pharmacological Subgroup (ATC level 3), and PT for the Initial Treatment Period and Maintenance Treatment Period separately.

6.5.1 Escape Treatment Medications

Concomitant medications fulfilling criteria of intercurrent events “escape treatment intervention” as described in Section 4.4 will be tabulated and listed in the FAS.

In general, every medication change which fulfills the criteria of the escape treatment intervention 1 will be summarized using the FAS.

6.6 Lifestyle

Lifestyle data collected in the eCRF will be summarized and listed using the SS.

6.7 Childbearing Potential

Childbearing Potential data collected in the eCRF will be listed using the SS

6.8 Immunosuppressant, Antimalarial and Corticosteroid at Baseline

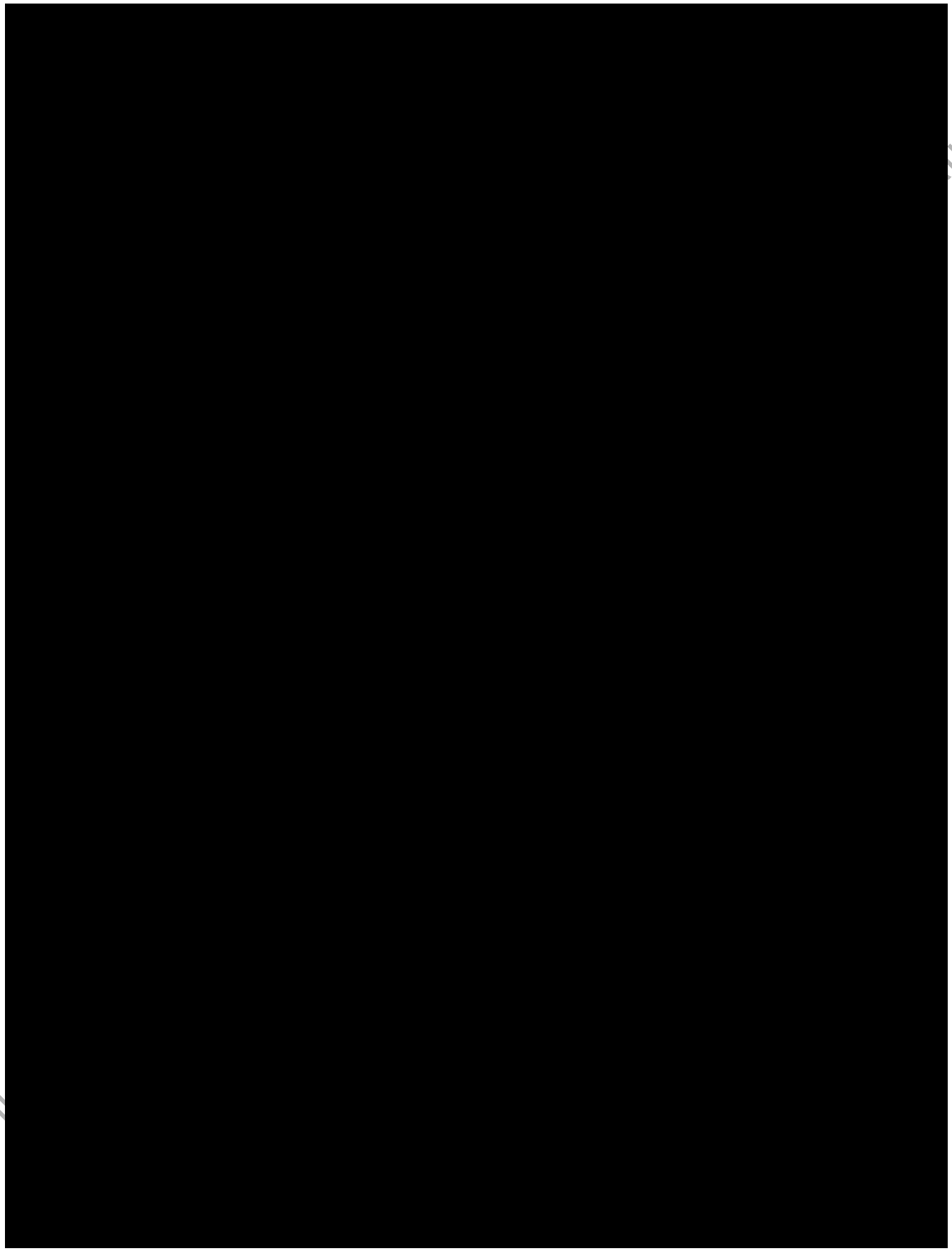
The following categories will be summarized using descriptive statistics on the SS (Note: All analyses on corticosteroid (prednisone equivalent) doses will be restricted to those for a SLE indication only).

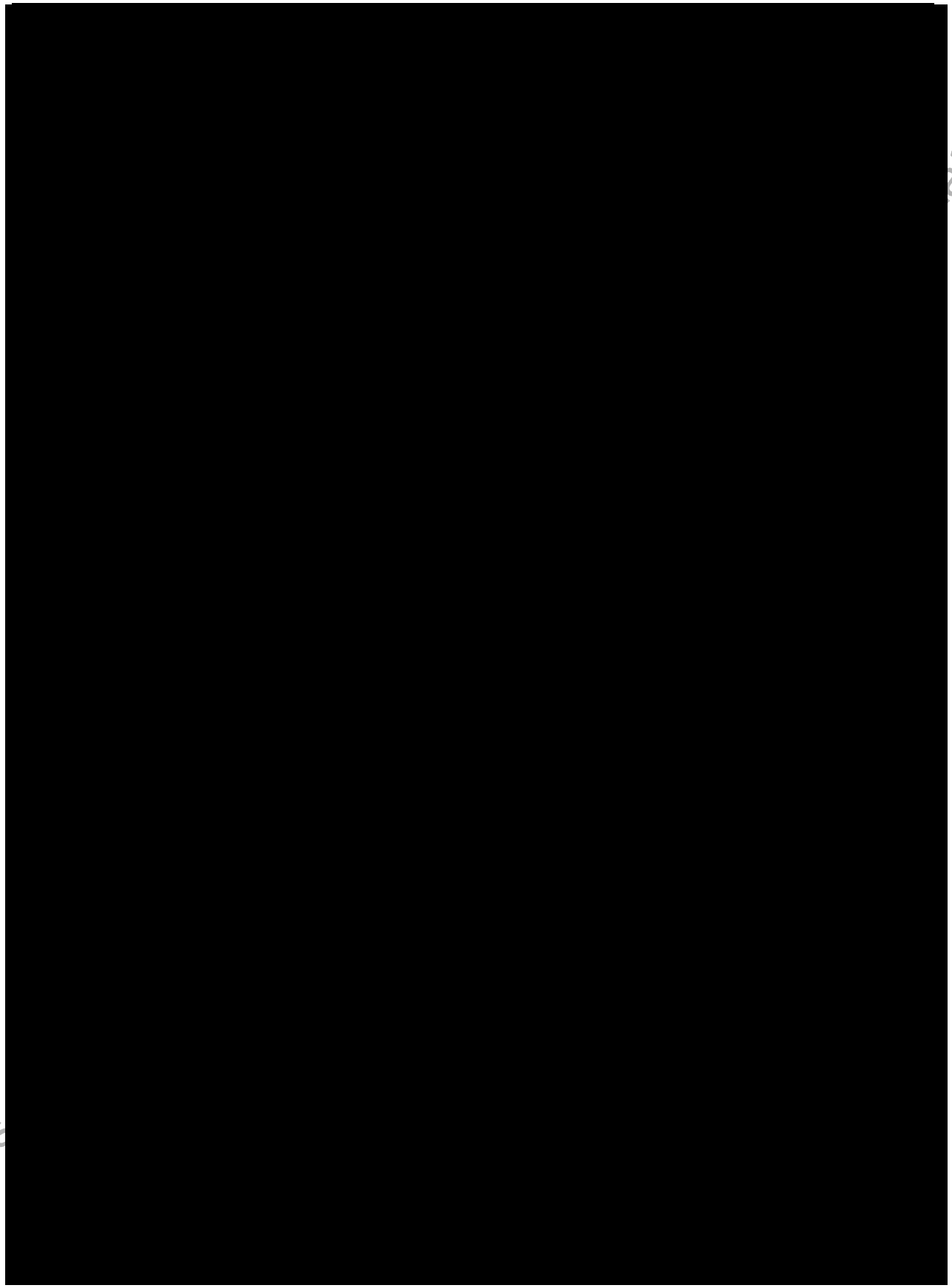
- Systemic Corticosteroid use: 0mg/day vs. >0mg/day
- Systemic Corticosteroid dose Category 1 (≤7.5mg/day vs. >7.5mg/day)
- Systemic Corticosteroid dose Category 2 (≤10mg/day vs. >10mg/day)
- Systemic Corticosteroid use only, no antimalarial or immunosuppressant (Yes/No)
- Antimalarial use (Yes/No)
- Antimalarial use only, no corticosteroid or immunosuppressant (Yes/No)
- Immunosuppressant use (Yes/No)
- Immunosuppressant use only, no corticosteroid or antimalarial (Yes/No)
- Immunosuppressant and antimalarial use only (Yes/No)
- Corticosteroid and immunosuppressant use only (Yes/No)
- Corticosteroid and antimalarial only (Yes/No)
- Corticosteroid, antimalarial and immunosuppressant use (Yes/No)
  - Receive immunosuppressant or have received immunosuppressant in the past (Yes/No)
  - Receive antimalarial or have received antimalarial in the past (Yes/No)
  - Receive corticosteroid or have received corticosteroid in the past (Yes/No)
- Mean corticosteroid dose at Baseline

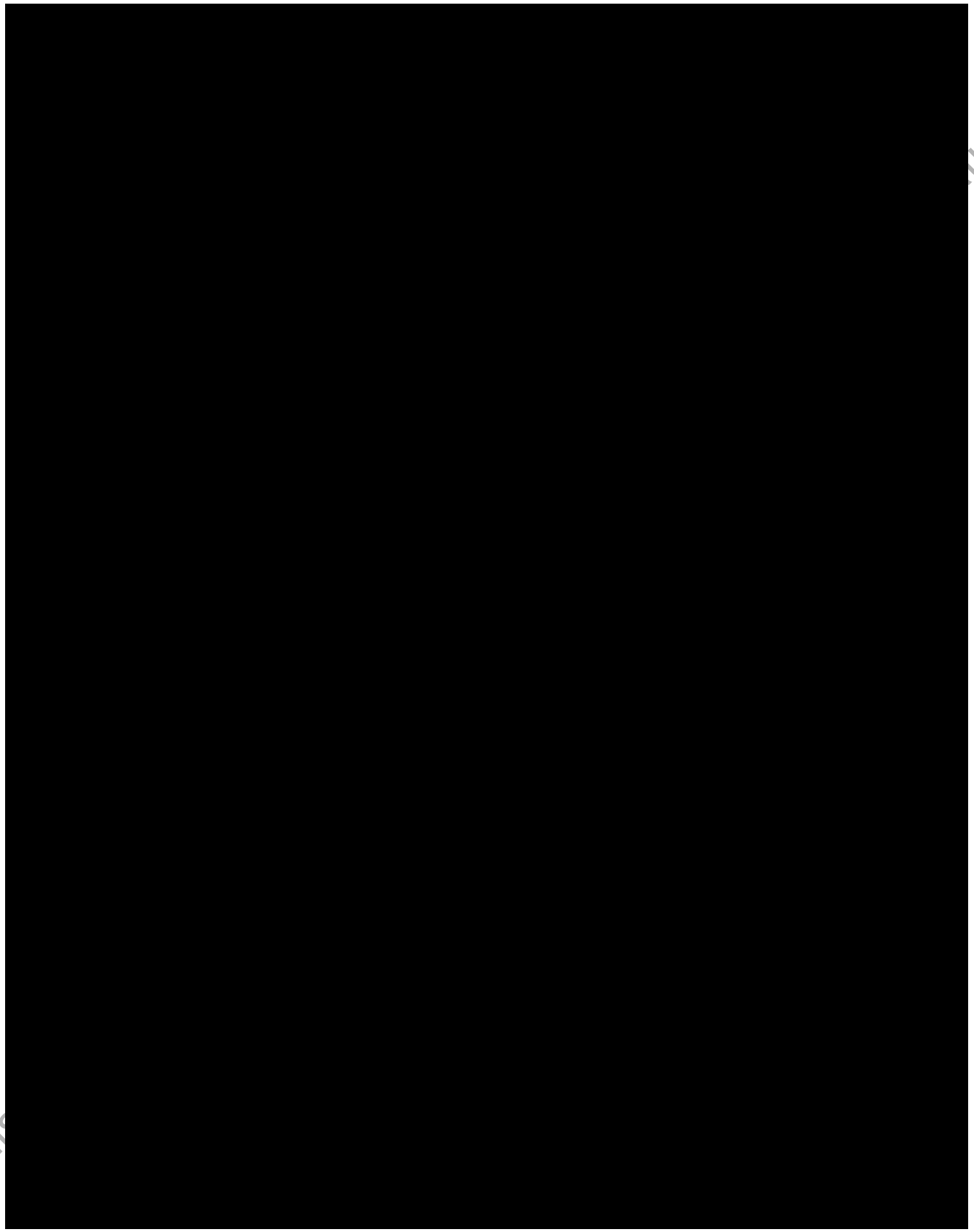
For both antimalarials and immunosuppressants, the systemic or non-systemic classification will be determined by medical review.

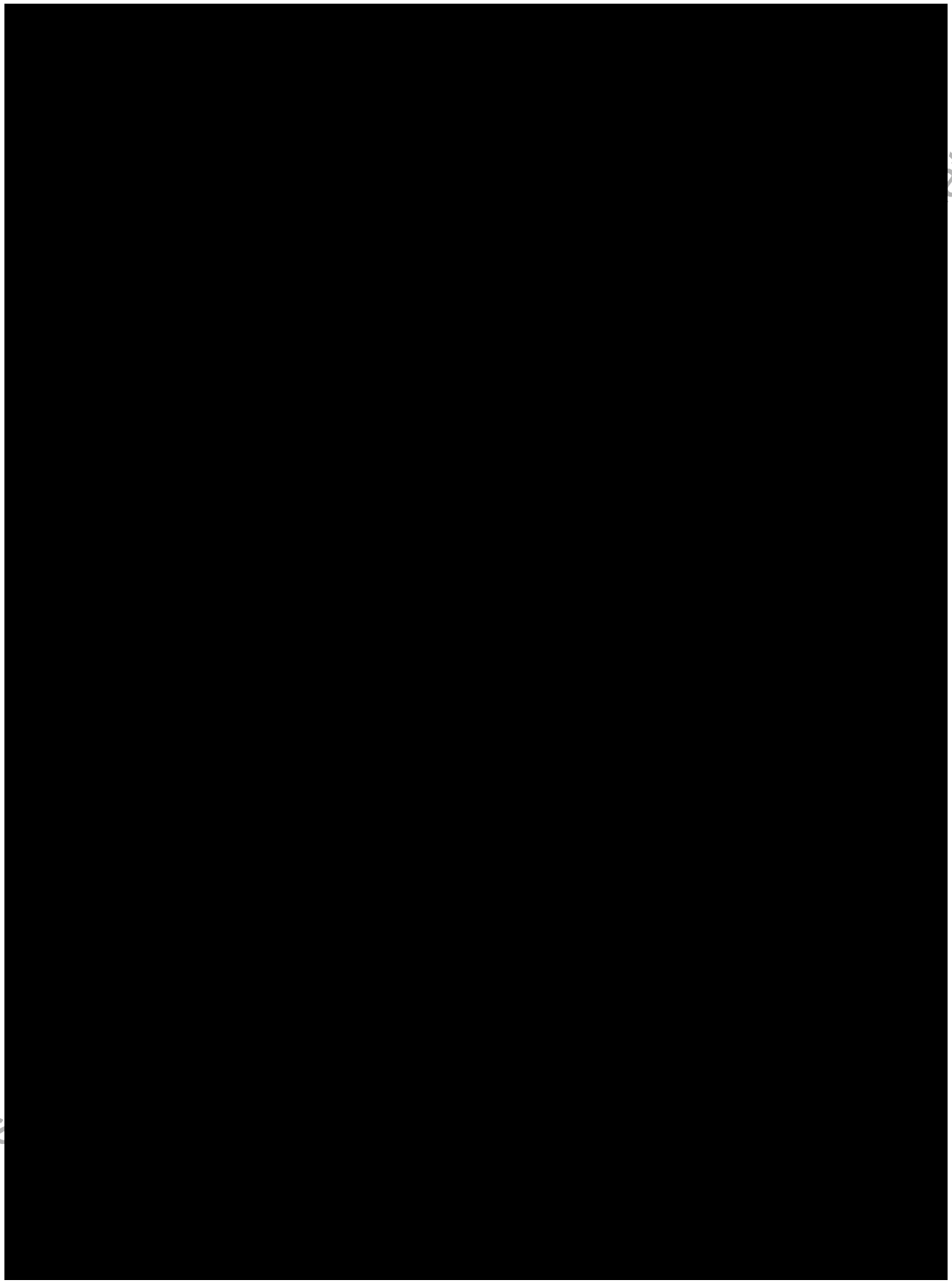
7 MEASUREMENTS OF TREATMENT COMPLIANCE

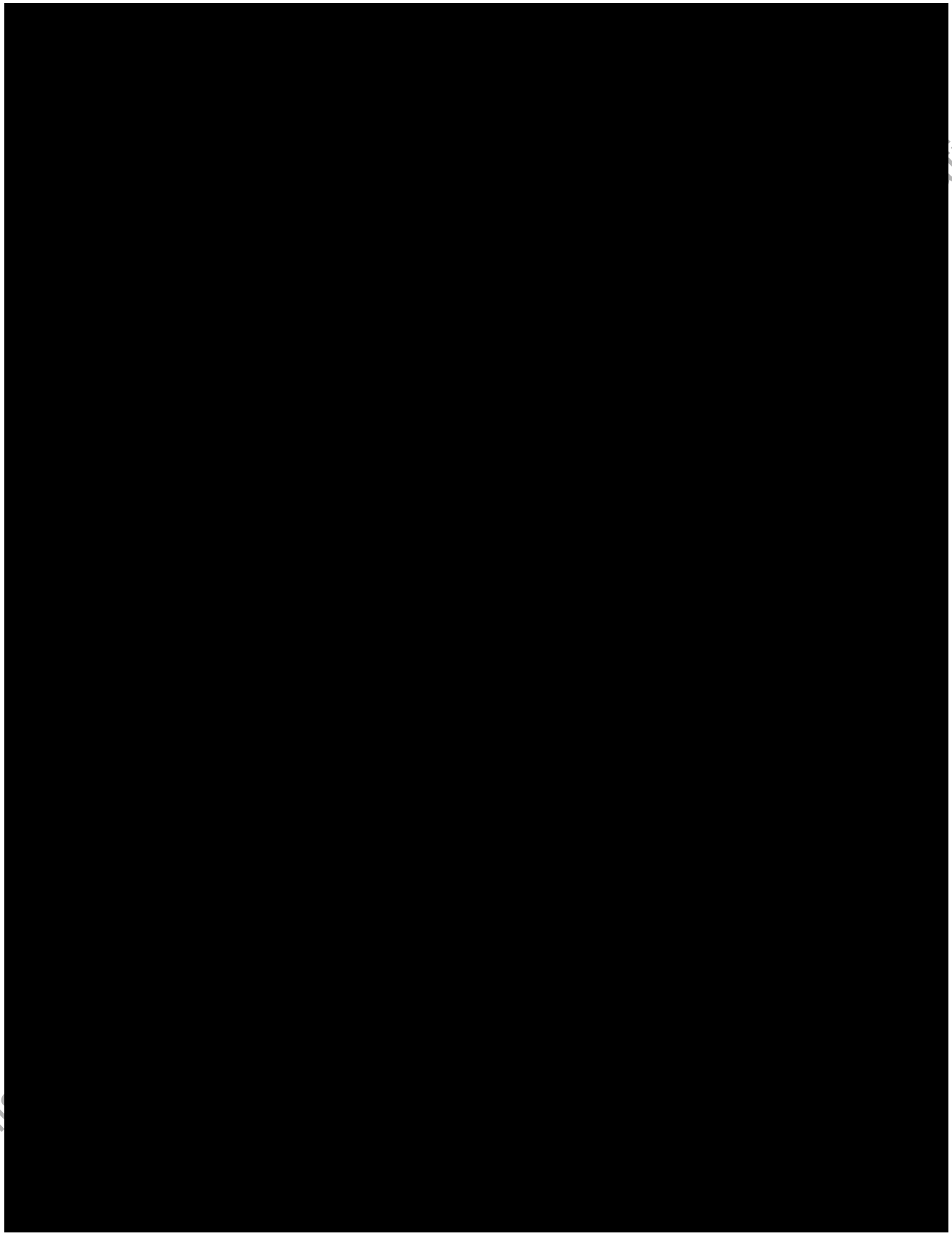
Please see Section 10.2 for details for treatment exposure and compliance.

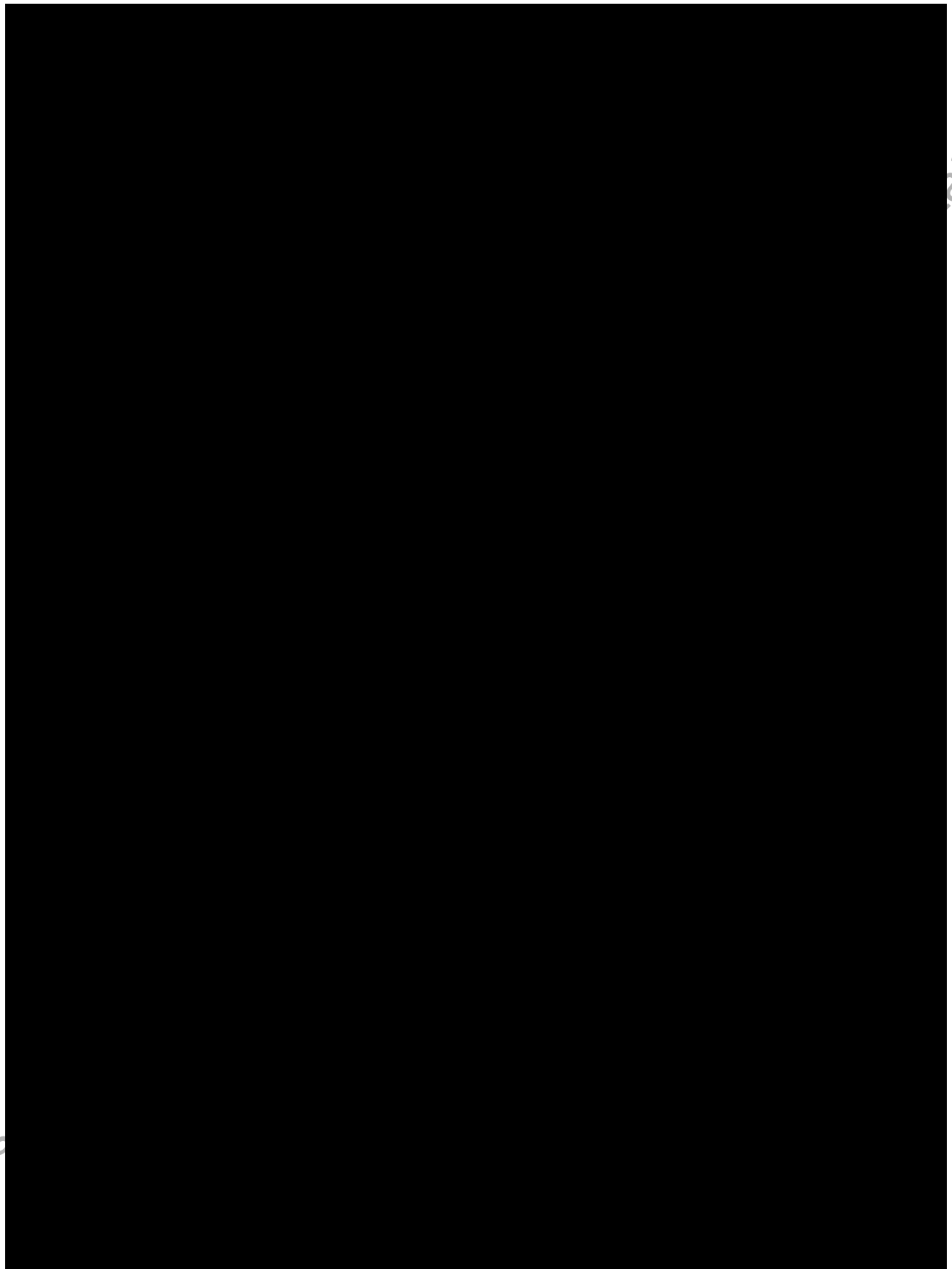


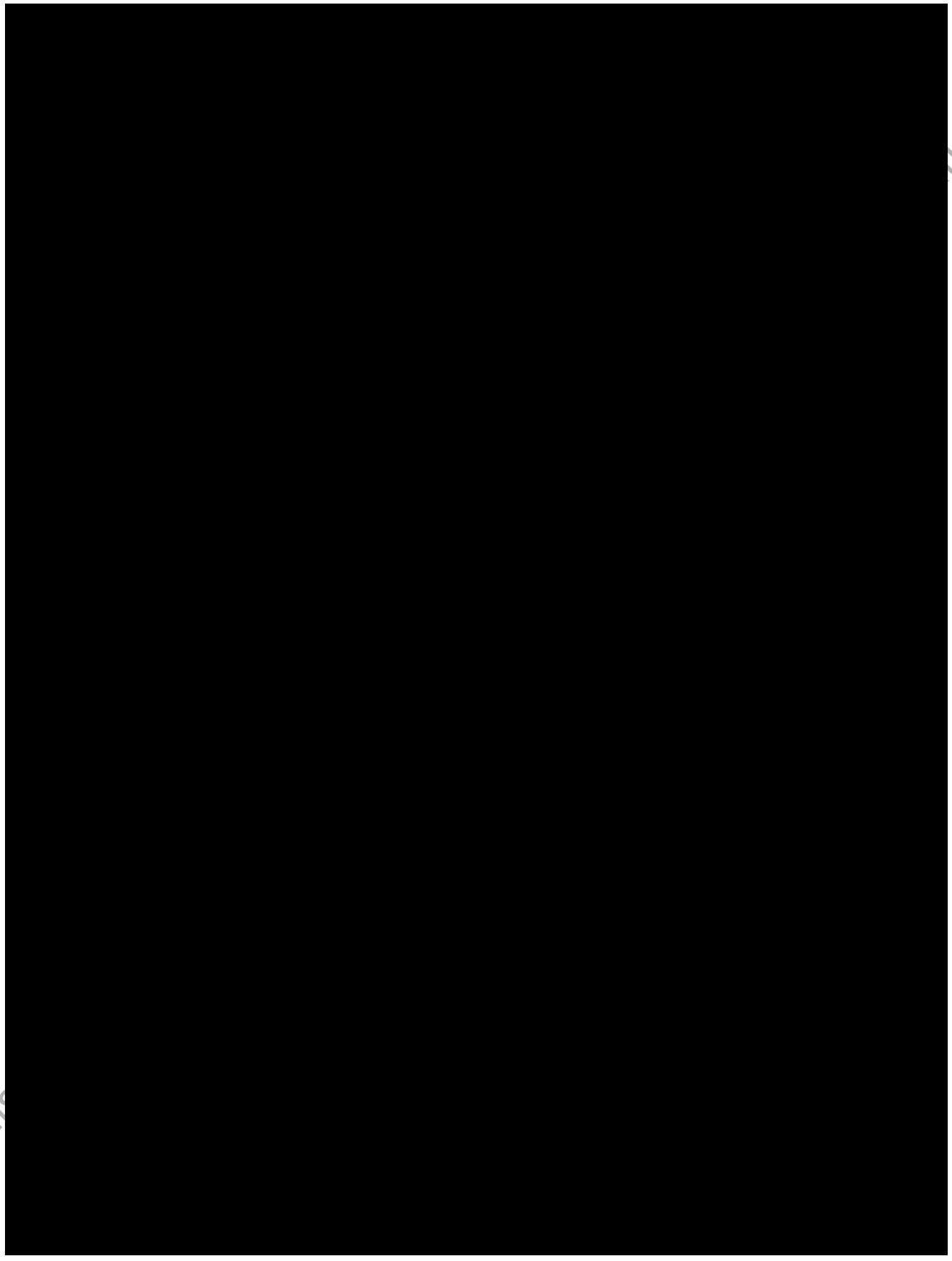


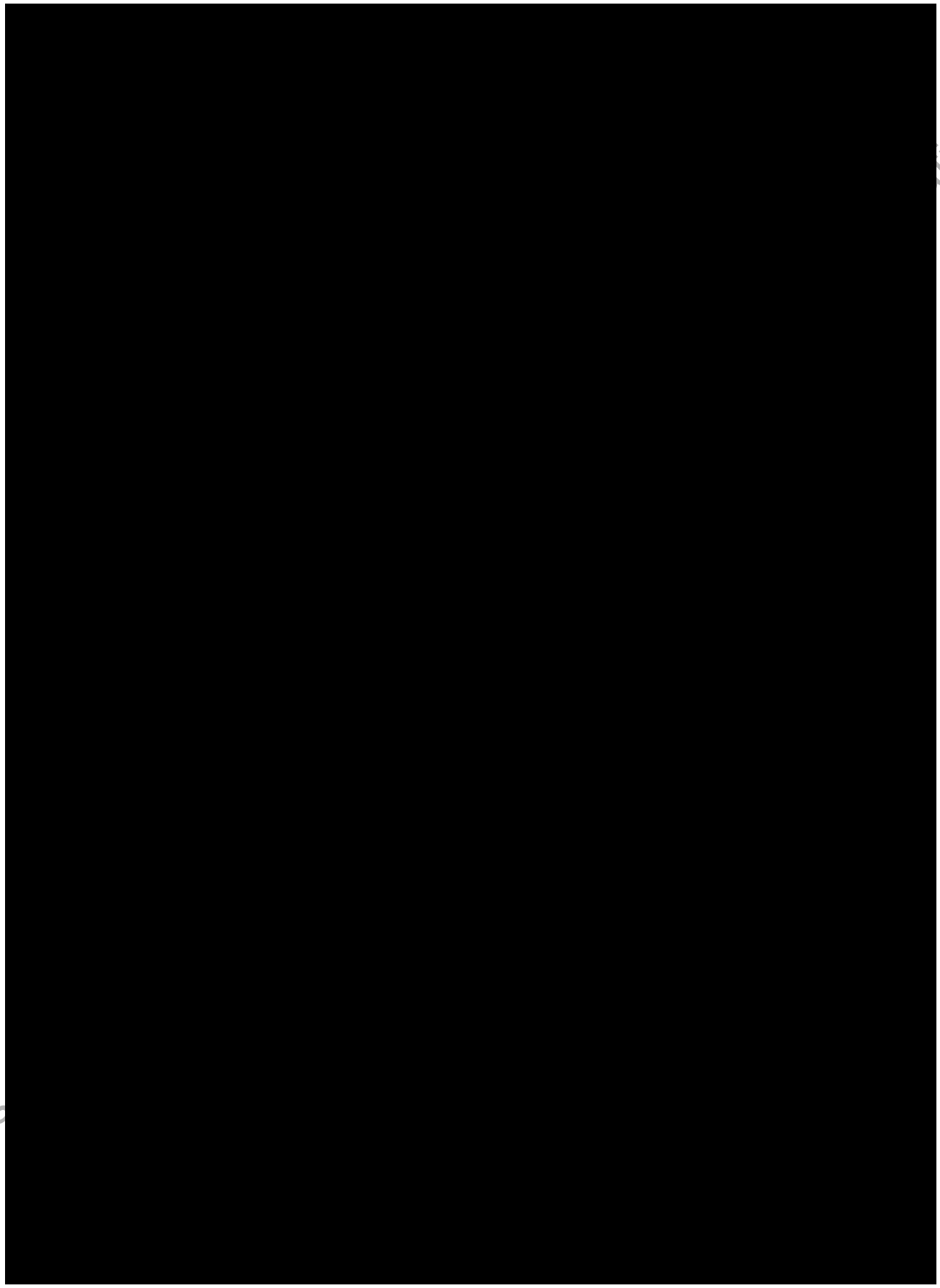


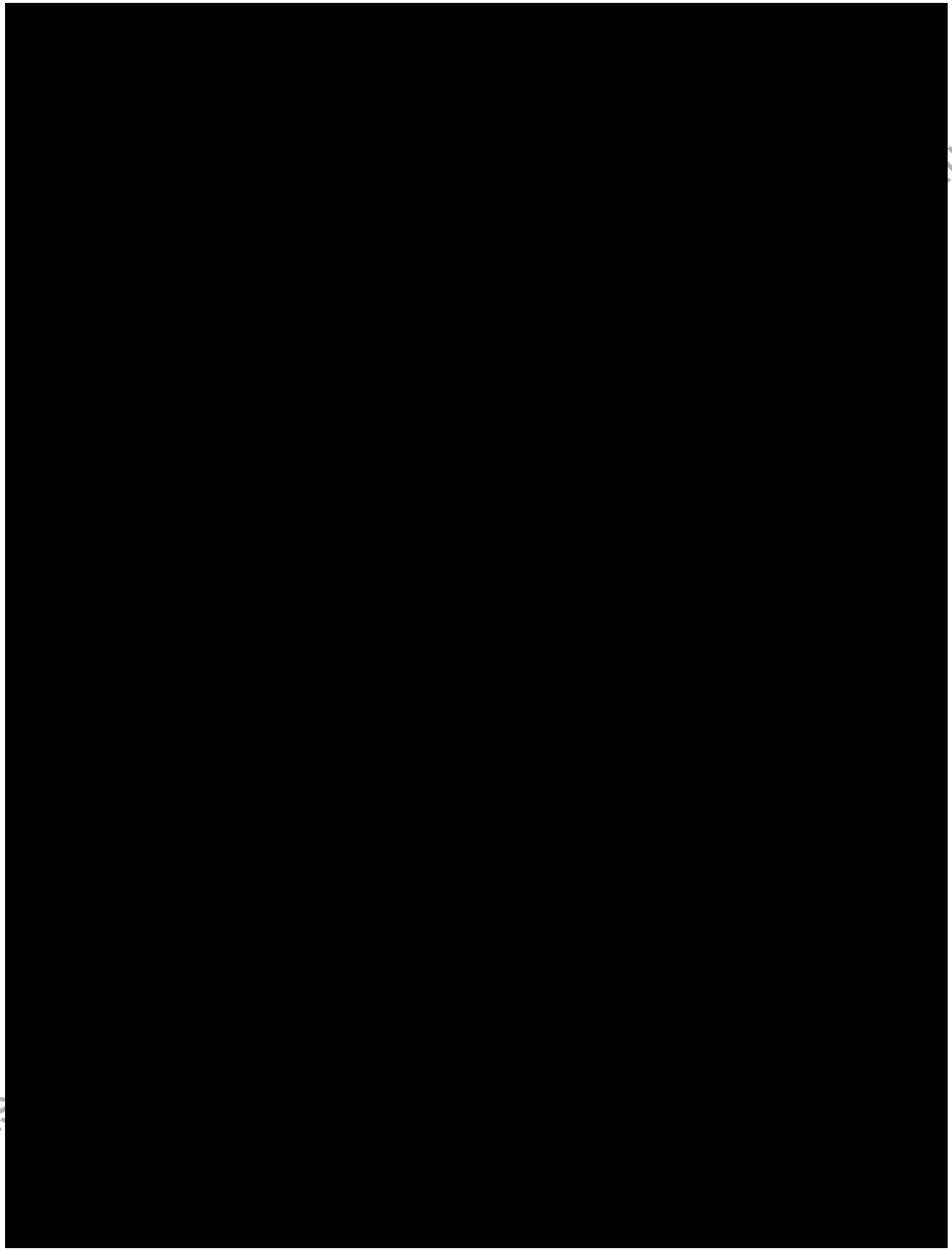


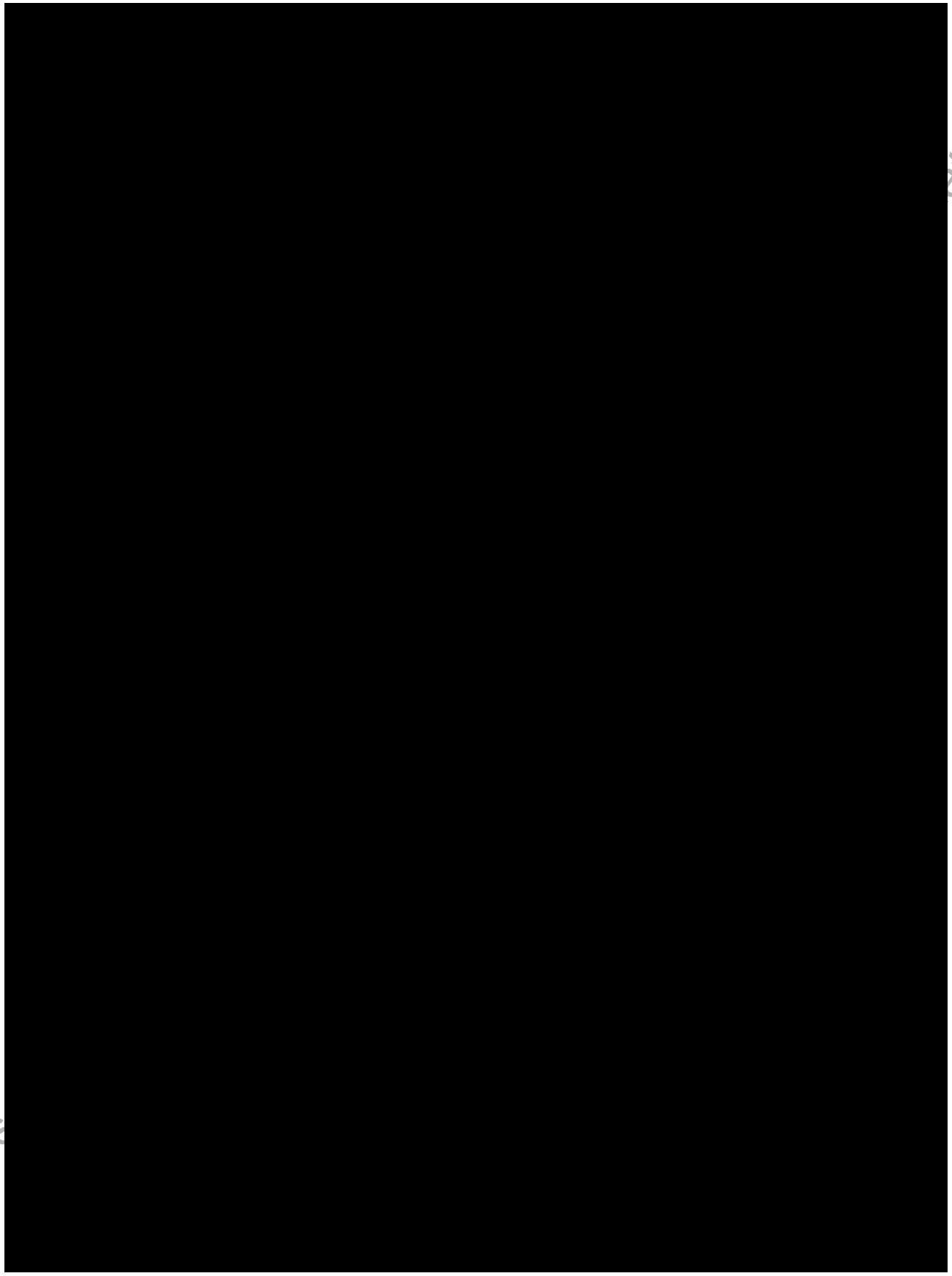


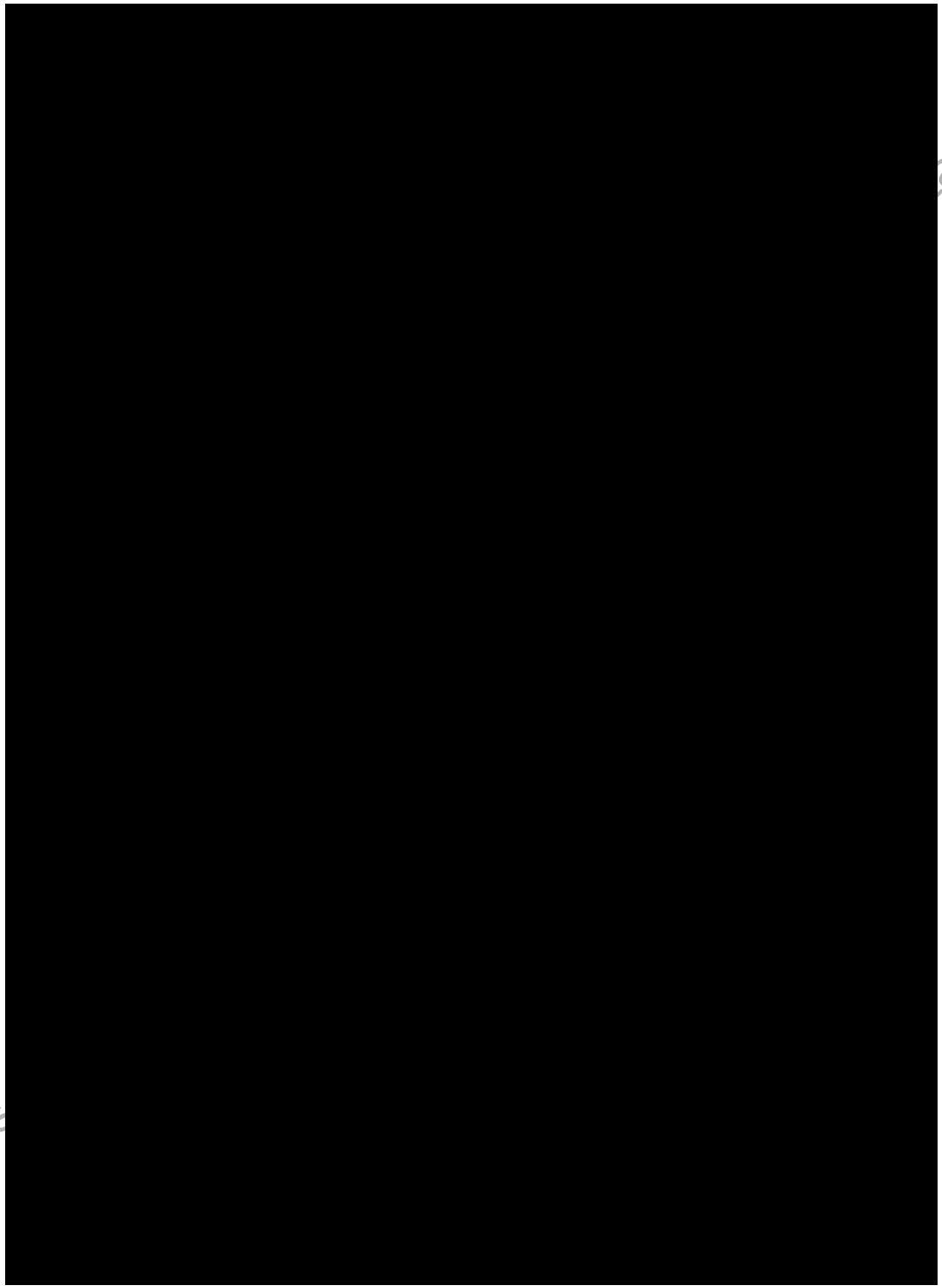


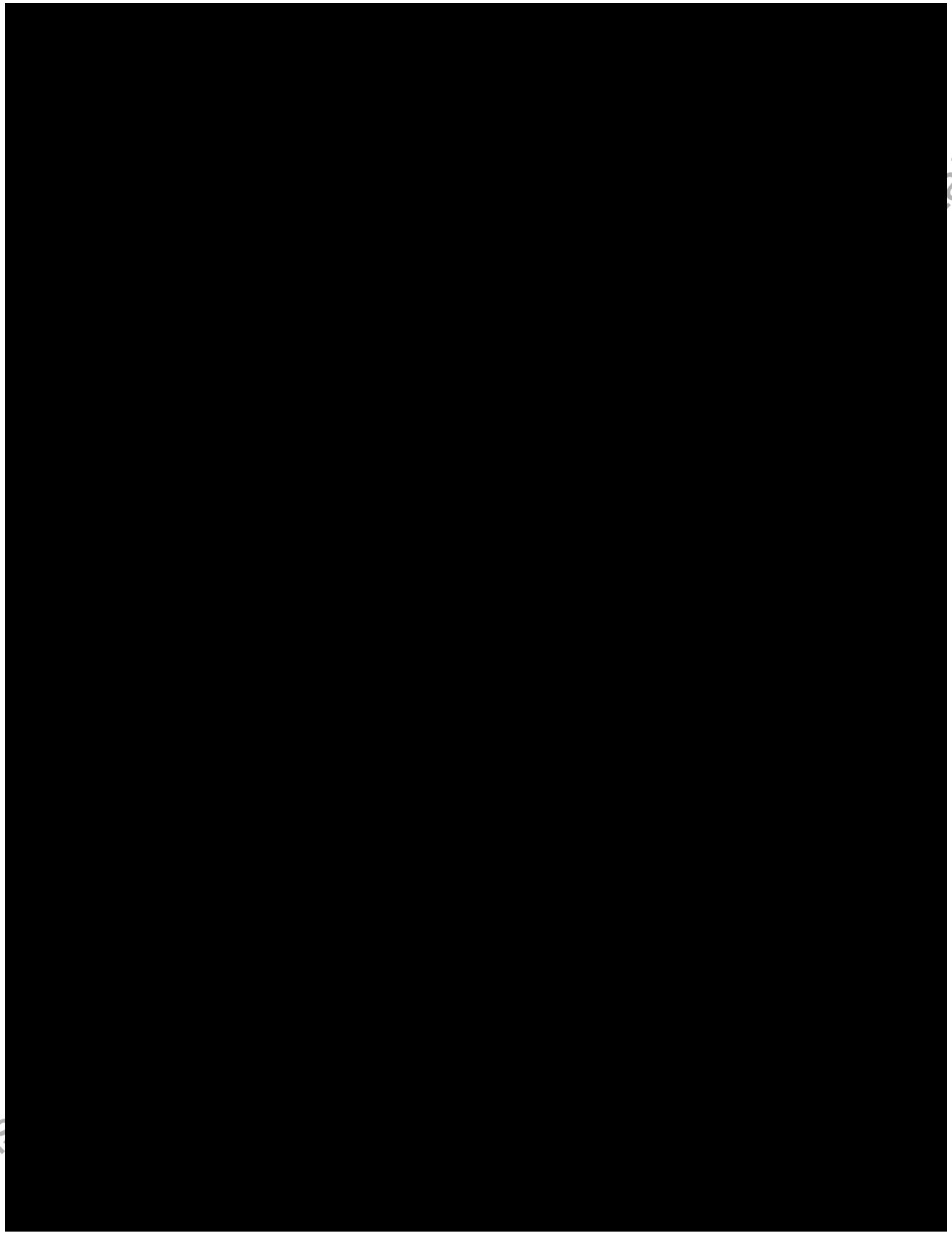


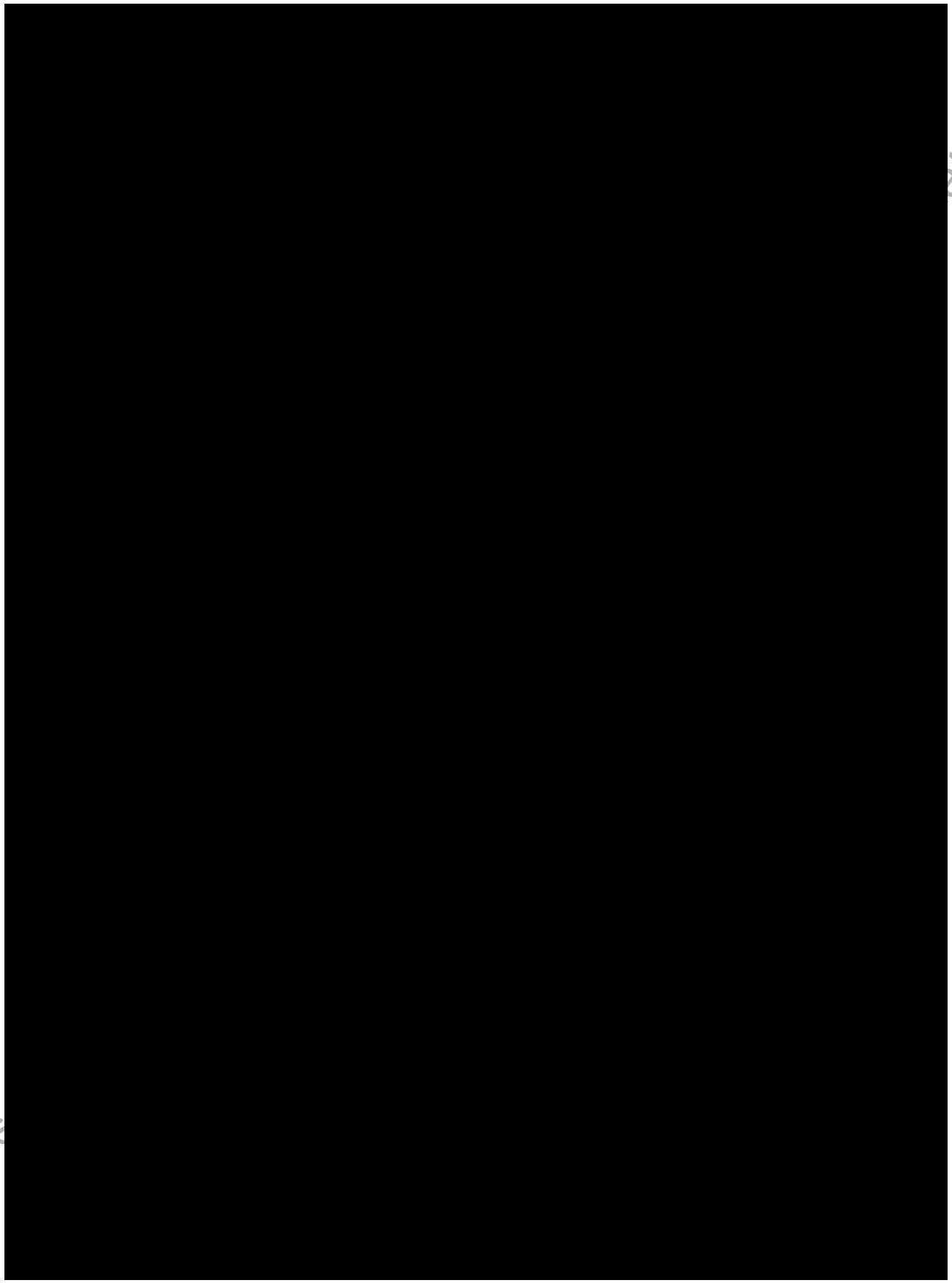


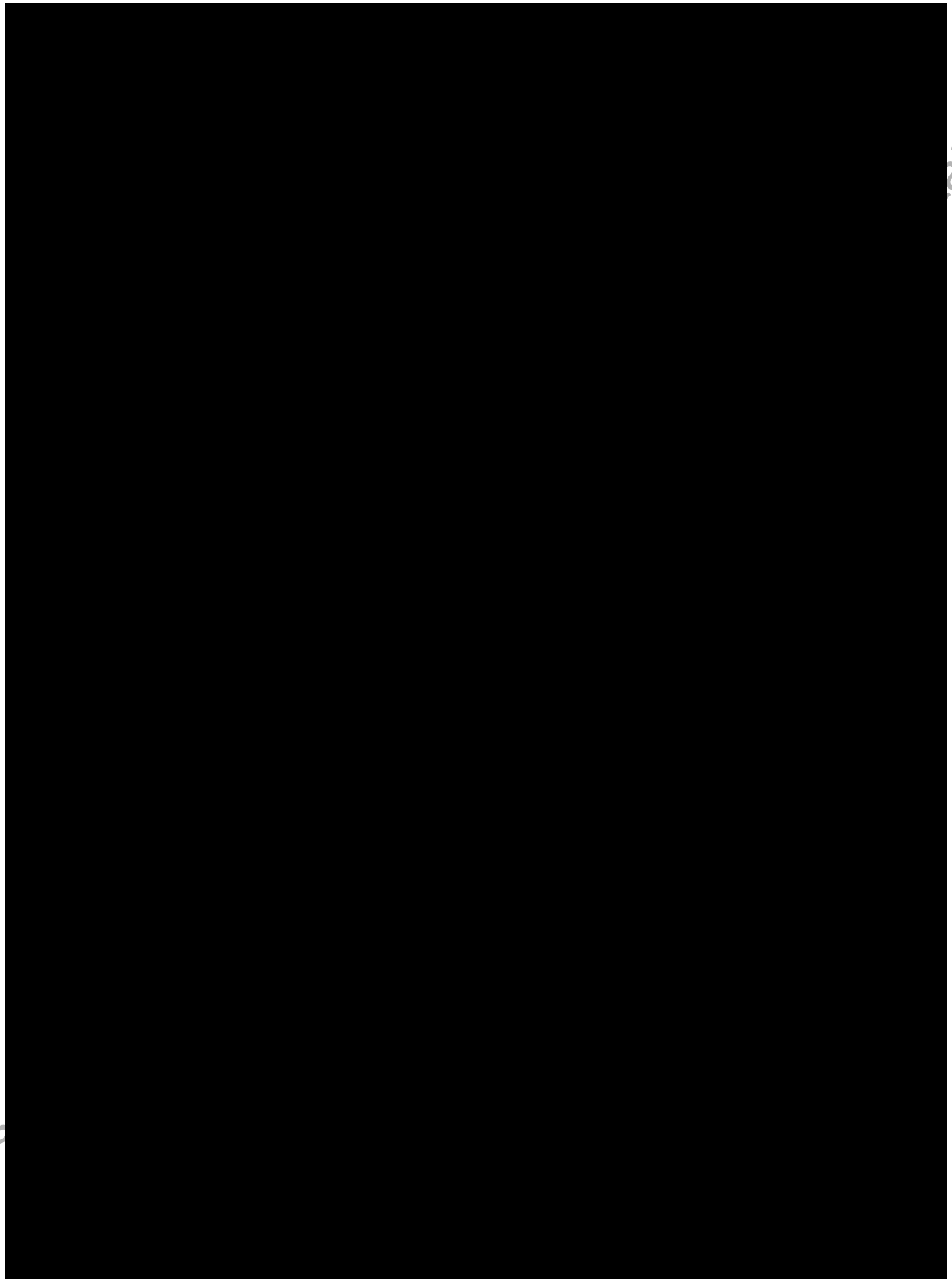


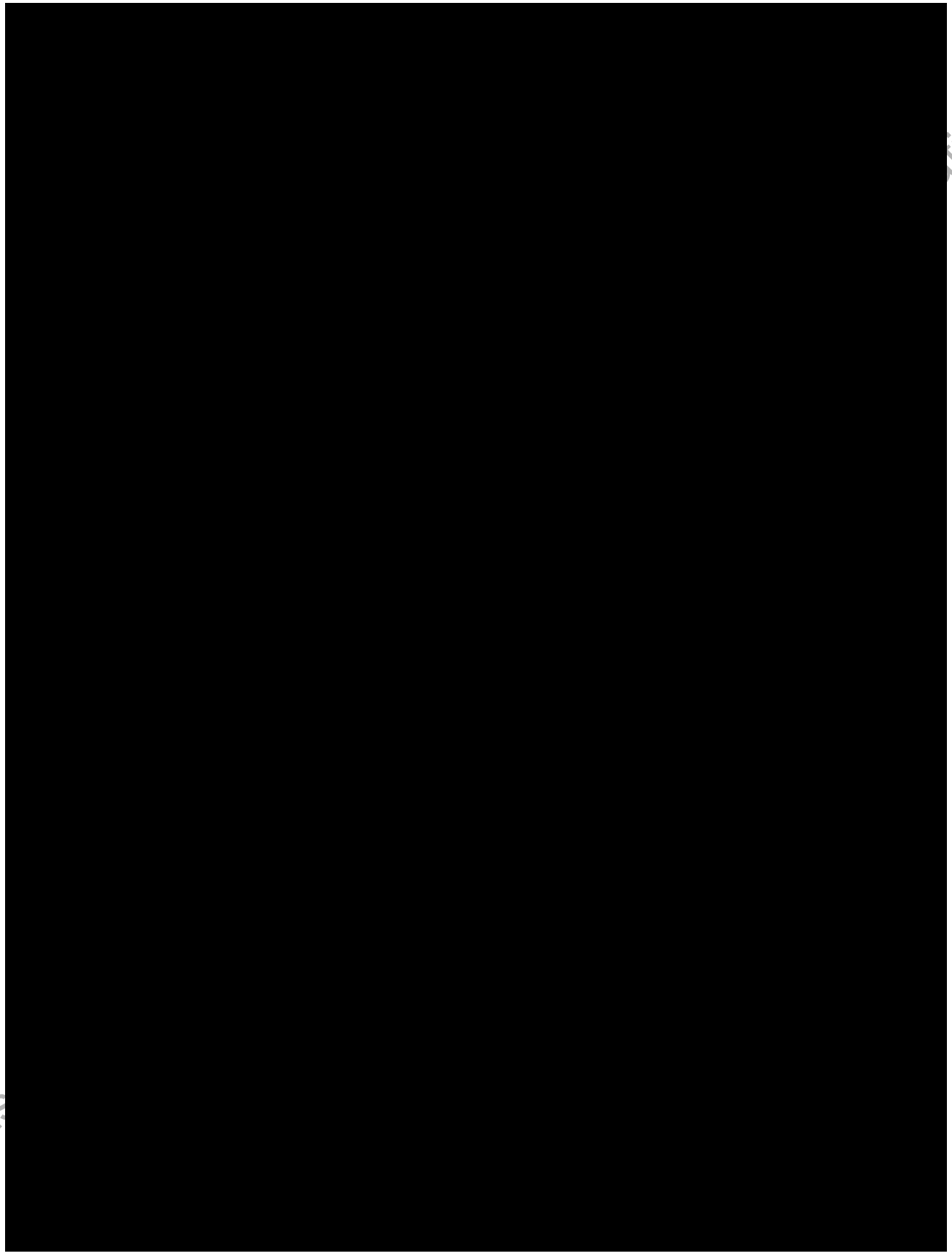


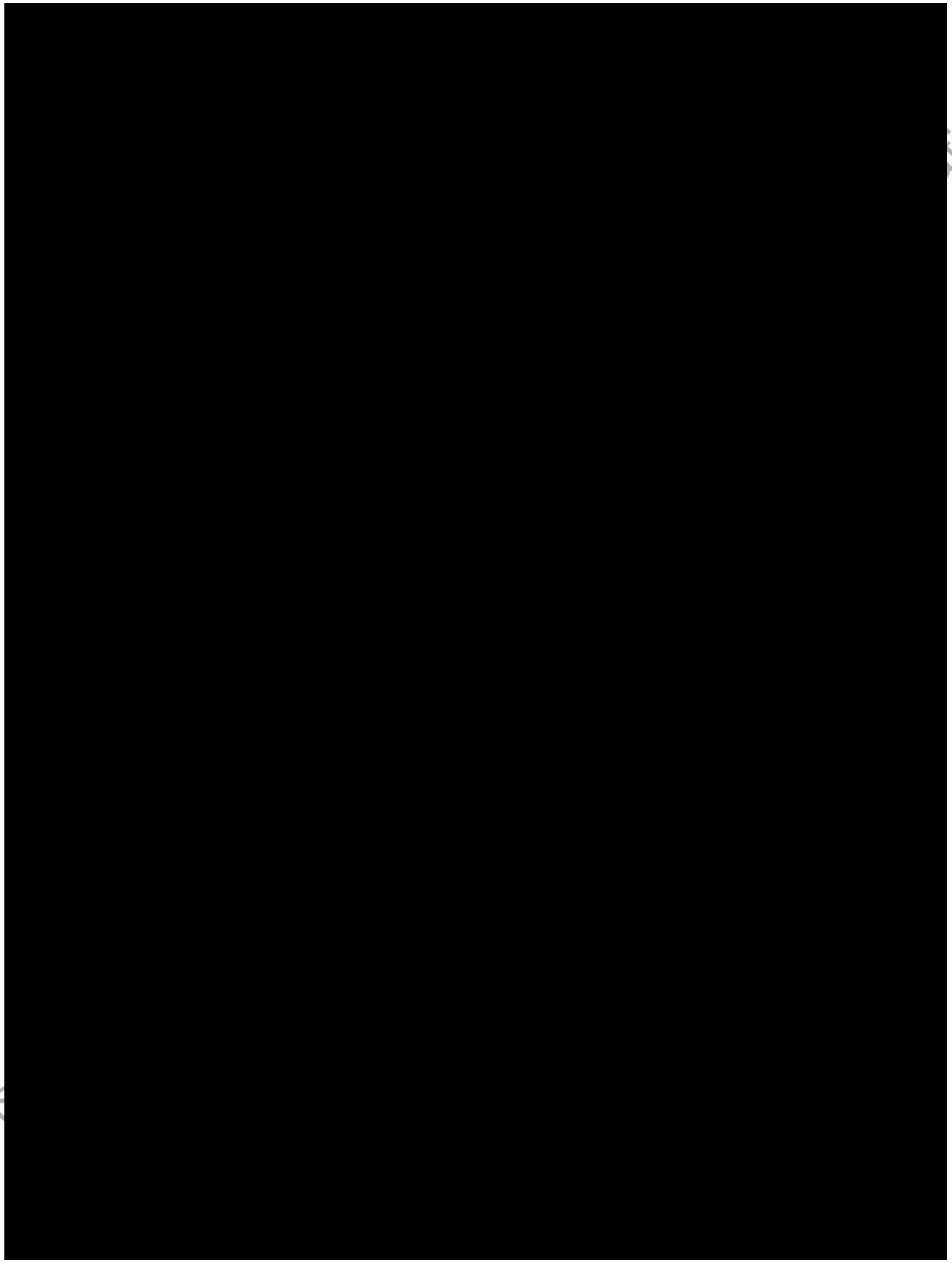












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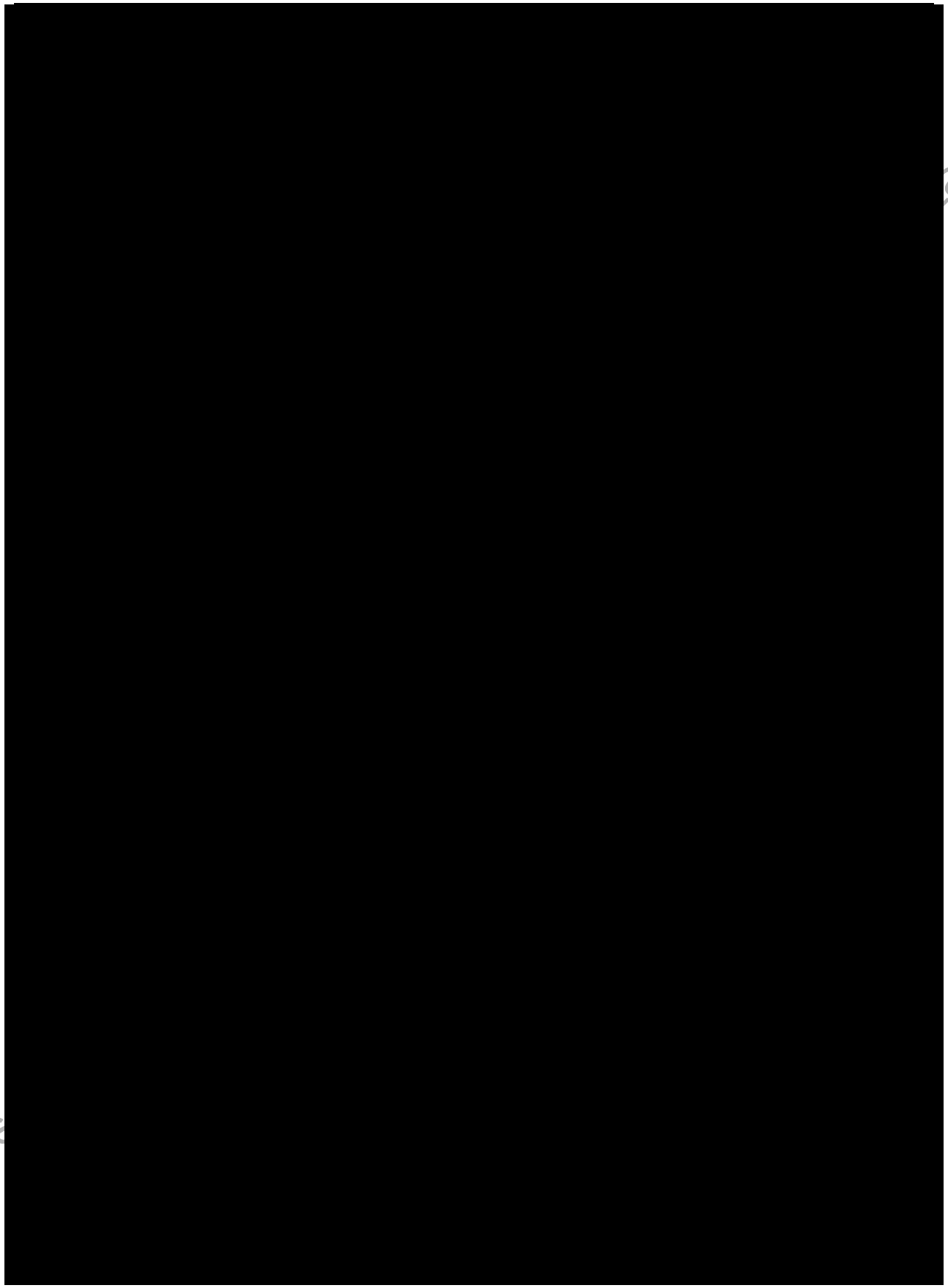
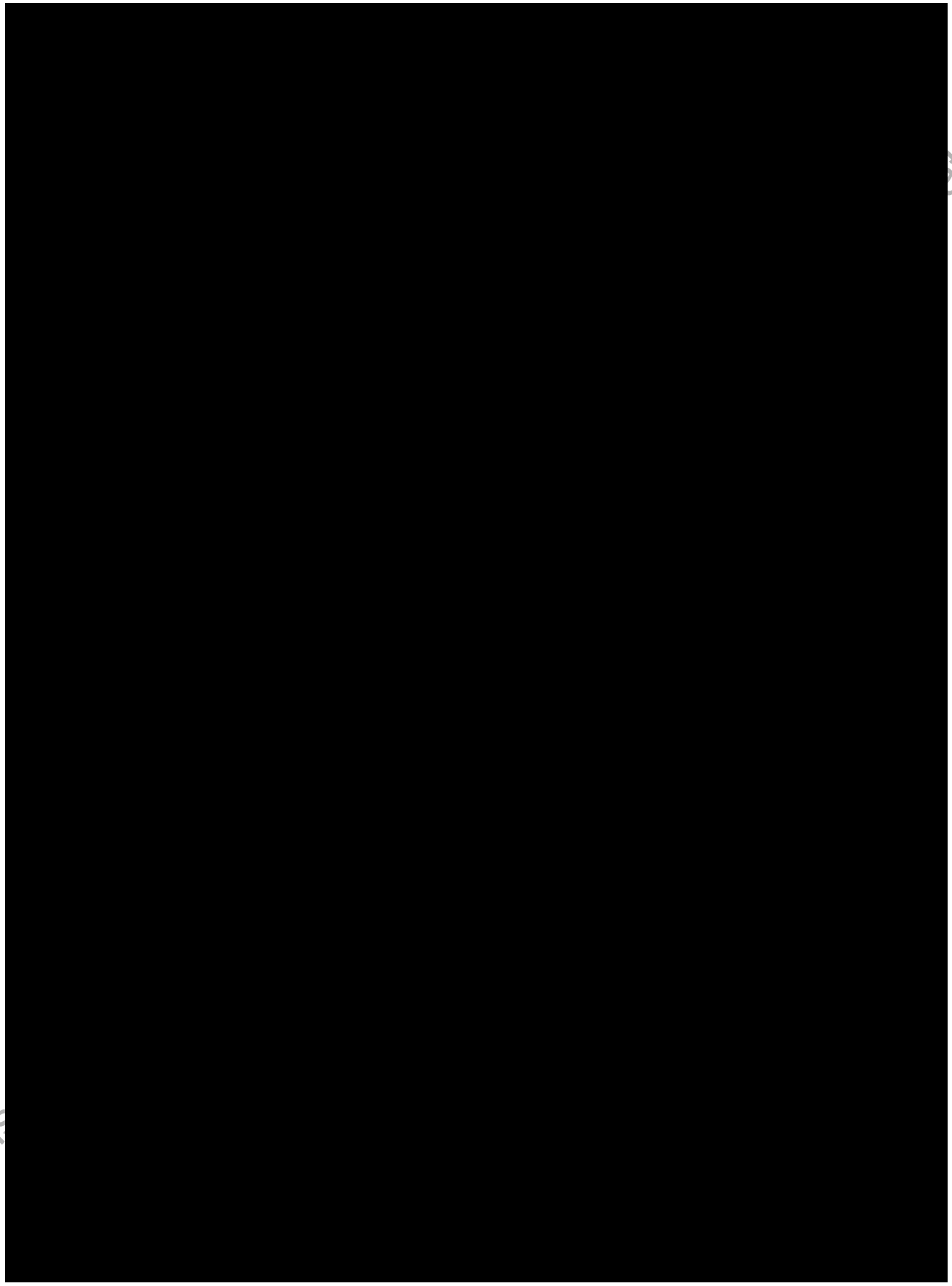
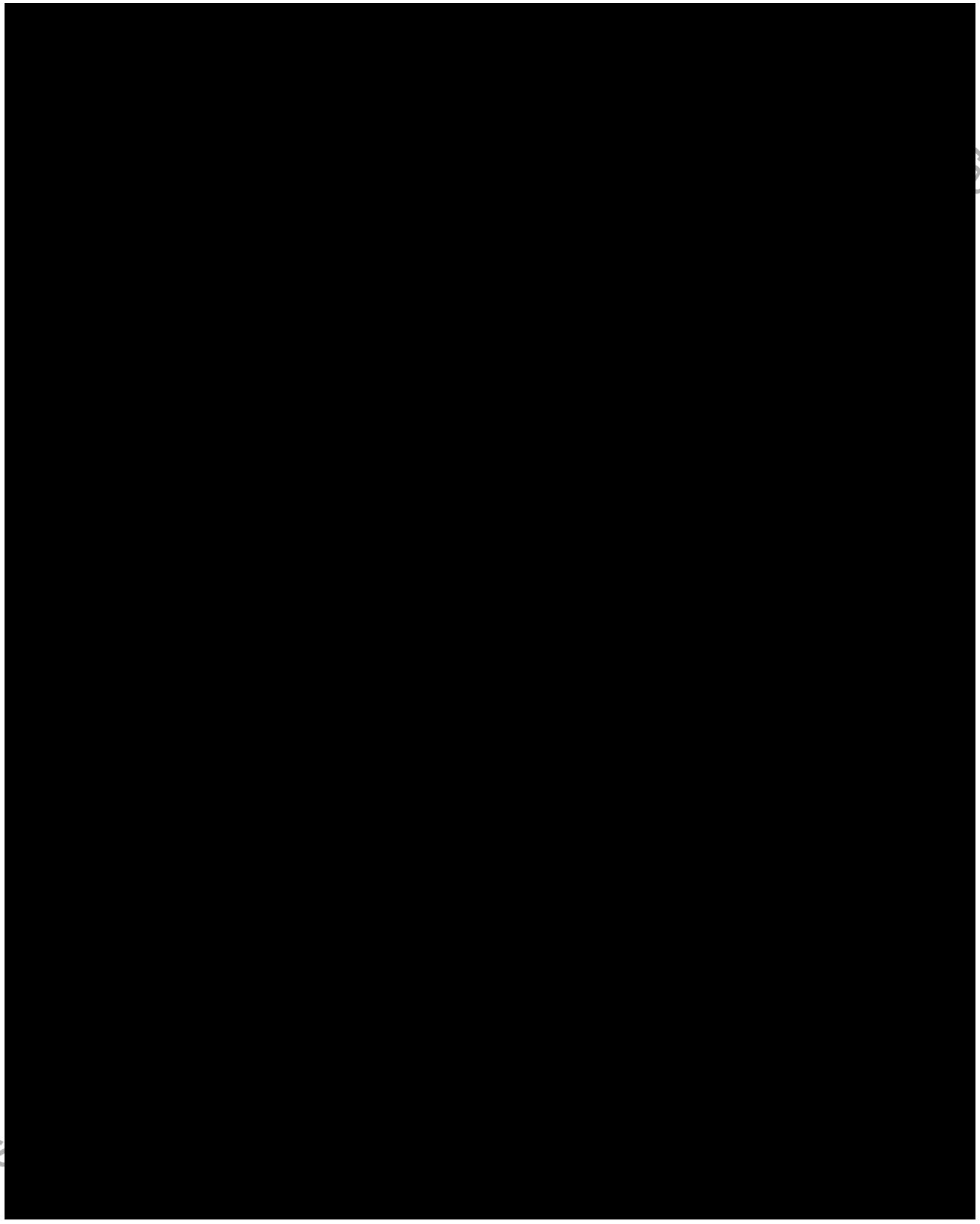
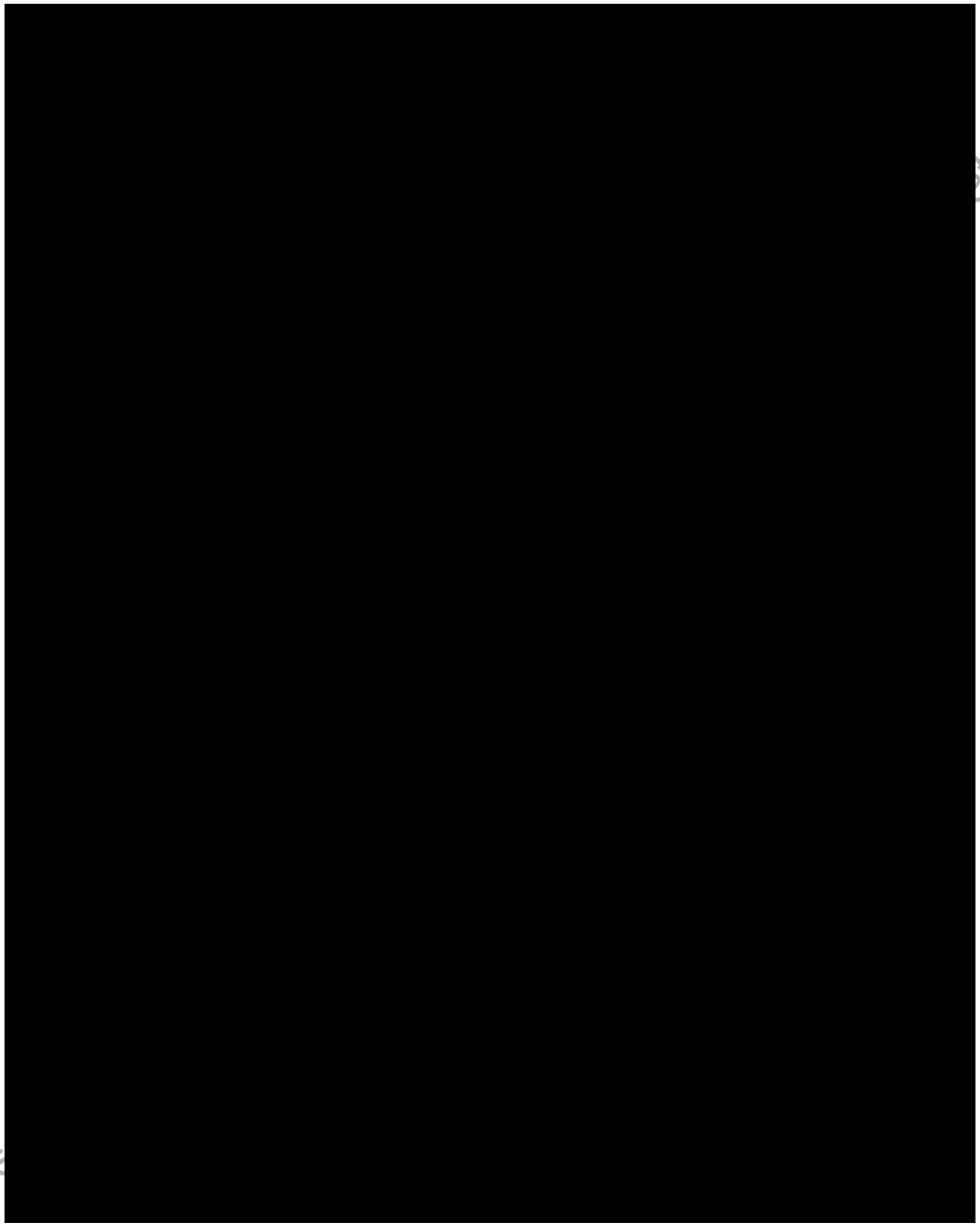
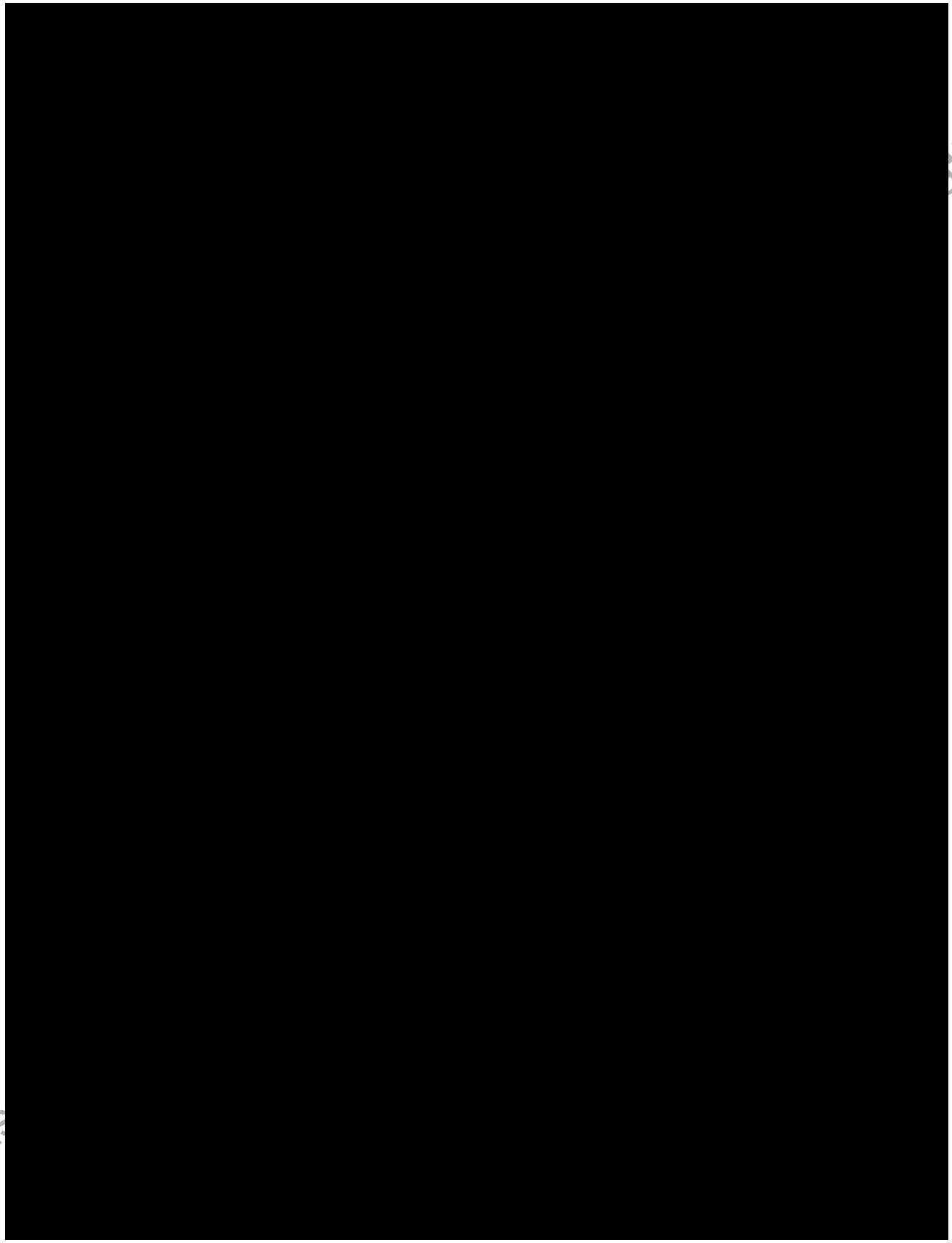
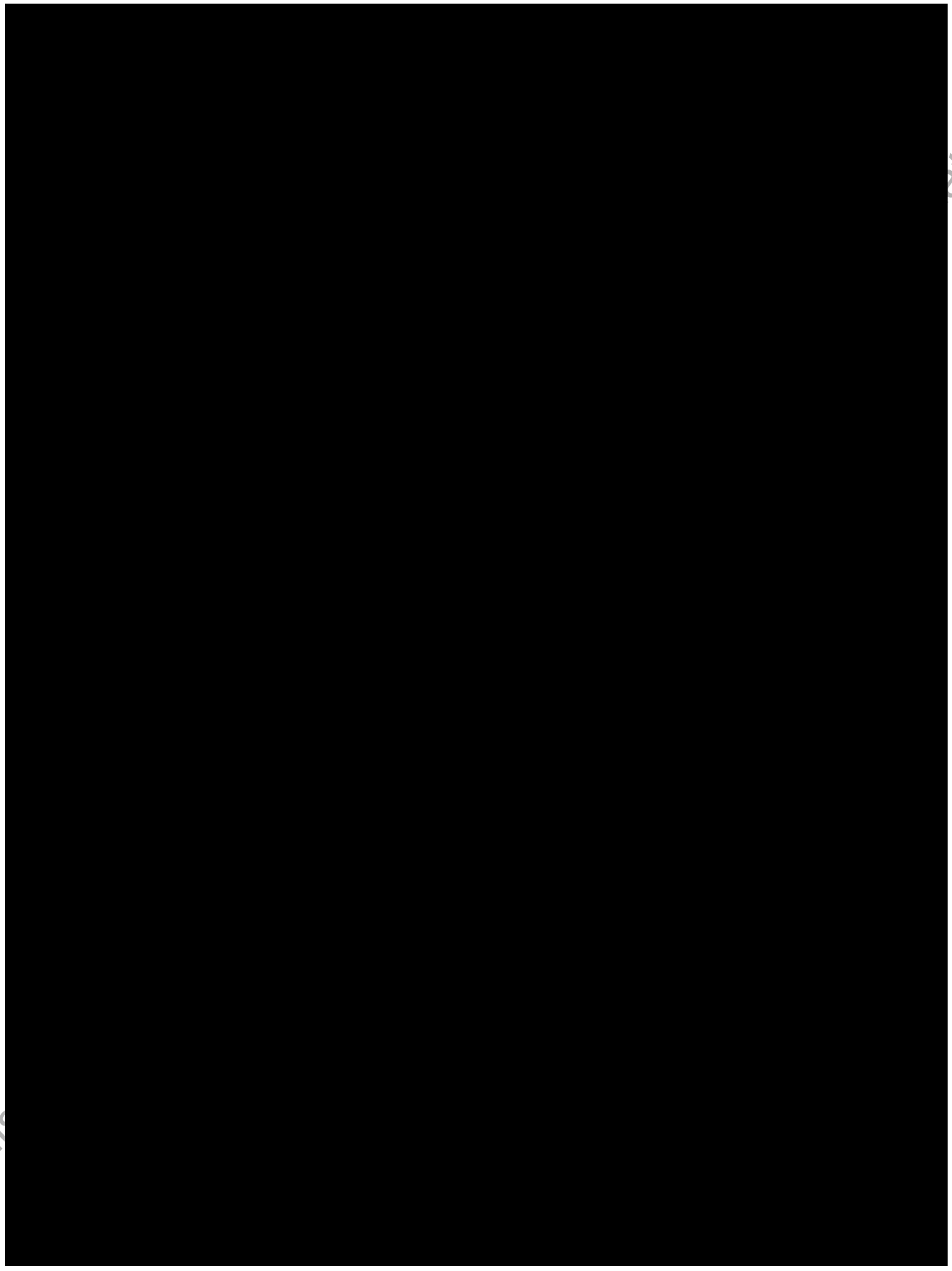


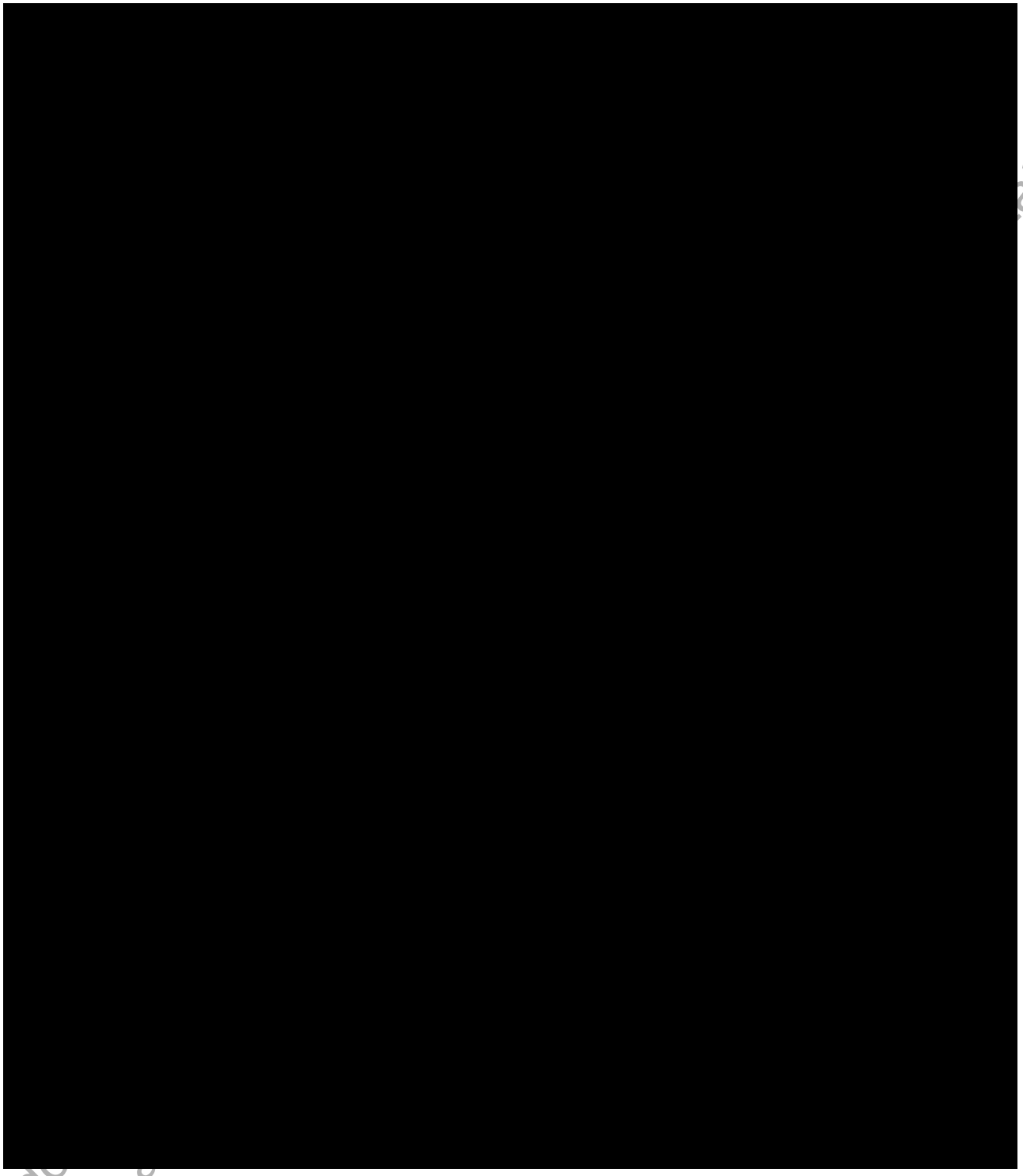












[redacted]

9 PHARMACOKINETICS AND PHARMACODYNAMICS

9.1 Pharmacokinetics (PK)

The following PK endpoints will be evaluated using the PK-PPS:

[redacted]

Samples from SOC+PBO participants will not be analyzed, except for the Week 48 assessment which will be considered the baseline for the OLE study SL0046. This data will be included in tables and figures of study SL0046 but not in SL0043. Individual study participant [redacted]

[redacted] will be displayed graphically in linear and log scales. Geometric means with 95% confidence interval per visit will also be displayed graphically in linear and log scales. These values will be summarized per visit using the statistics described for continuous variables and in addition the number of participants with quantifiable samples, the geometric mean and the geometric coefficient of variation (assuming log normally distributed data). Tables and figures will only include data from the SOC+DPZ arm. Additional concentration by ADA participant status will be also generated. A listing will include all the data.

[redacted]

The lower limit of quantification (LLOQ) for DZP concentration in plasma is 0.2µg/mL , [redacted] For the summary statistics, if a sample is BLQ, it will be considered as half of the LLOQ.

Descriptive summary statistics will be calculated only if 2/3 of the values are above the LLOQ at a given visit. If this is not case, only median, minimum and maximum values will be presented.

If data merit, a population PK analysis and PK/PD/Efficacy analyses may be conducted for the clinical efficacy endpoints and PD variables of interest. All population PK and PK/PD/Efficacy analyses will be described in more detail in a separate Data Analysis Plan, and results will be reported in a separate report.

9.2 Immunogenicity analyses

[redacted]

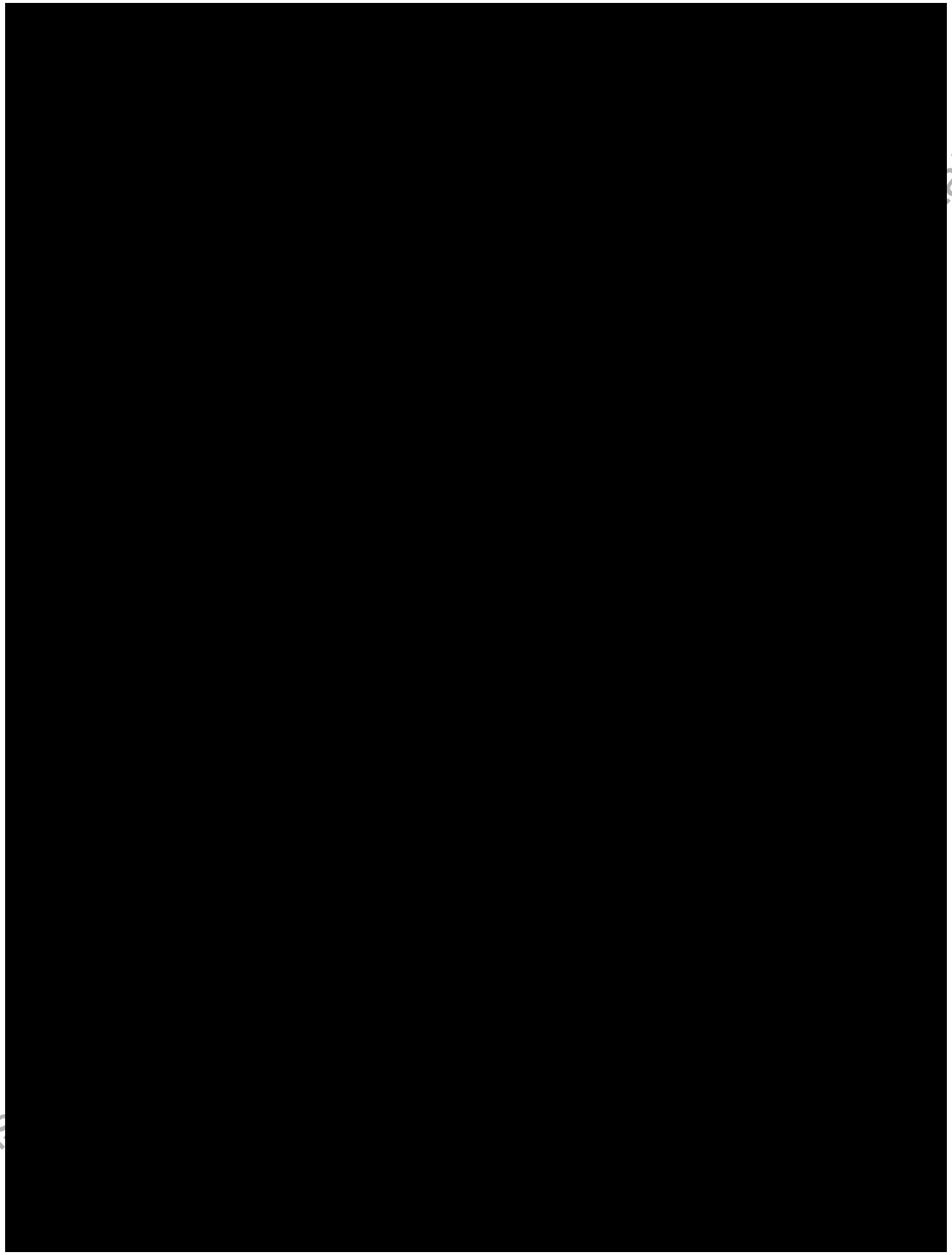
9.2.1 ADA and Nab Sample Status

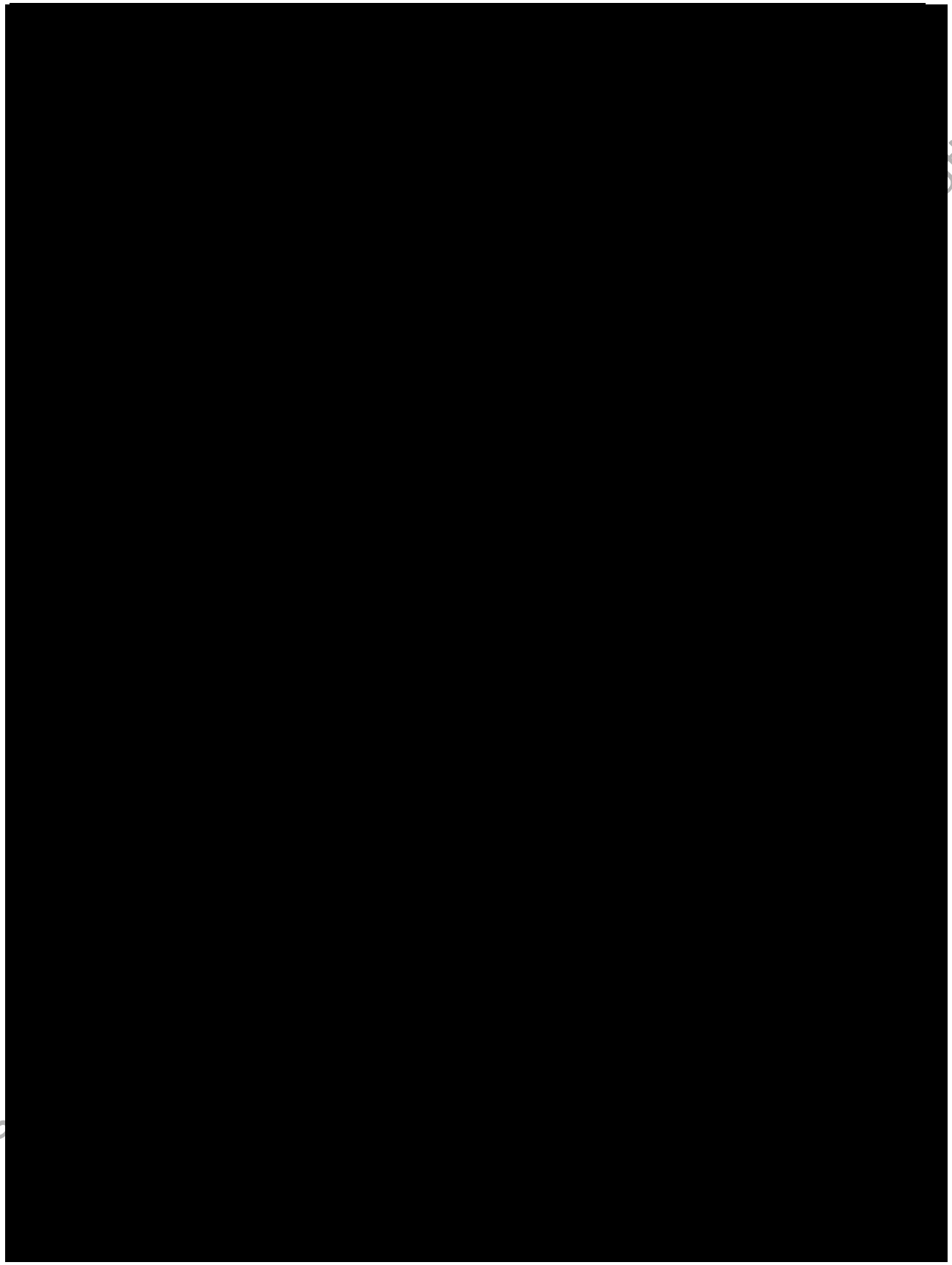
[redacted]

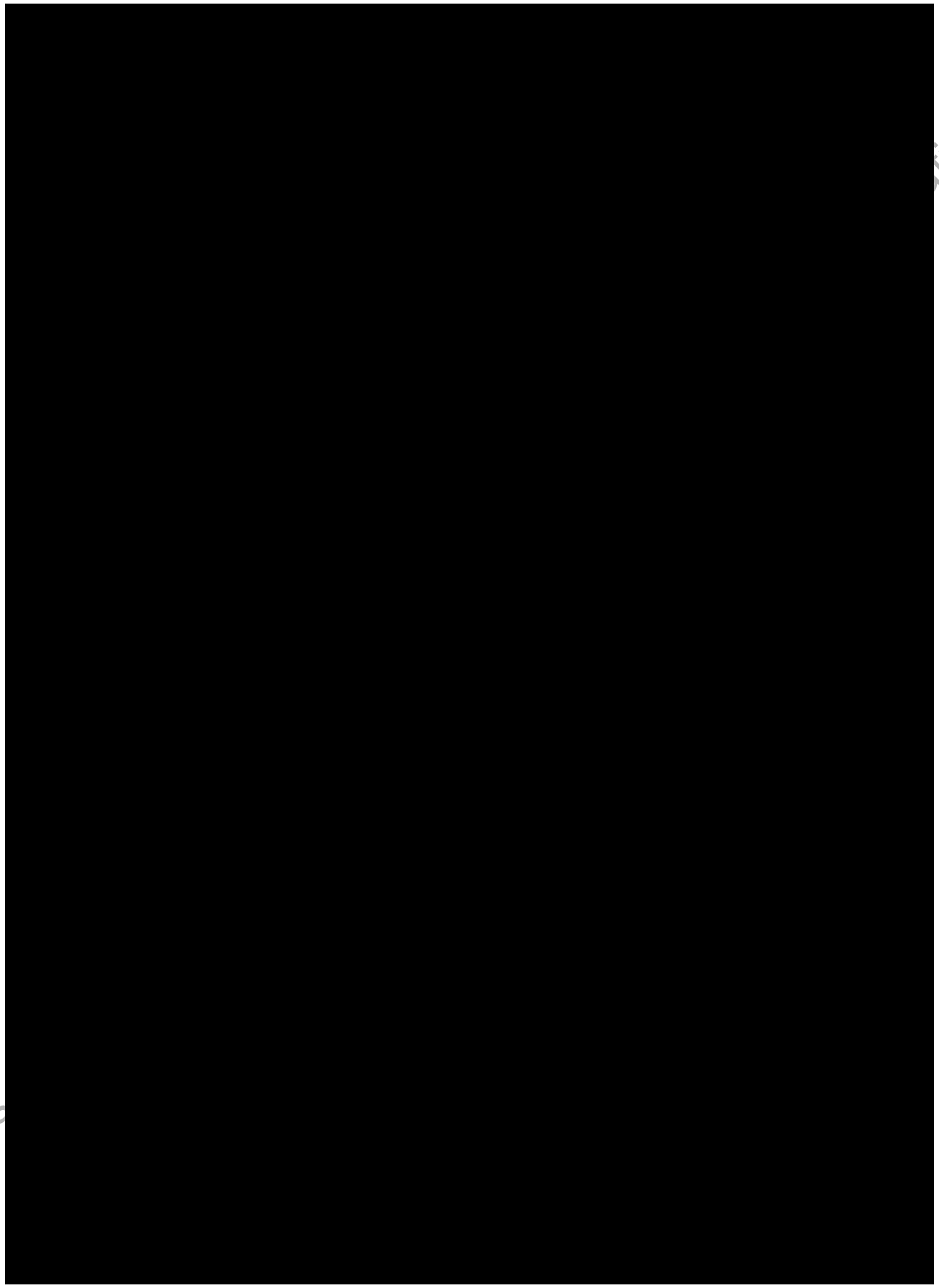
[redacted]

9.2.2 ADA/Nab Participant Status

[redacted]







[redacted]

9.3 Pharmacodynamics (PD) and Immunological analyses

Markers of the immune system will be assessed, including:

[redacted]

All summaries of immunological variables will be produced on the SS, unless otherwise specified.

All immunological parameters will be listed by participant and time point including changes from Baseline for numeric variables and flags for measurements outside the clinical reference ranges (where applicable). Values that are below the lower limit of the reference range will be

flagged as 'L' (low) and values that are above the upper limit of the reference range will be flagged as 'H' (high) and listed as well.

Summary tables and figures will be presented for both absolute values, changes from Baseline and percentage changes from Baseline for the following immunological parameters in all patients: [redacted]

For the following immunological parameters [redacted] with a defined upper limit normal (ULN), a defined lower limit normal (LLN), or both, the number of participants and percentages who are within and outside of these normal ranges will be tabulated by treatment group and visit. This will be done in separate tables for ULN and for LLN, with pages for each immunological parameter within these, such that there are distinct displays for each of the following:

- Values ≤ULN and values >ULN
- Values ≥LLN and values <LLN
- Values ≤ULN and values >ULN for the subgroup of participants for each parameter whose value was >ULN for that parameter at Baseline
- Values ≥LLN and values <LLN for the subgroup of participants for each parameter whose value was <LLN for that parameter at Baseline

A shift table will be presented for each of the following selected immunological parameters with number and percentages provided by visit for participants with:

[redacted]

In addition to the overall summary tables and figures for values, changes from Baseline and percentage changes from Baseline values by visit, for selected parameters there will also be

summary tables and figures for values, changes from Baseline values and percentage changes from Baseline values for the subgroup of participants who had an abnormality for that parameter at Baseline. Each selected parameter and the subgroup of participants to be used for the additional summary of that parameter are listed below:

[redacted]

Antiphospholipid (aPL)

The additional following tables will be created using the SS:

– Shift table on aPL positivity from Screening to post Screening (Week 24 and Week 48)

The aPL analysis will be done using two different approaches for defining aPL positivity. A first analysis (aPLs based on Criteria tests) will be done using Criteria tests only, which includes [redacted] test results. A second analysis (aPLs expanded to include PS/PT) will incorporate the results of Criteria tests and also the [redacted] assessments.

The following criteria apply for the aPLs based on Criteria tests analysis:

Triple positivity is defined as meeting all 3 of the following criteria:

[redacted]

Double positivity is defined as not meeting triple positivity *and* meeting at least one "set" (a AND b) of criteria below:

[redacted]

[redacted]

Single positivity is defined as not meeting triple positivity nor double positivity, *and* meeting at least one of the criteria below:

[redacted]

The following criteria apply for aPLs expanded to include PS/PT analysis:

Triple positivity is defined as:

[redacted] and at least 2 of the following:

[redacted]

Double positivity is defined as not meeting triple positivity *and* meeting at least one "set" (a AND b) of criteria below:

[redacted]

Single positivity is defined as not meeting triple positivity nor double positivity, *and* meeting at least one of the criteria below:

[redacted]

[redacted]

The criteria for double positivity in both analyses (aPLs based on Criteria tests only, and aPLs expanded to include PS/PT) require that the isotype of both aPLs considered in an individual criterion must be the same.

Note: see Section 13.16 for details about aPL scoring.

10 SAFETY ANALYSES

10.1 Adverse events

All Adverse Events (AEs) occurring during the study (ie, after signature of the informed consent document) will be recorded in the eCRF and reported using the SS.

For each AE the following information will be recorded in the eCRF: AE term (verbatim term), date of onset, whether or not the AE was an infusion reaction, if yes, whether this infusion reaction fulfills the Sampson criteria (for the definition of Sampson criteria, see Sampson et al, 2006), pattern of event, whether or not the AE was classified as a SAE or as an AE of special interest or special monitoring, intensity, relationship to concomitant medications, relationship to the investigational medicinal product (IMP), action taken with IMP, other action taken, outcome, date of outcome and whether the AE led to study premature termination. All AE data will be listed.

AEs are characterized as either pre-treatment or treatment-emergent according to the following criteria:

- Pre-treatment AEs are the events with onset date prior to the first administration of study medication (DZP or PBO).
- Treatment-emergent AEs are those with onset date on or after the first administration of study drug, and up to 60 days after last dose. The events that emerge after the final drug administration up to 60 days after last dose, will therefore also be considered as treatment-emergent even if recorded during the SFU period.

Time to onset of AE (noted as “Days Since First Dose” on AE listings) is calculated as the time (in days) between first dose and onset of AE. Time to onset of AE is not calculated for pre-treatment AEs.

The time to onset for each AE (relative to the first dose) will be calculated as follows for all TEAEs:

- Time to onset since first dose (Date of AE onset − Date of first dose of IMP).
- If the date of AE onset and date of first dose of IMP are the same, then the time to onset since first dose will be shown as <1 day.

In addition, the time to onset (in days) since the most recent dose prior to the TEAE will be calculated:

- Time to onset since most recent dose = (Date of AE onset − Date of most recent dose of IMP prior to the TEAE start) .

- If the date of AE onset and date of most recent dose of IMP prior to the TEAE start are the same, Time to onset since most recent dose will be shown as <1 day.
- The duration of each AE will be calculated as follows:

  AE Duration (days) = (Date of outcome − date of onset)
- Imputations for missing start dates will be handled according to the 'Imputation of Partial Start Dates' rules in Section 4.3.5.
- Imputations for missing end dates will not be performed for classification as treatment emergent and for calculation of time to onset as this is not required.
- In the listings, where AE onset and end date are the same, AE duration will be presented as <1 day.
- For AEs with end date >onset date, the duration will be presented in days. For the calculation of duration for AEs with missing start dates, the dates will be imputed as described in Section 4.3.5.
- In case of uncoded AEs, these AEs should be designated as “UNCODED” at all MedDRA levels, and such AEs will be included in summary tables and participant listings based on this classification.
- All TEAEs will be flagged in the listings. In addition, all TEAEs will be summarized, but pre-treatment and post-treatment AEs will only be listed.
- The following summaries will be created:

  (1) Incidence of treatment-emergent adverse events (TEAEs) by MedDRA system organ class, high level term, and preferred term

  (2) Exposure adjusted incidence rate of TEAEs (incidence rate/event rate) to include the number of events, number and proportion of participants with the event (ie, incidence proportion), the exposure-adjusted incidence rate per 100 participant years with the associated 95% confidence interval, and the exposure adjusted event rate per 100 participant years.

  For exposure adjusted incidence rate, the numerator will be the total number of participants experiencing the AE, each participant counted only once even if the participant has the event multiple times. The denominator will be in 100 participant-years. That is, the total summation of individual participant-years at risk up to the first occurrence of the TEAE for participants with that AE, and the total participant-years at risk for those participants not experiencing that AE, divided by 100. Incidence rates will be presented with a 95% confidence interval. Exact Poisson 95% CIs for incidence rates are calculated using the relationship between the Poisson and the Chi-square distribution (Ulm, 1990).

  For exposure adjusted event rate, the numerator will be the number of AEs including repeat occurrences in individual participants. The denominator will be in 100 participant-years. That is, the total summation of individual participant-years at risk (total sum of "time at risk (last dose – first dose + 60)" for all participants) divided by 100. No confidence interval will be computed.

(3) Incidence of Serious TEAEs

(4) Incidence of serious TEAEs by relationship

(5) Incidences of TEAEs by intensity, maximum intensity and by relationship at any time during the study

(6) Incidence of TEAE of special interest (AESI)

Defined as any TEAE that a regulatory authority has mandated be reported on an expedited basis, regardless of the seriousness, expectedness, or relatedness of the AE to the administration of a UCB product/compound. For DZP, the following events require immediate reporting (within 24 hours regardless of seriousness) to UCB:

Hy's Law:

- Potential Hy's Law, defined as ≥3xULN ALT or AST with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN ALP, with no alternative explanation for the biochemical abnormality (ie, without waiting for any additional etiologic investigations to have been concluded). Follow-up information should be reported if an alternative etiology is identified during investigation and monitoring of the participant.
- Malignancies: haematological malignant tumours (SMQ), haematological tumours of unspecified malignancy (SMQ), non-haematological malignant tumours (SMQ) and non-haematological tumours of unspecified malignancy (SMQ).

(7) Incidence of TEAE of special monitoring (AESM) as determined by the investigator. These are events of interest defined by the sponsor to be reported on an expedited basis to the sponsor, regardless of seriousness, expectedness, or relatedness of the AE to the administration of DZP

(8) Incidence of TEAEs leading to temporary study drug discontinuation

(9) Incidence of TEAEs leading to permanent study drug discontinuation or withdrawal from the study

(10) Incidence of TEAEs occurring during treatment period (defined as last infusion + 28 days)

(11) Incidence of opportunistic infection TEAEs (based on narrow SMQ for opportunistic infection)

(12) Incidence of thromboembolic TEAEs (based on the "Embolic and thrombotic events" SMQ) (Note: this incidence table will be presented by maximum intensity)

(13) Incidence of thromboembolic TEAEs as confirmed by the adjudication committee

(14) Incidence of TEAEs fulfilling the definition of MACE, defined as events coded to MedDRA PTs under the narrow SMQ Central nervous system haemorrhages and cerebrovascular conditions, narrow SMQ Ischaemic heart disease, and narrow SMQ Cardiac failure, as well as the following additional MedDRA PTs: Cardiac death, Angioplasty, Arterial angioplasty, Atherosclerotic plaque rupture and Intra-aortic balloon placement

(15) Incidence of TEAEs starting on the day or the day after an infusion.

(16) Incidence of infusion reaction TEAEs in participants with infusion reactions (as indicated by the investigator on the CRF)

(17) Incidence of infusion reactions meeting Sampson's criteria of Anaphylaxis as determined by the investigator

(18) Incidence of TEAEs suggestive of [redacted] based on the narrow SMQ for [redacted]

(19) Incidence of [redacted] TEAEs based on narrow SMQ for [redacted] starting on the day or the day after an infusion

(20) Incidence of [redacted] TEAEs based on narrow SMQ for [redacted] starting later than the day after an infusion

(21) Incidence of TEAEs in SMQ Anaphylactic reaction where scope='Narrow'

(22) Incidence of TEAEs suggestive of suicidal events based on Suicide/self-injury (SMQ)

(23) Incidence of TEAEs suggestive of depressive or suicidal events based on depression and suicide/self-injury (SMQ)

(24) Incidence of TEAEs in the SMQ depression and suicide/self-injury where scope=narrow

(25) Incidence of non-serious TEAEs occurring in ≥5% of participants within any individual treatment group (incidence is compared to the threshold prior to any rounding)

(26) Incidence of non-serious TEAEs by relationship

(27) Incidence of TEAEs leading to permanent study drug discontinuation or withdraw from the study, by relationship

(28) Incidence of fatal TEAEs by relationship

(29) Incidence of TEAEs excluding adverse events related to COVID-19 vaccines as determined by the investigator

(30) Incidence of TEAEs by Decreasing Incidence of MedDRA Preferred Term

(31) Incidence of TEAEs Suggestive of Herpes Zoster TEAEs by Medication Subgroup

Figures:

- Relative Risk of Most Frequent AEs (Preferred Term) – All TEAEs
- Relative Risk of Most Frequent AEs (Higher Level Term) – All TEAEs

Note: most frequent will include top 30 most frequent TEAEs

10.1.1 Evaluation of relationship of ADA with TEAEs

[redacted]

10.2 Extent of exposure

Study medication administration and extent of exposure to the IMP as captured in the Study Medication Administration eCRF and treatment percent compliance (see note below for derivation) will be summarized and listed using the SS. The kit number and batch number

corresponding to each infusion will also be included within a listing of study medication administration.

The following categories will be included:

- Number of infusions received by study participant
- The duration of infusion will be calculated as follows:

  Duration of infusion (min) = Stop time of infusion – start time of infusion + 1
- The total duration of exposure will be calculated as follows:

  Exposure (days) = (Date of last dose − Date of first dose) + 28
- Time at risk (days) = (Date of last dose − Date of first dose) + 60
- Compliance: Compliance (%) will be defined as (Total volume delivered (mL) /volume planned) x 100% by visit. The following categories will be also included in the summary: Compliance <80%, ≥80 to ≤-120 and >120% by visit
- Percentage of missed doses vs. the complete number of infusions intended per the protocol (12 infusions)
- Percentage of infusions where the length of infusion was too short. The length of infusion at Baseline is planned for the first dose 120 min (number and percentage of participants with length of infusion too short will be defined as <90 minutes). For all the post Baseline visit it is planned to be 60 minutes (number and percentage of participants with length of infusion too short will be defined as <45 minutes)

When SL0043 initially began, the planned infusion volume was 150mL. This was later changed to 200mL. Sites adopted the change from 150mL to 200mL infusions between Oct 2020 and April 2021.

10.2.1 Calculation of planned and actual dose received

The total planned dose given at each visit will then be calculated to 1 decimal place as follows:

Planned dose (mg) = Body weight (kg) x Randomized Dose (mg/kg).

The actual dose (mg) received will be calculated to 1 decimal place, and is based on the infusion volume given (mL) and the actual concentration of DZP in the infusion bag (mg/mL):

Actual dose (mg) = Infusion volume given (mL) x Concentration DZP in infusion (mg/mL).

The concentration of DZP in the infusion IV bag (mg/mL) is based on the number of mL of reconstituted solution from vials of DZP that were included in the IV bag and the total volume of the IV bag. There were 100mg DZP per every 1 mL of reconstituted solution from the vials.

Concentration DZP in infusion (mg/mL) =
{ [Sum across all vials used (amount of reconstituted solution taken from the vial (mL)) x 100mg/mL (DZP in the reconstituted solution)] / Total volume of IV bag prepared (mL) }

Percent of planned dose administered (%) is based on the actual dose compared to the planned dose, thus representing both the volume of infusion given as well as the actual contents of the IV bag, and will be calculated to 1 decimal place for each visit.

10.3 Clinical laboratory evaluations

Laboratory evaluations will be analyzed in the SS for observed cases, where all data is included.

Measurements outside the clinical reference ranges will be assessed by the investigator. In addition, laboratory values will be graded (where possible) according to CTCAE Version 5.0.

All laboratory data will be listed by participant and time point including changes from Baseline and percentage changes from Baseline for numeric variables, as well as flags for measurements outside the normal ranges (to flag markedly abnormal results).

Values that are below the lower limit of the reference range will be flagged as 'L' (low) and values that are above the upper limit of the reference range will be flagged as 'H' (high). The flag and the CTCAE grade will be included in the listings.

Any laboratory parameters that are given as '<xx' or '>xx' in the database will be imputed with the absolute value of the number without the sign (<2.2 will be imputed as 2.2) for the calculation of the changes from Baseline.

Summary tables will be provided for both absolute values, changes from Baseline and percent changes from Baseline. Shift tables by markedly abnormal lab parameters (see Section 13.18) will be presented for clinical chemistry, hematology parameters. For each of clinical chemistry and hematology, there will be:

- One table for lab parameters that have marked abnormal value based on values that are <LLN. This table will show the number and percentage of participants who have a marked abnormal value at any time of the study post Baseline compared to Baseline
- One table for lab parameters that have marked abnormal value based on values that are >ULN. This table will show the number and percentage of participants who have a marked abnormal value at any time of the study post Baseline compared to Baseline

The denominator for the percentages in both types marked abnormal lab value shift tables will be the number of participants in the SS.

The number and percentage of participants with a treatment-emergent markedly abnormal result will be presented for each parameter where markedly abnormal criteria are defined, by visit and treatment group, including a tabulation of incidence at any post-BL time point (regardless of visit).

Urinalysis and urine sediment results will be listed.

Furthermore, figures will be provided both for the mean value by visit and for the mean changes from Baseline by visit for continuous laboratory parameters (as observed).

The urinary albumin: creatinine ratio (mg/mmol) and urinary protein: creatinine ratio (mg/mmol) will be calculated by the laboratory from the corresponding urinary albumin, protein and creatinine measurements obtained at Visit 1 (Screening) to 15/EOS (Week 54). A summary table showing descriptive statistics for the change from Baseline values by visit for urinary protein: creatinine ratio and urinary albumin: creatinine ratio will be provided for the subset of participants with a urinary protein: creatinine ratio >56mg/mmol at Baseline.

Laboratory results for participants meeting the criteria for potential drug induced liver injury (see Figure 7-1 in the protocol) will be displayed in a table and a listing. A listing for participants who meet Hy's Law Criteria will also be provided.

HIV test at Screening, hepatitis test at Screening and Tuberculosis test are done as part of the inclusion/exclusion criteria, therefore, they will only be listed.

Local laboratory results are only required in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study treatment decision or response evaluation, the results must be entered into the eCRF. If central labs are unavailable, local labs will be utilized for evaluating the efficacy response (such as BILAG). However, the findings from local labs will only be included in listings and not in safety summaries.

10.4 Vital signs, physical findings, and other observations related to safety

10.4.1 Vital signs

The following vital signs measurements will be assessed:

- Pulse rate (PR) (bpm)
- Systolic blood pressure (SBP) (mmHg)
- Diastolic blood pressure (DBP) (mmHg)
- Respiratory Rate (breaths per minute)
- Body temperature (ºC)
- Body weight (kg)
- Body height (cm)
- BMI (kg/m^2)

Vital sign will be analyzed in the SS for observed cases, where all data is included. Absolute values and Changes from Baseline for pre-infusion vital signs measurements will be presented by visit. Additionally, changes from pre-infusion to post-infusion time points at infusion visits will be summarized.

Listings will be provided of vital sign measurements by visit and timing relative to dosing. It will include the change from the Baseline visit for pre-infusion vitals at each post-Baseline visit, as well as changes from pre-infusion to post-infusion time points within visits. The listing will also include details of abnormal values.

Vital signs with values below the lower limit of normal and a decrease greater than the limit given in the following table or vital signs with values above the upper limit of normal and an increase greater than the given value in the table will be classified as abnormal.

A summary of the number and percentage of participants with a vital sign abnormality will also be provided by vital sign measurement, by visit and overall.

Please see below for abnormality criteria for vital sign and body weight parameters:

Table 10-1: Abnormality criteria for vital sign parameters

PARAMETER	AGE RANGE	ABNORMALITY CRITERIA
Pulse Rate (beats/minute)	≥16y	<45 and a decrease from Baseline of ≥15 >90 and an increase from Baseline of ≥15
Systolic Blood Pressure (mmHg)	≥16y	<90 and a decrease from Baseline of ≥15 >140 and an increase from Baseline of ≥15
Diastolic Blood Pressure (mmHg)	≥16y	<40 and a decrease from Baseline of ≥15 >90 and an increase from Baseline of ≥15
Respiratory Rate (breaths/min)	≥16y	<10 >25
Body Temperature (°C)	≥16y	<35.9 >37.6

Abbreviations: m = month, y = year. A month is defined as 30.44 days; a year is defined as 365.25 days.

Table 10-2: Abnormality criteria for body weight

PARAMETER	AGE RANGE	ABNORMALITY CRITERIA
Body weight (kg)	≥16y	⩾10% decrease from Baseline ⩾10% increase from Baseline

10.4.2 Electrocardiograms

Electrocardiogram data are collected at Visit 1, Visit 2, Visit 3, Visit 8 and Visit 14. ECGs will be analyzed in the SS for observed cases, where all data is included. ECG outcomes (as determined by investigators) will be listed by participant, visit, and timing relative to dosing.

A summary table of treatment emergent ECGs values (quantitative parameters as provided by central readers, including observed value and change from Baseline) will be presented displaying descriptive statistics by visit. This data will also be listed.

Outlier analysis (eg, QTcF, PR, QRS and HR) using central readers data will be provided (see Table 10-3 for details). The number and percentage of participants with an outlier at any post-BL time point will be presented by treatment group for each parameter.

A summary of the number and percentage of participants with a treatment emergent ECG finding (as provided by central readers) at the Baseline visit, and any post-Baseline time point by treatment will also be provided.

Abnormal ECGs and findings (as determined by central reader) will be listed by participant, visit, and timing relative to dosing.

The overall assessment provided by sites (investigators) will not be used for table summaries but will be presented in participant data listings.

Table 10-3: Abnormal criteria for ECG parameters

PARAMETER	AGE RANGE	ABNORMALITY CRITERIA
QTcF	≥16y	Treatment-emergent value of >450 and ≤480 ms when not present at Baseline (new onset) Treatment-emergent value of >480 and ≤500 ms when not present at Baseline (new onset) Treatment-emergent value of >500 ms when not present at Baseline (new onset) Increase of QTcF from Baseline of >30 and ≤60 ms Increase of QTcF from Baseline >60 ms
PR	≥16y	Increase of PR from Baseline >25% resulting in PR >200 ms
QRS	≥16y	Increase of QRS from Baseline >25% resulting in QRS >100 ms
HR	≥16y	Decrease of HR from Baseline >25% resulting in HR <50 bpm Increase of HR from Baseline >25% resulting in HR >100 bpm

10.4.3 Physical examination

Physical examination findings will be recorded in the eCRF at Screening. Clinically relevant changes in subsequent physical examinations will be reflected as AEs if not related to SLE. If physical examination findings are related to SLE, they will be documented within the BILAG 2004 and/or SLEDAI-2K assessment eCOA. The outcome of physical examinations and the interim medical history must be documented in source documentation.

A complete physical examination will include, at a minimum, general appearance; ear, nose, and throat; eyes, hair, and skin; and assessments of the respiratory, cardiovascular, gastrointestinal, musculoskeletal, hepatic, and neurological (including focused assessment of reflexes, sensitivity, and muscle strength) systems and mental status. Height (only at Screening) and weight will also be measured and recorded.

Results of physical examination abnormalities will be listed.

10.4.4 Assessment of Suicidal Ideation and Behavior

Suicidal ideation and behavior will be assessed using the C-SSRS (Columbia Suicide Severity Rating Scale). This scale will be used at Screening and Visits 2 through 15 to assess suicidal ideation and behavior.

At Screening, participants will be asked to assess suicidal ideation and behavior for their lifetime and for the past 6 months and for the past 2 years (respectively) prior to Screening.

At Visit 2 through Visit 15, participants will be asked to assess suicidal ideation and behavior since the last study visit.

The C-SSRS includes 10 categories with binary responses (yes/no):

Category 1: Wish to be dead
Category 2: Non-specific Active Suicidal Thoughts
Category 3: Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act

Category 4: Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Category 5: Active Suicidal Ideation with Specific Plan and Intent
Category 6: Preparatory Acts or Behavior
Category 7: Aborted Attempt
Category 8: Interrupted Attempt
Category 9: Actual Attempt (non-fatal)
Category 10: Completed Suicide

The C-SSRS also includes the following:

- Features (which should be rated with respect to the most severe type of ideation (ie, 1-5 from above, with 1 being the least severe and 5 being the most severe), since last visit which defines the intensity of ideation (frequency, duration, controllability, deterrents and the reason for ideation)
- Suicidal behavior (actual attempts, has subject engaged in non-suicidal self-injurious behavior?, interrupted attempt, aborted attempt, preparatory acts or behavior, suicidal behavior, suicide and for actual attempts only: actual lethality/medical damage, potential Lethality).

Endpoints based on the above categories are defined as:

Suicidal ideation: A "yes" answer at any time during treatment to any one of the 5 suicidal ideation questions (Categories 1-5) on the C-SSRS.

Suicidal behavior: A "yes" answer at any time during treatment to any one of the 5 suicidal behavior questions (Categories 6-10) on the C-SSRS.

Suicidal ideation or behavior: A "yes" answer at any time during treatment to any one of the 10 suicidal ideation and behavior questions (Categories 1-10) on the C-SSRS.

A listing will be provided including all data for only those participants who have a 'Yes' response in any category at any visit. The listing will be by visit and will indicate the reference timepoint upon which each C-SSRS category was evaluated (eg, 'Lifetime' for Screening visit, and 'Previous visit' for all visits after Screening).

10.5 Tuberculosis (TB) Questionnaire: Evaluation of Signs and Symptoms of Tuberculosis

TB questionnaire data collected in the eCOA will be listed using the SS.

11 COVID-19 IMPACT

The following data to evaluate the impact of COVID-19 global pandemic on the study will be captured in the COVID-19 eCRF:

1. Impacted Visit
2. Impact Category
    - Visit not done
    - Visit performed out of window
    - Visit performed by video call
    - Visit performed by telephone
    - Temporary discontinuation of study drug
    - Permanent discontinuation of study drug

- Termination of study participation
- Other, specify

3. Relationship to COVID-19
    - Confirmed COVID-19 infection
    - Suspected COVID-19 infection
    - General circumstances around COVID-19 without infection
    - Other, specify

- A summary and a listing of impact of COVID-19 for any reason (including impact category and visit (timepoint)) by treatment arm using the FAS will be created
- A summary of impact of COVID-19 due to confirmed or suspected COVID-19 infection (including impact category and visit (ie, timepoint)) by treatment arm using the FAS will be created
- Summary of Overall Missed or Discarded Assessments (visits) by Key Endpoints (primary, key secondary and secondary endpoints)
- Summary of Covid-19 Impact by Impact Category: number of visits performed by video call or by phone

[redacted] will be assessed in the scope of exploratory biomarker analysis as a separate analysis outside the scope of the SAP and will be summarized in a separate report.

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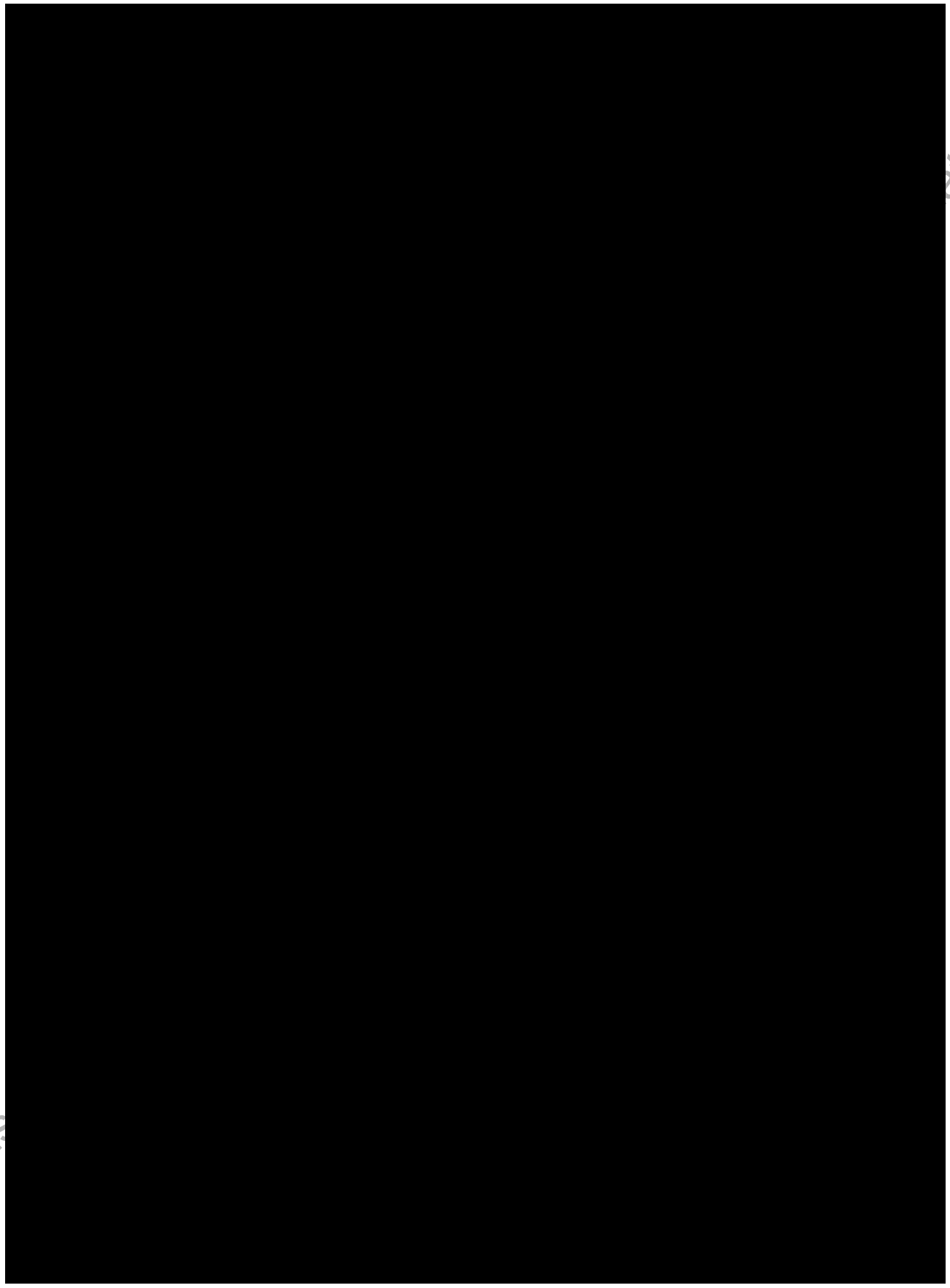

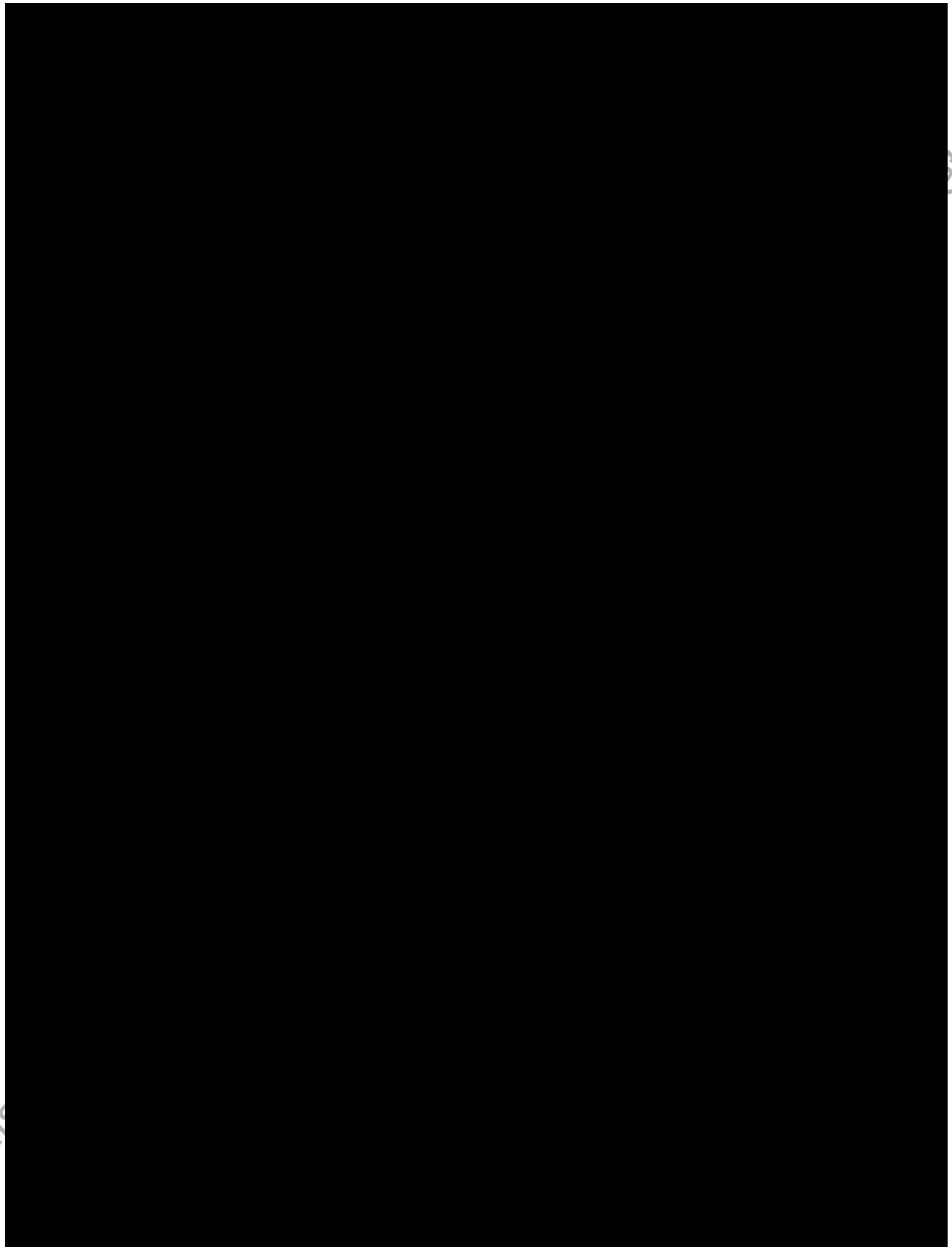

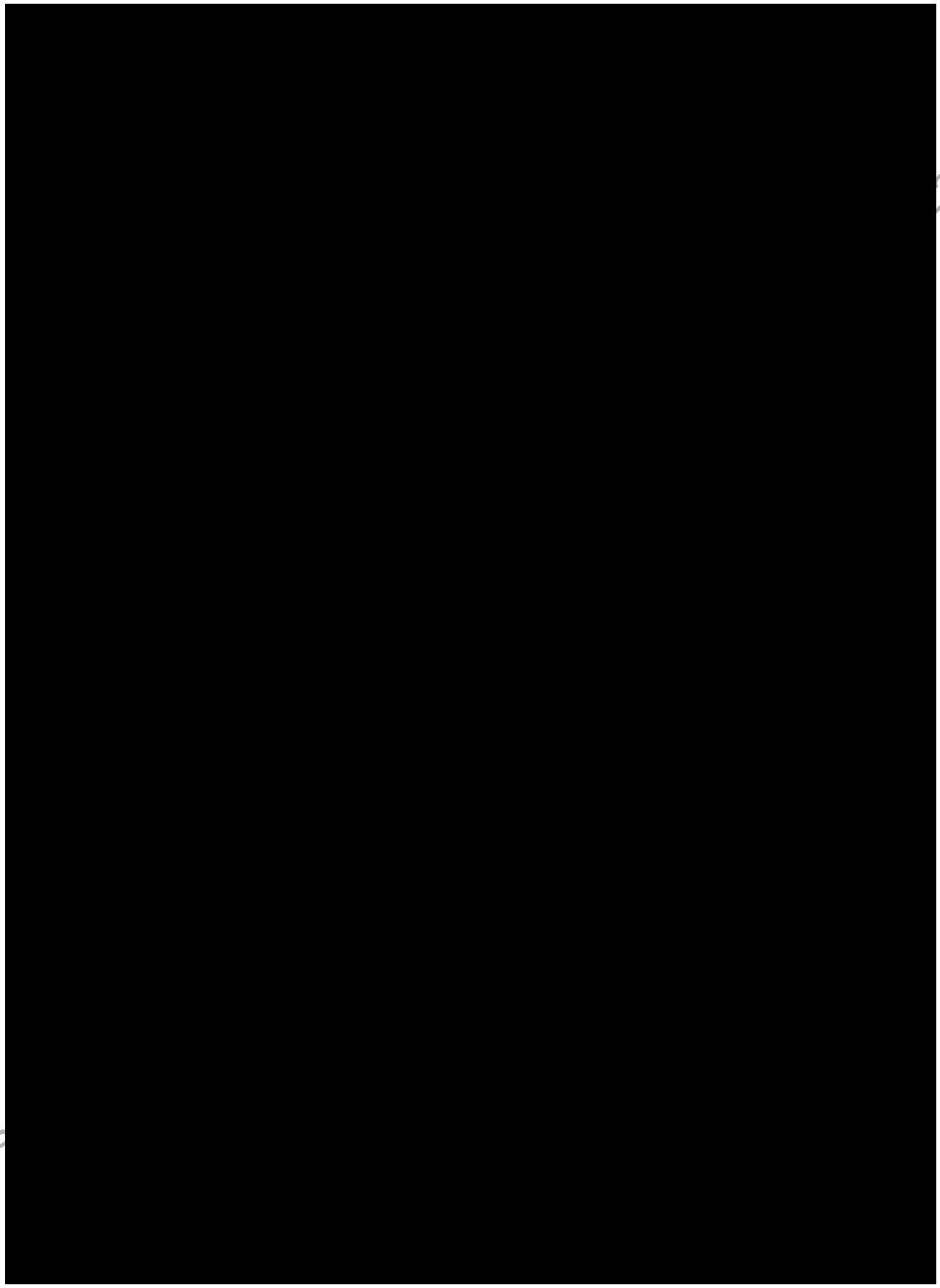

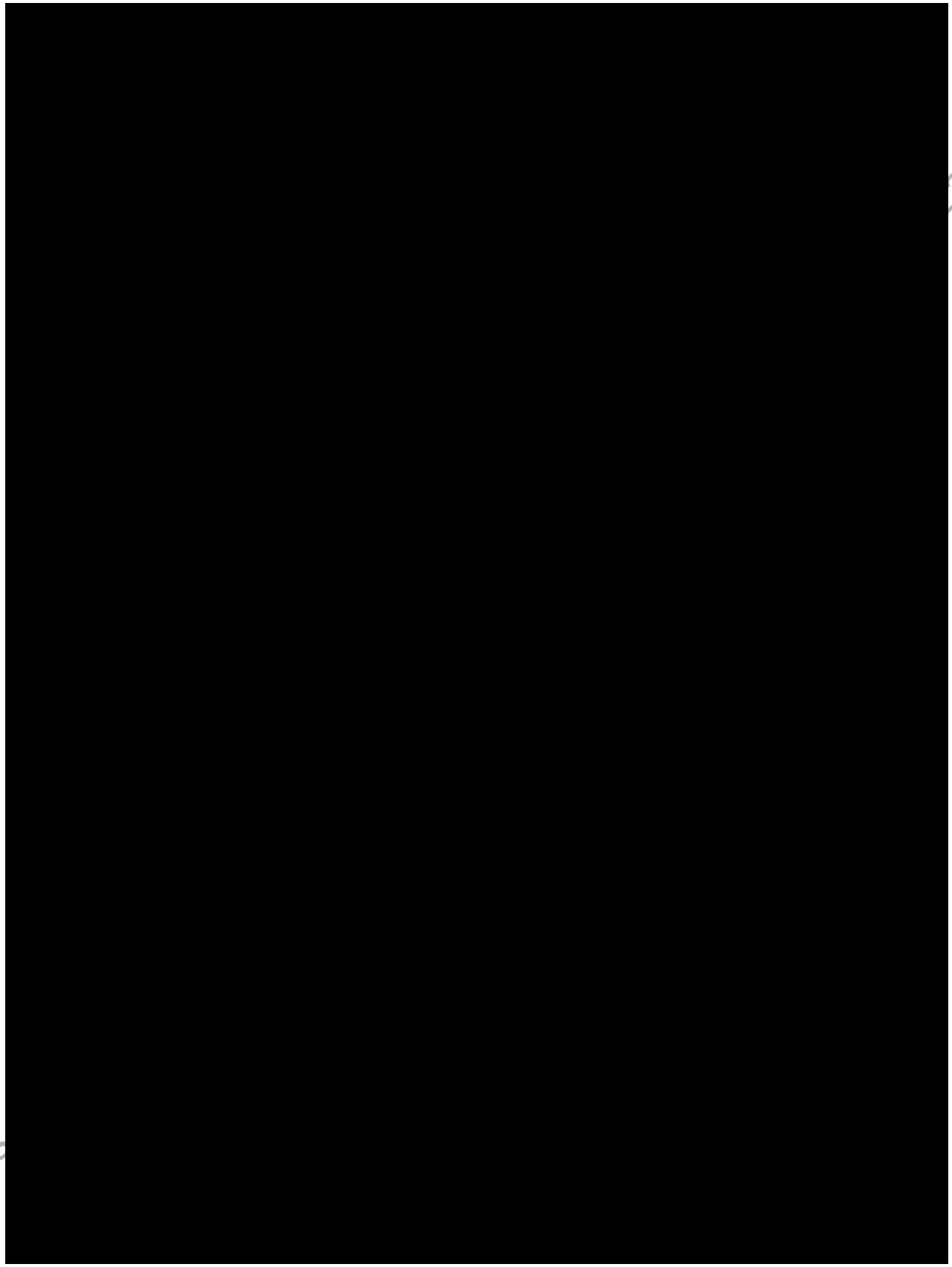

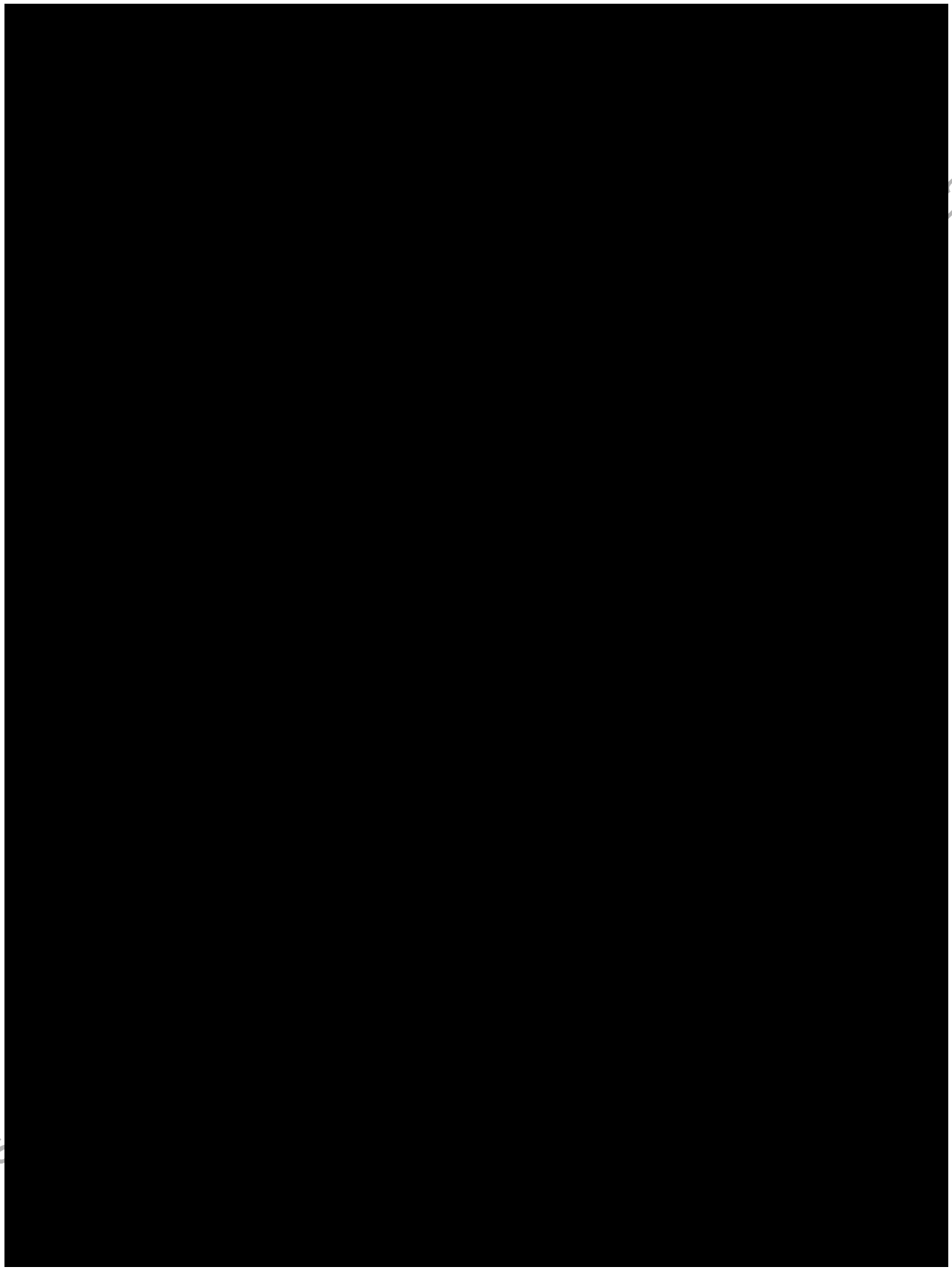

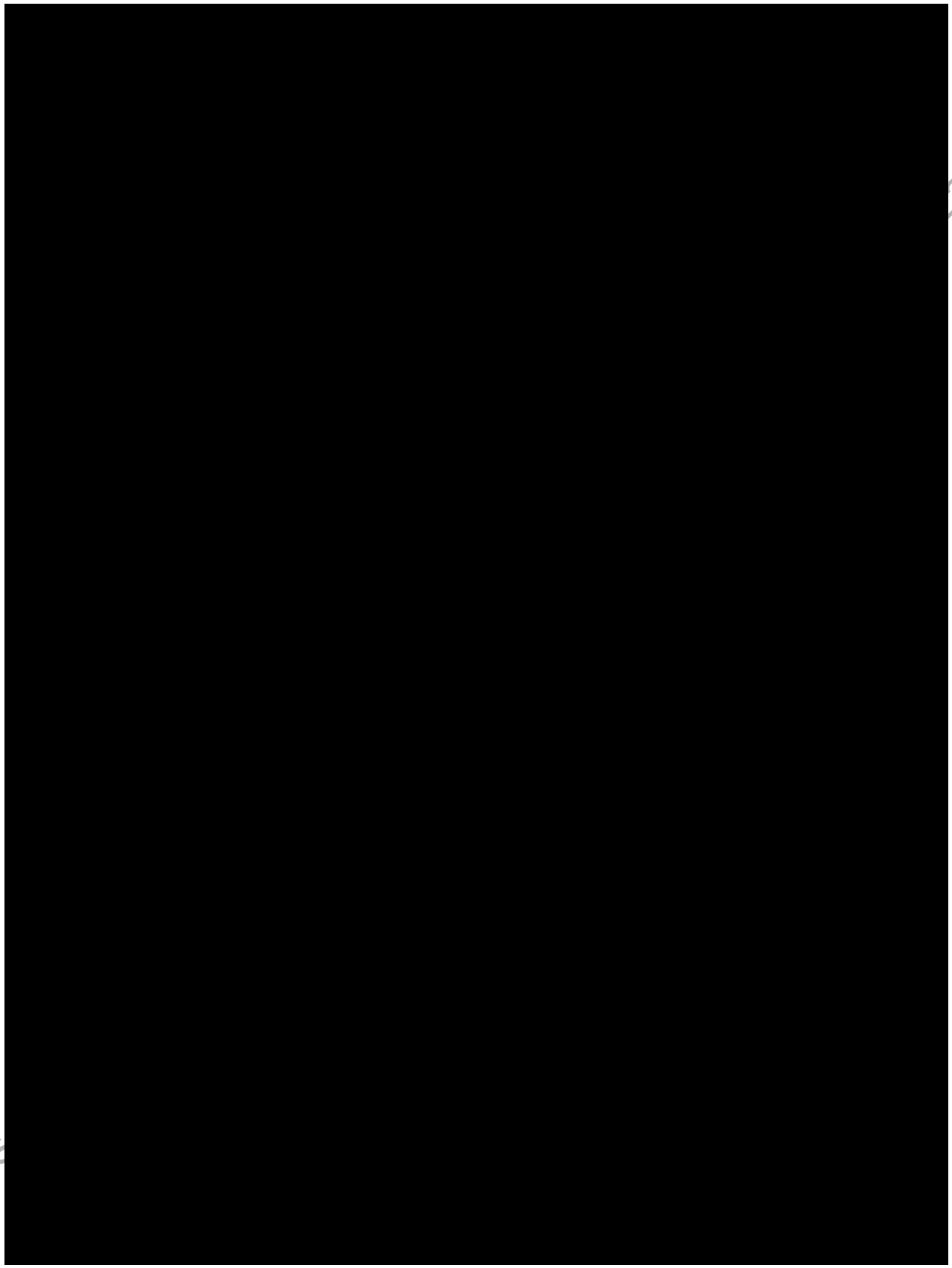

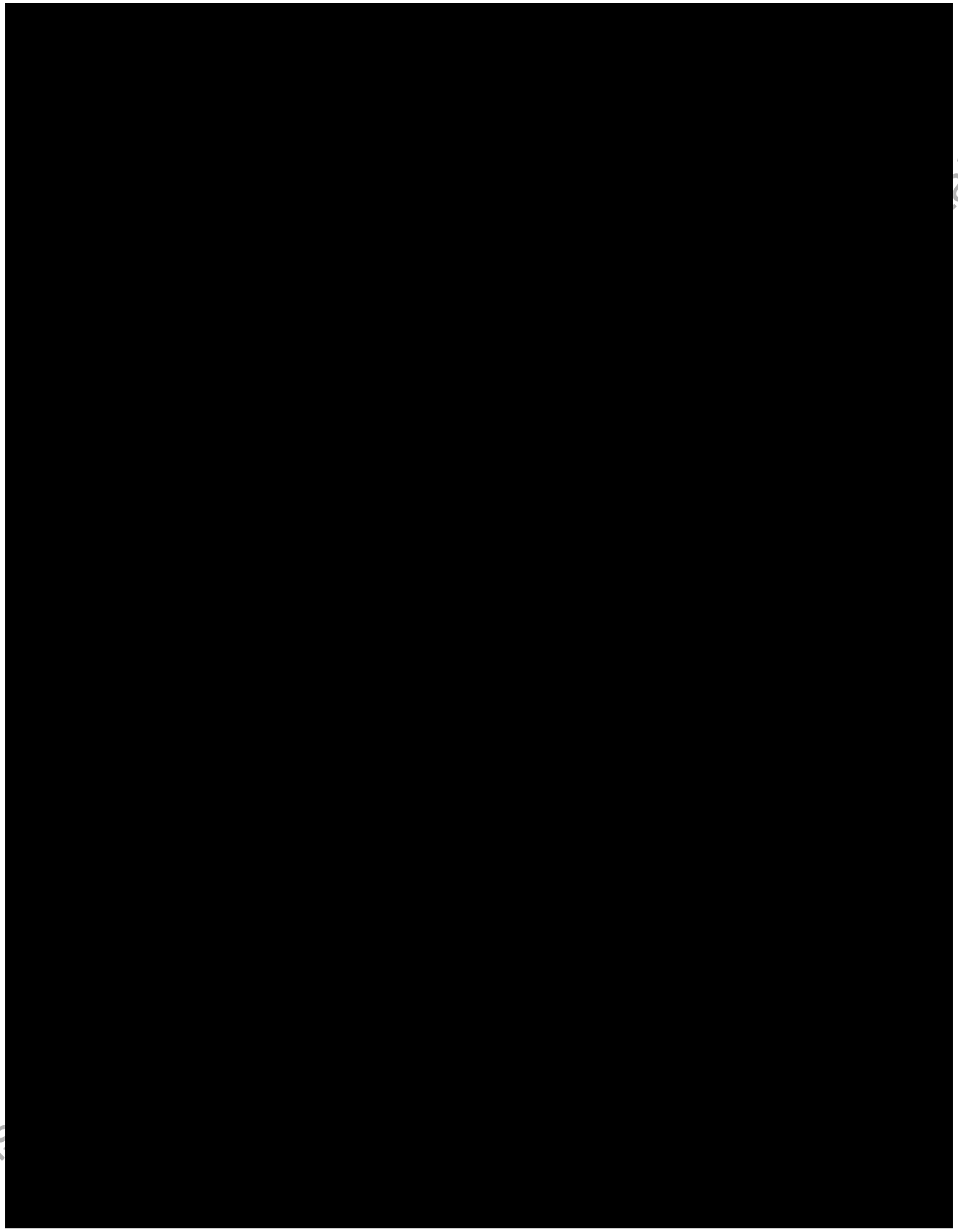

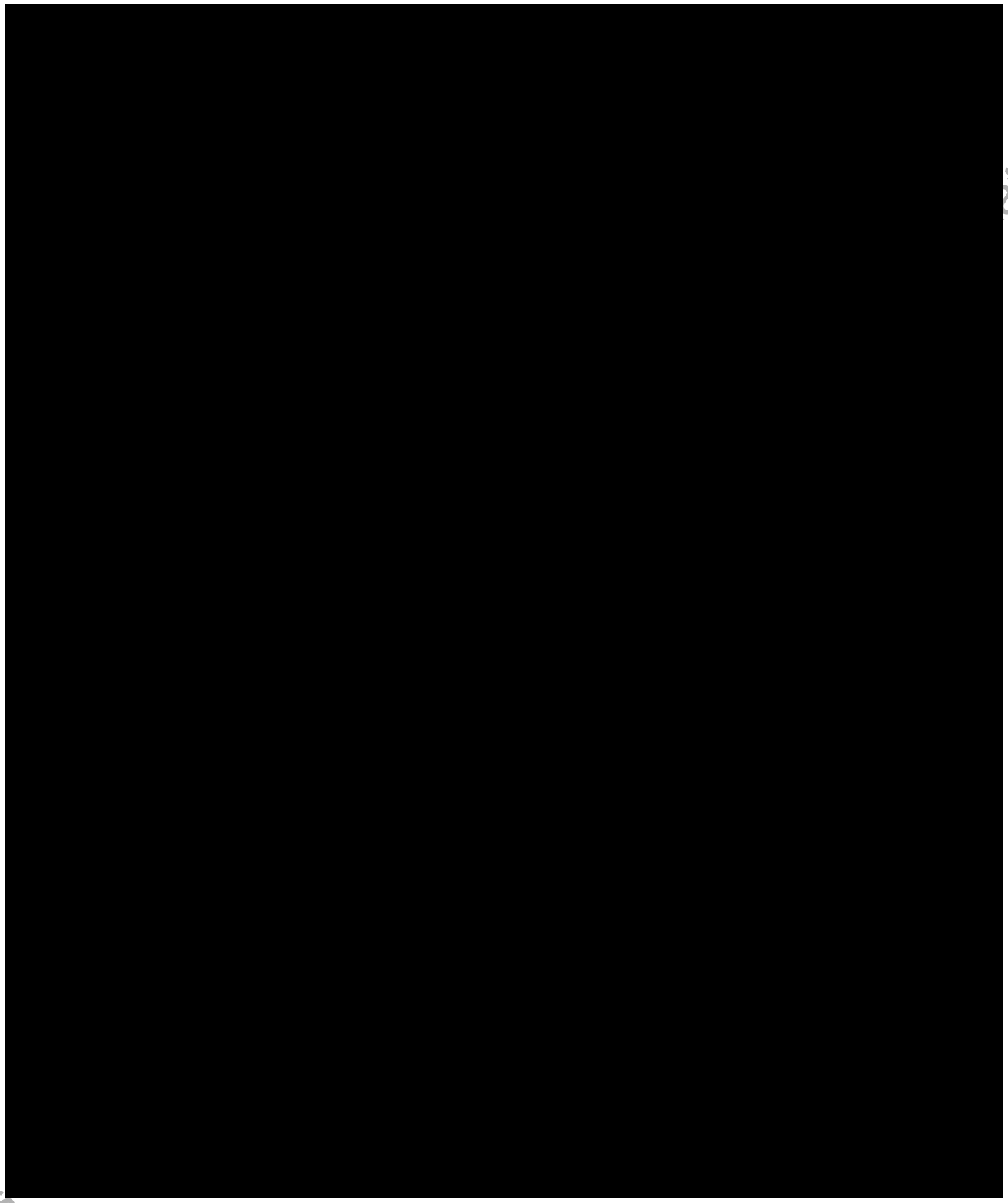

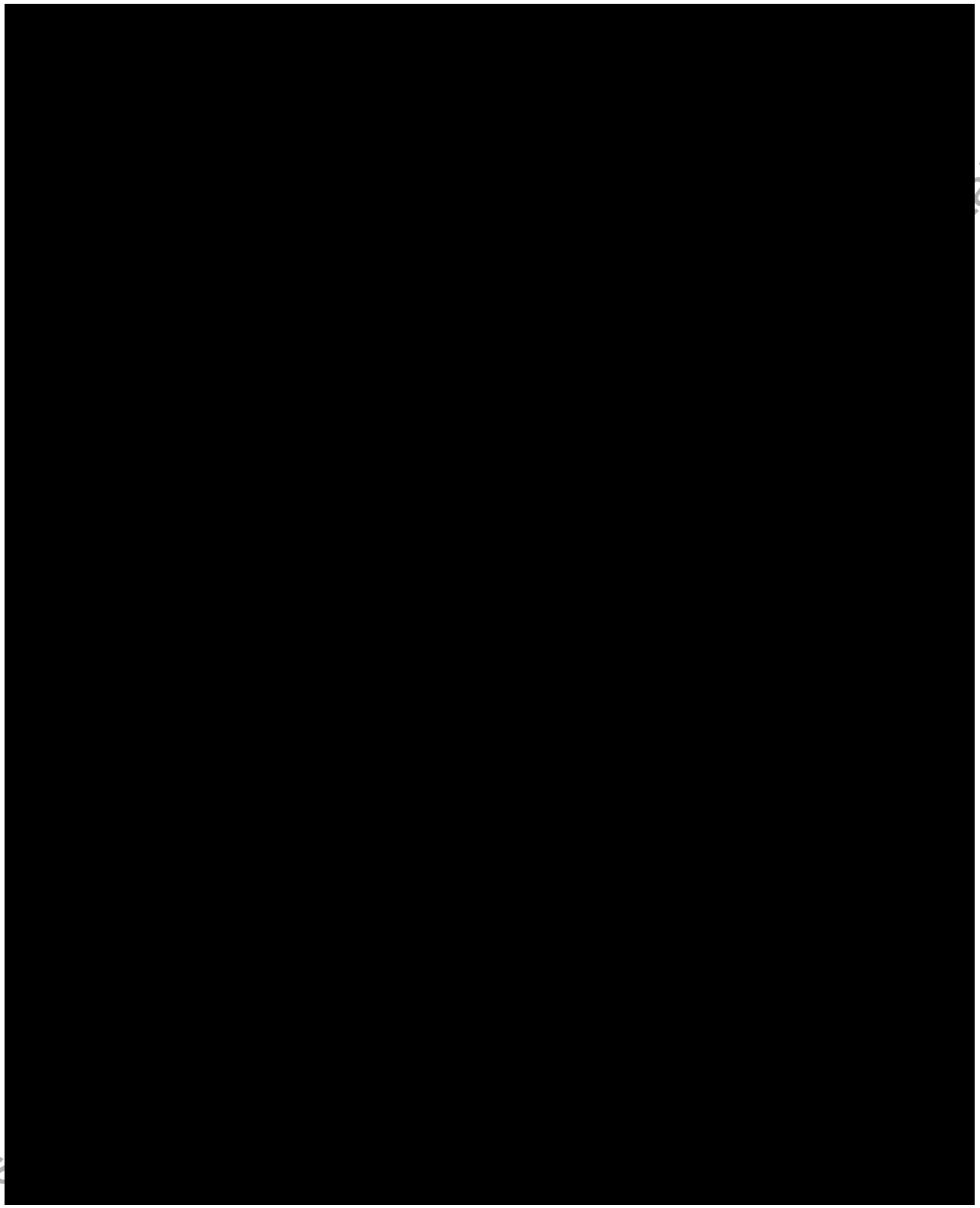

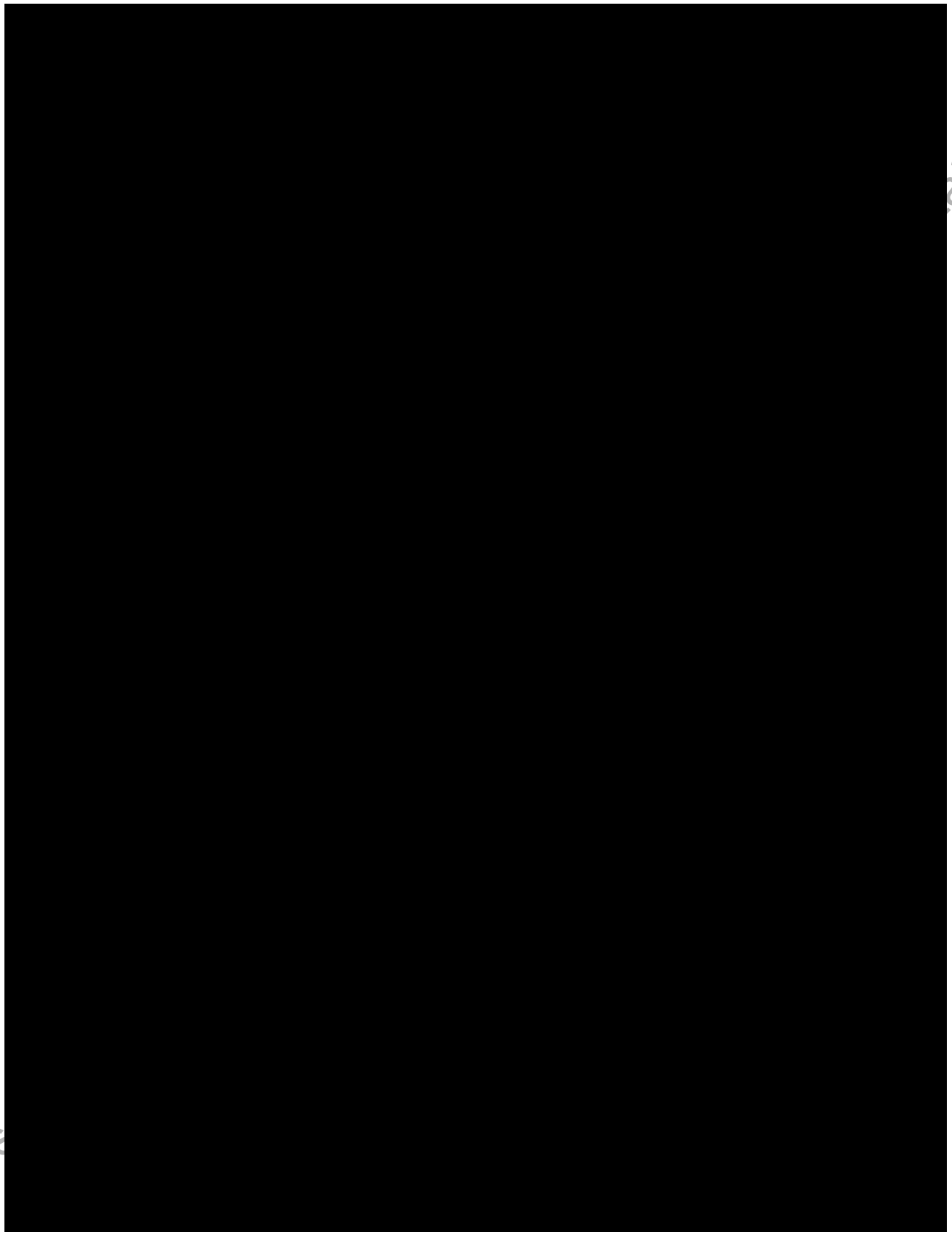

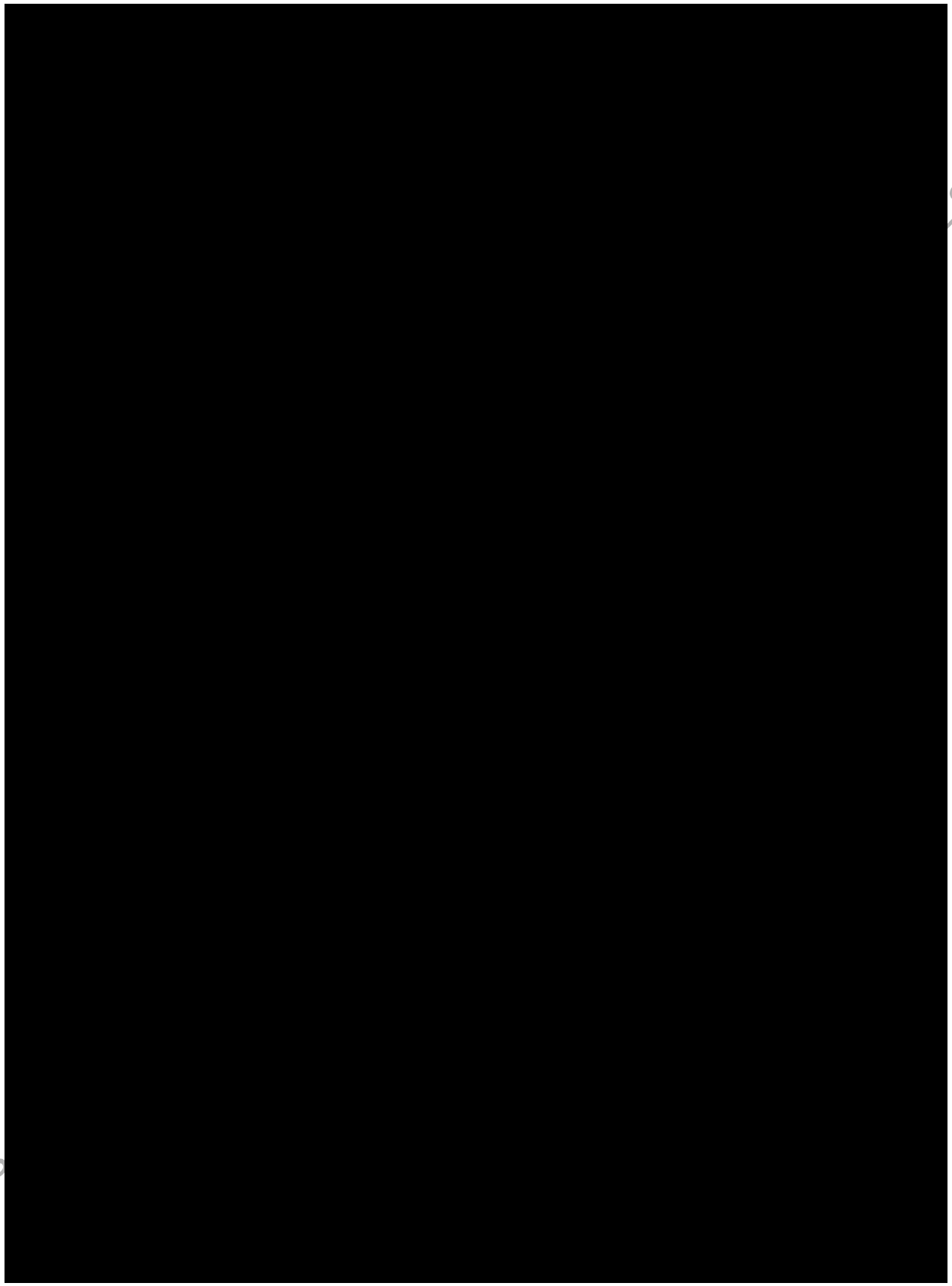

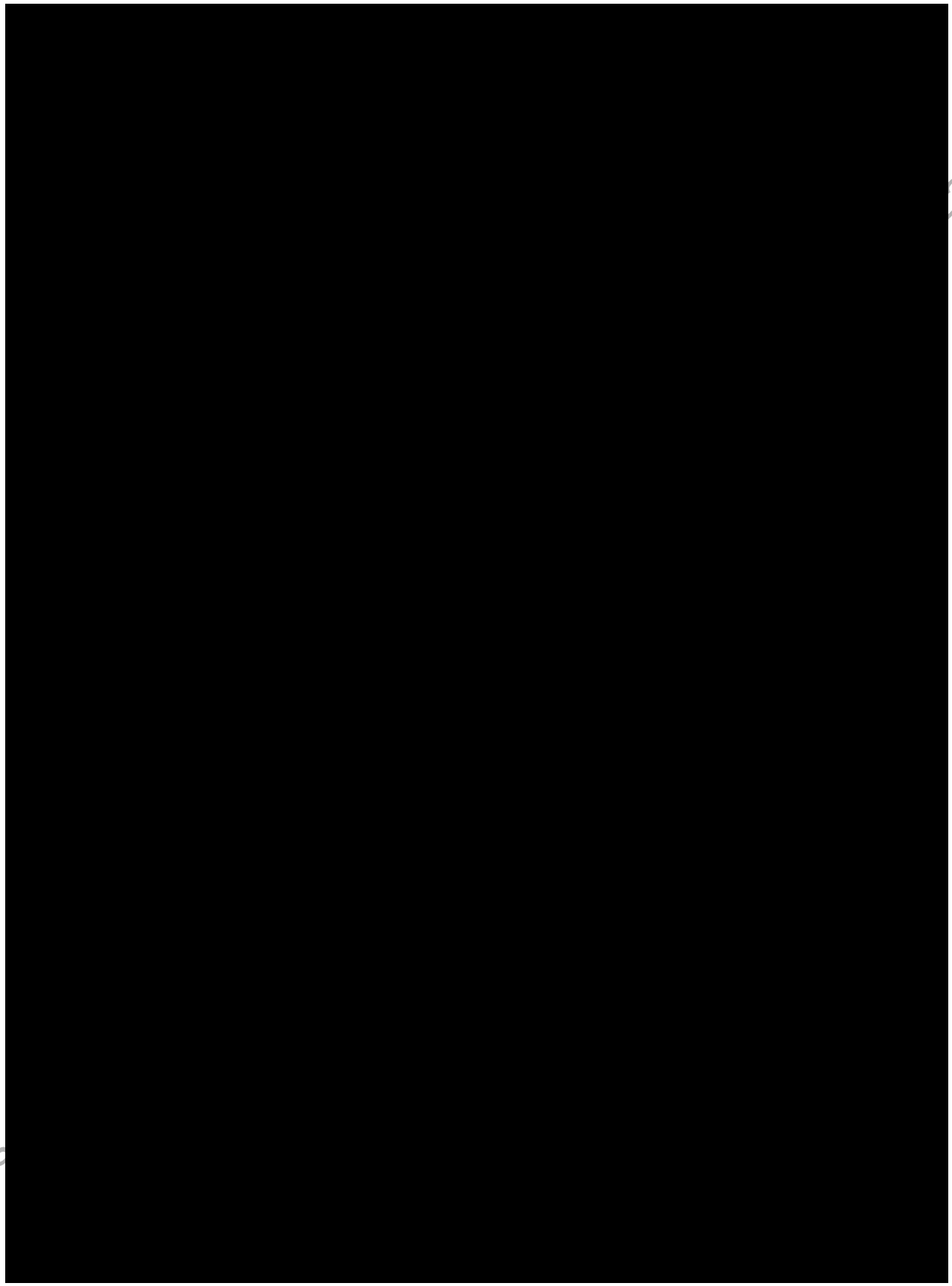

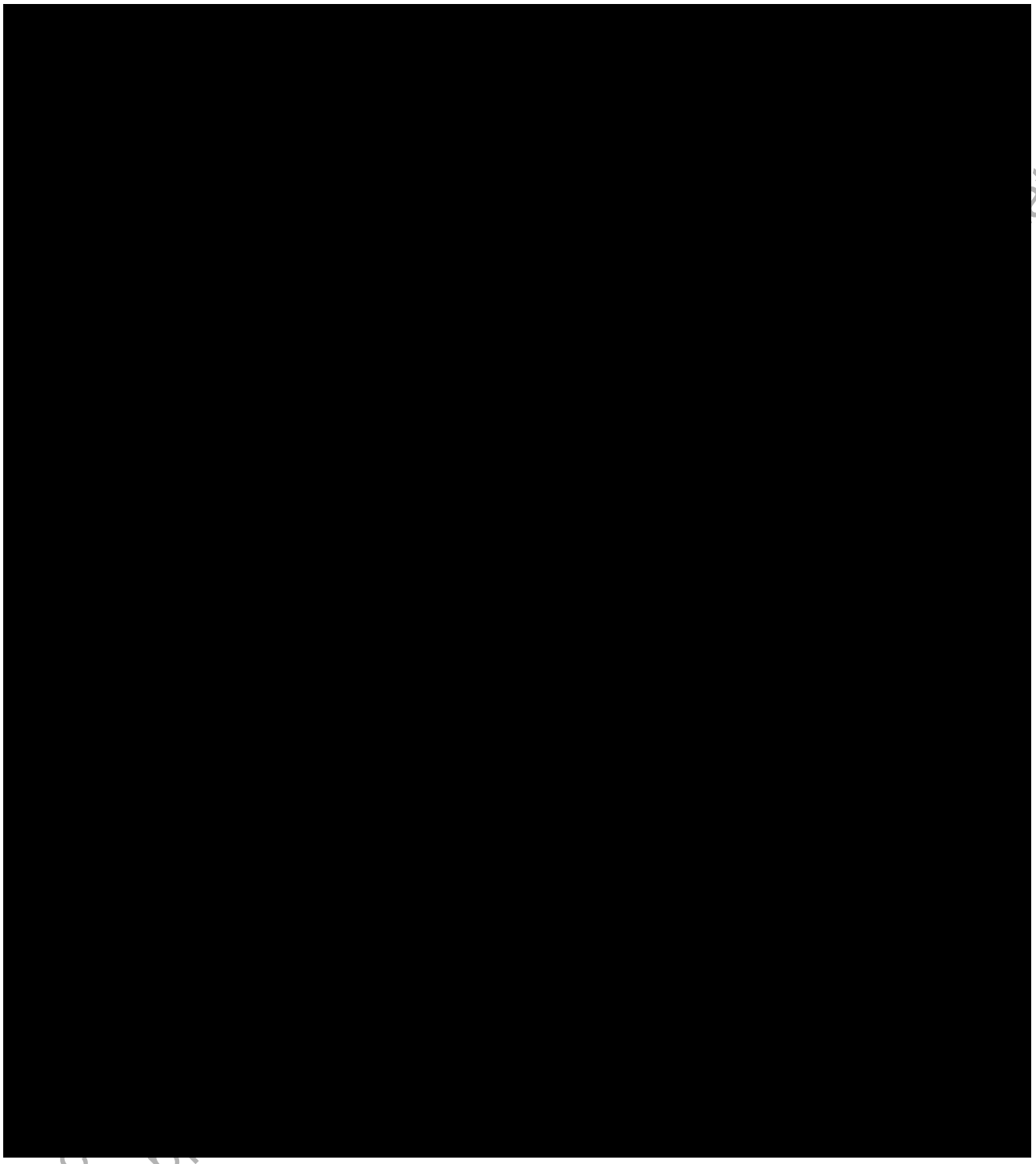

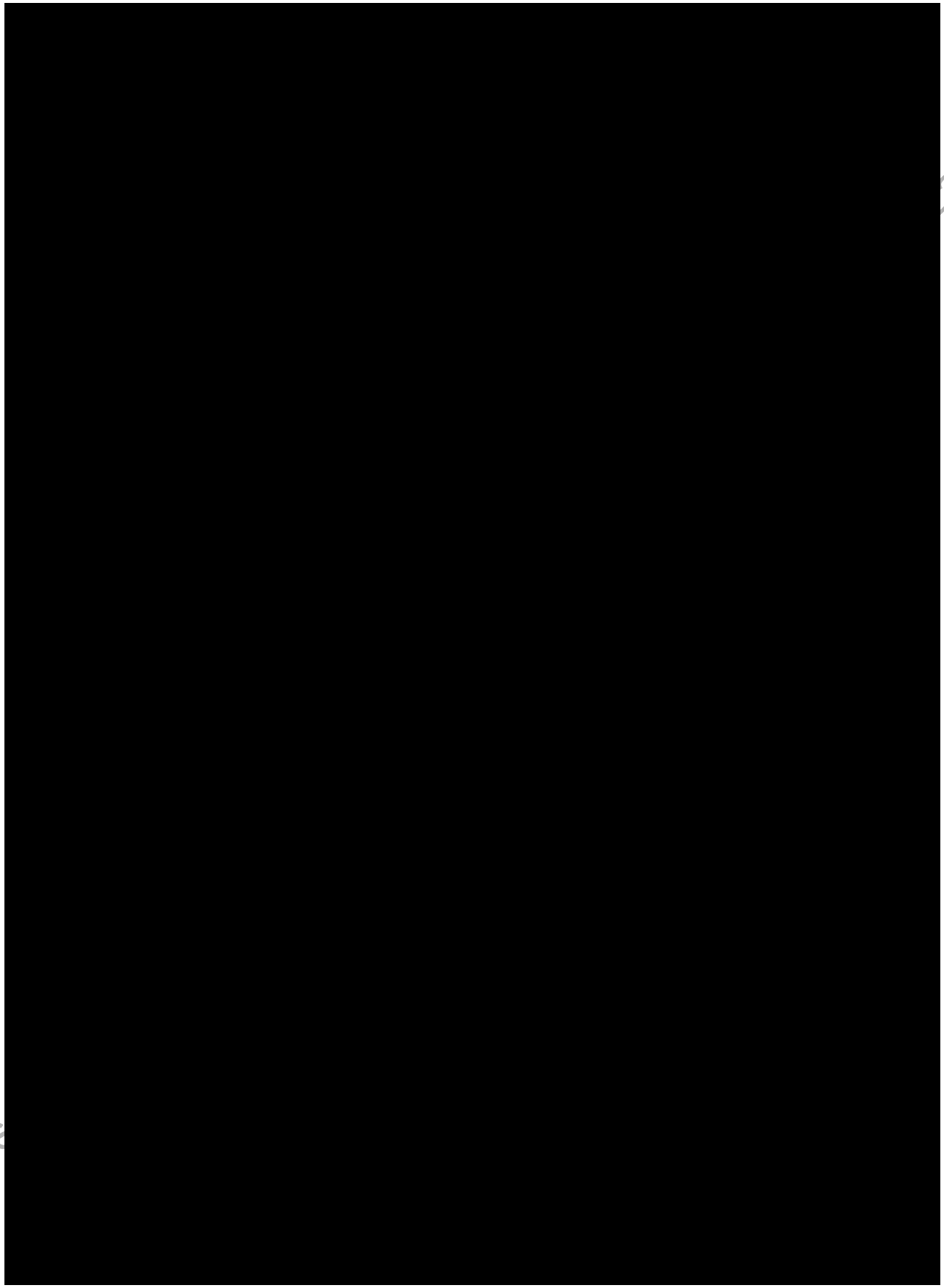

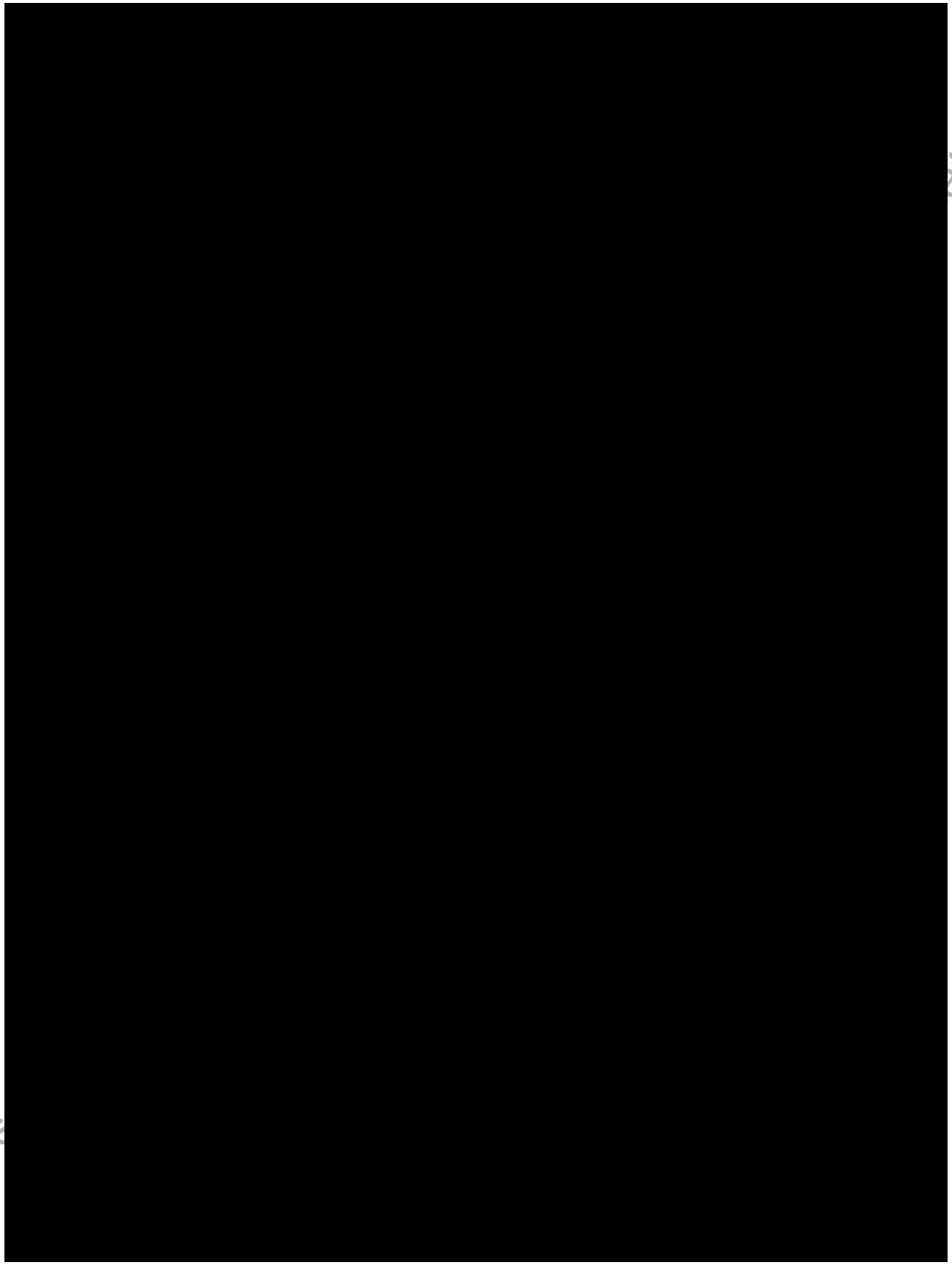

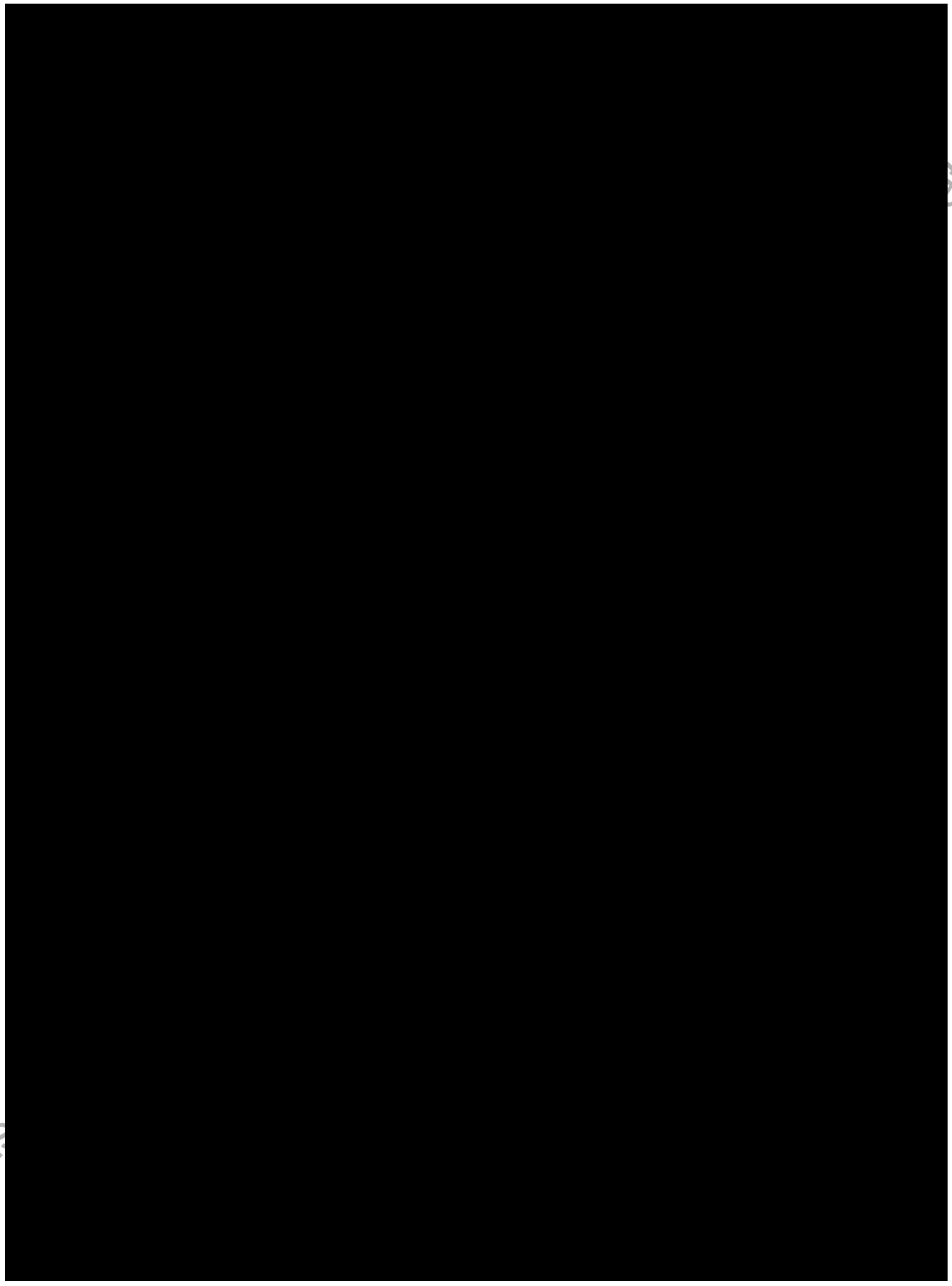

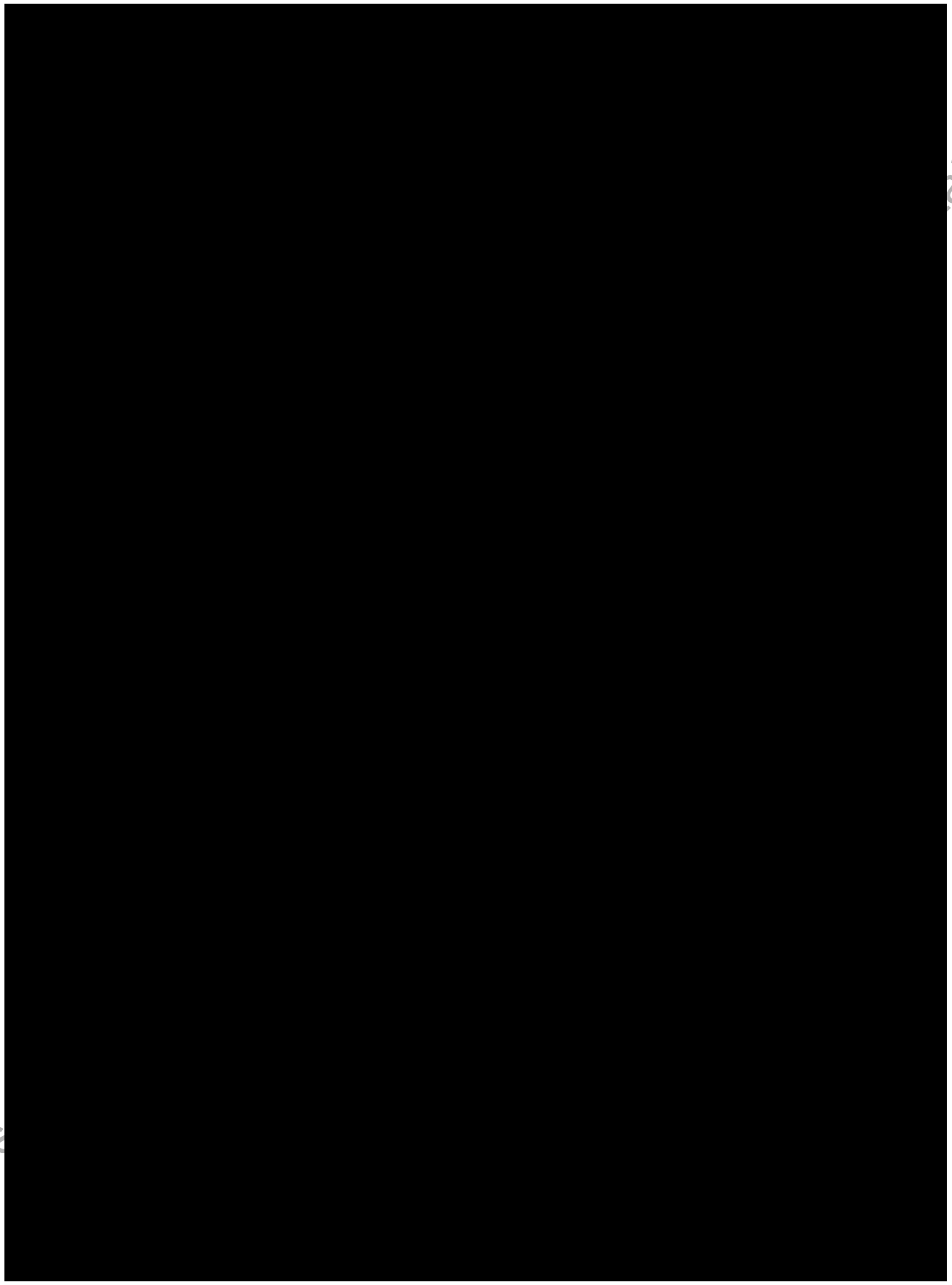

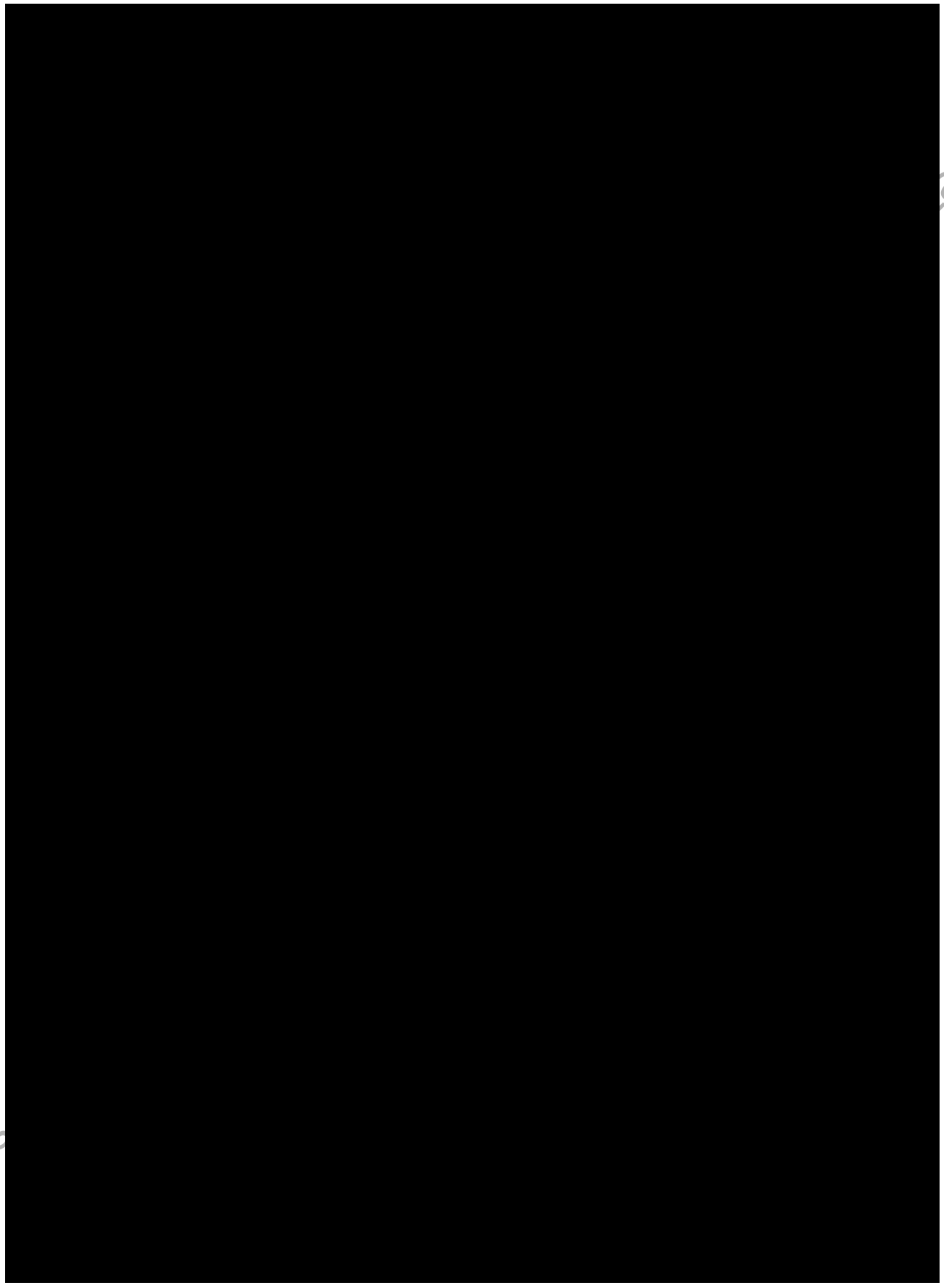

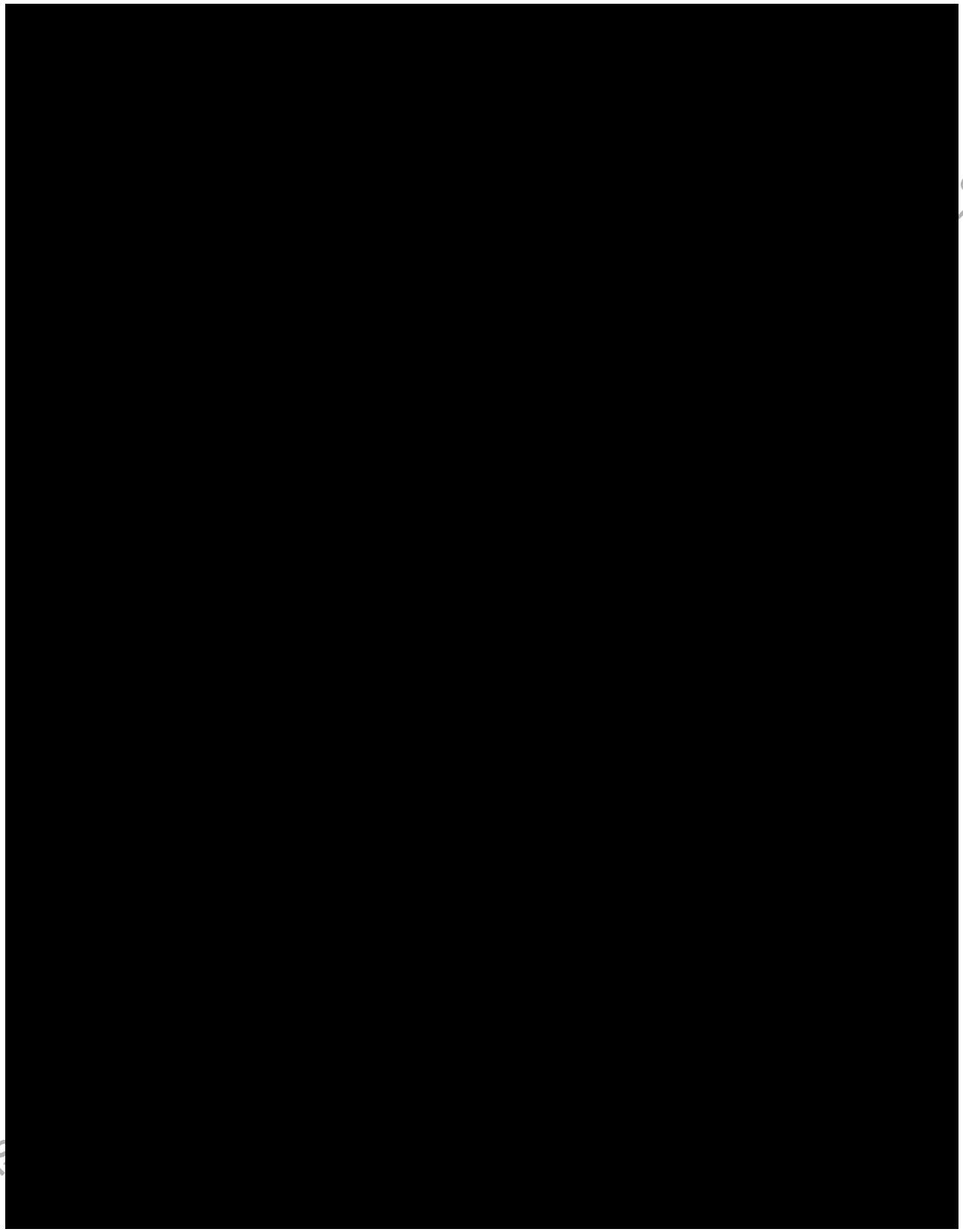

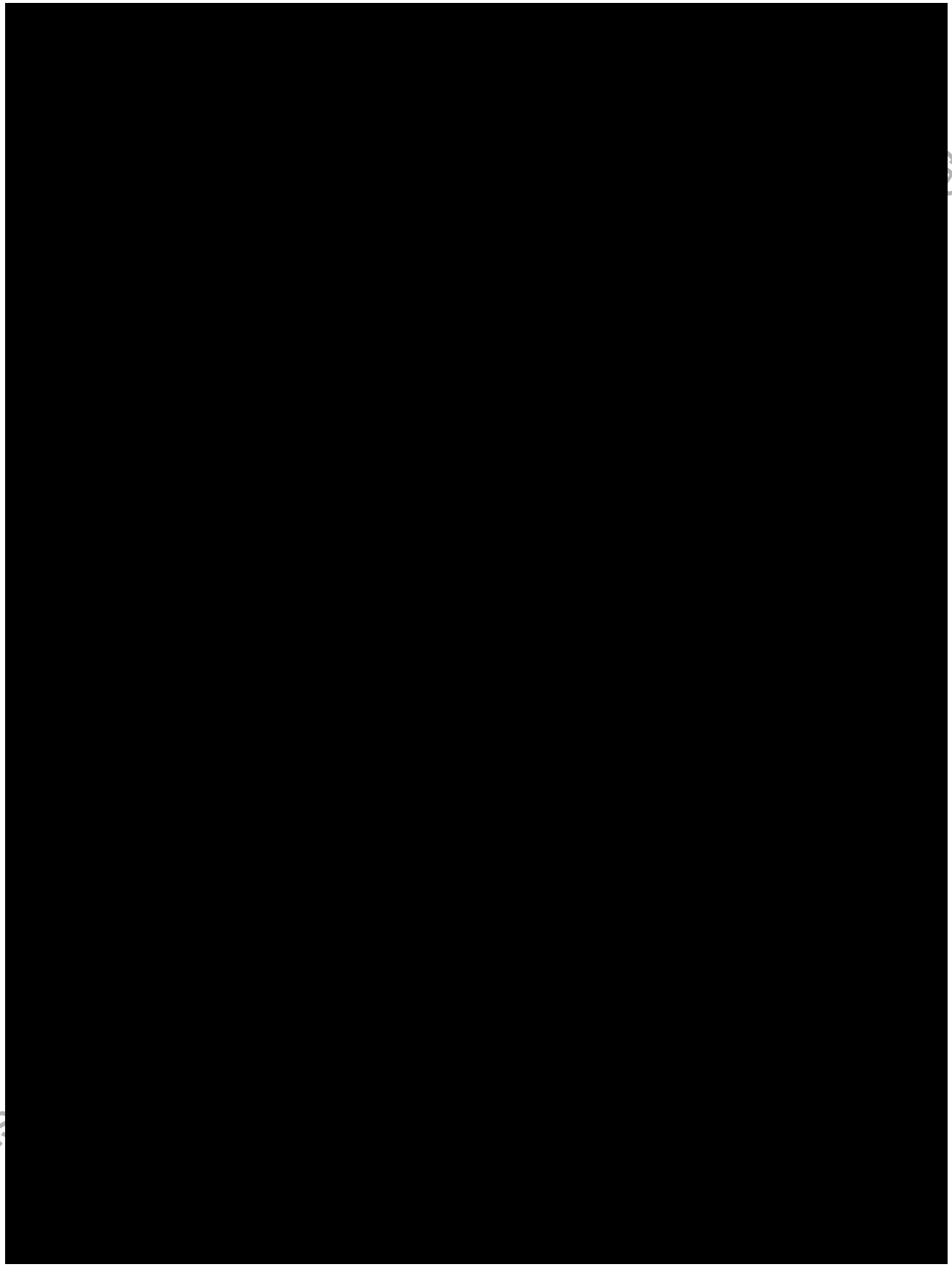

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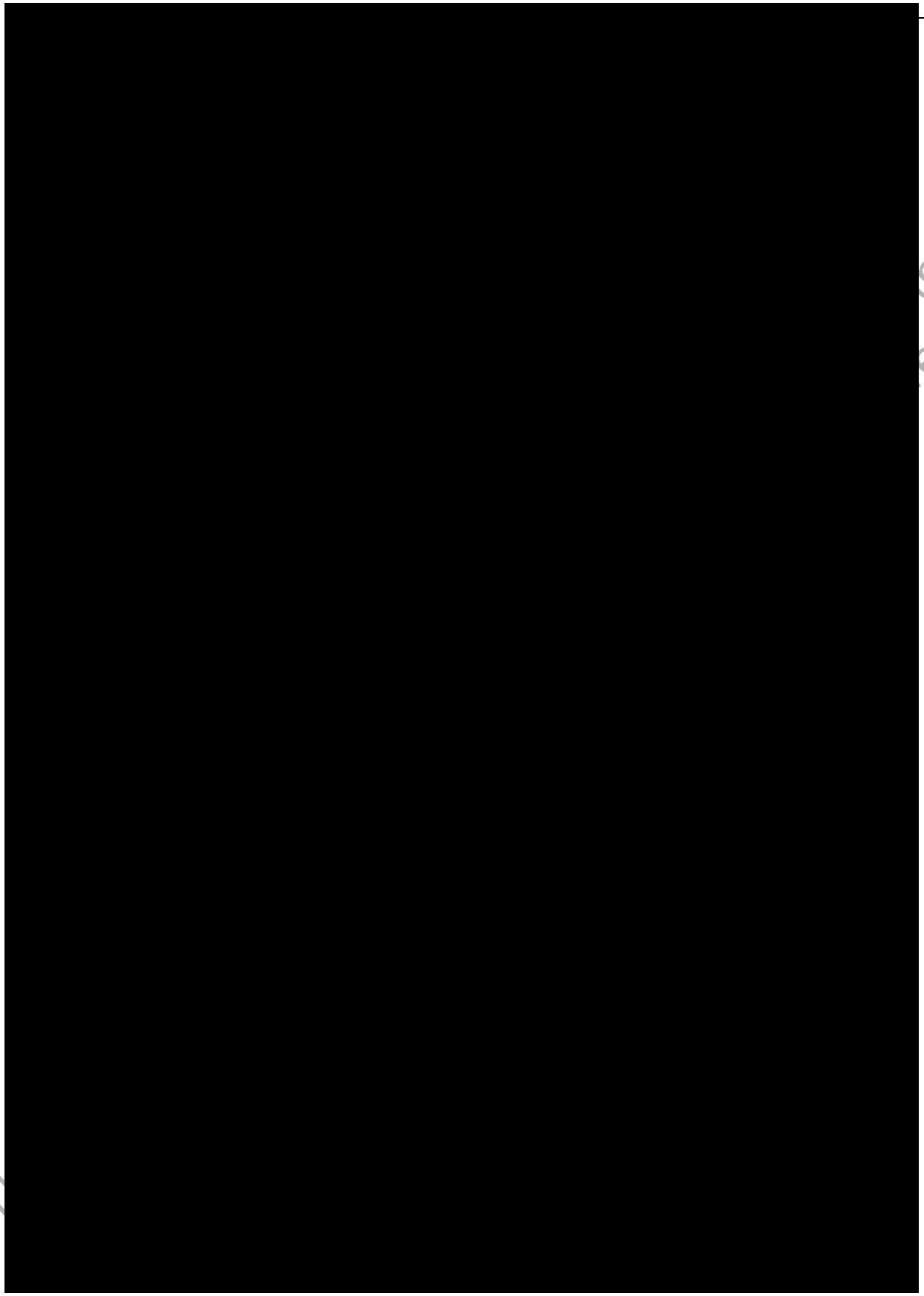

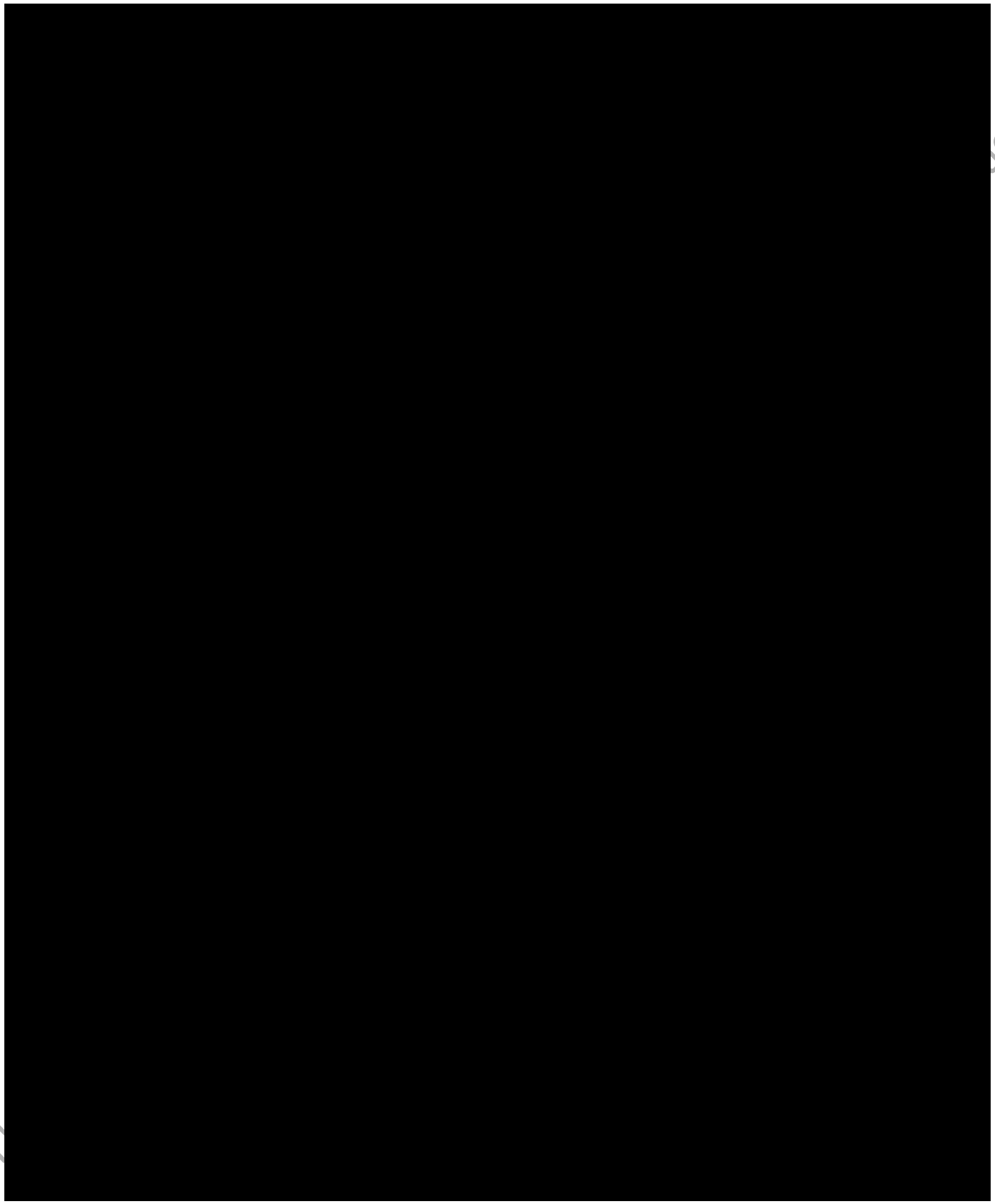

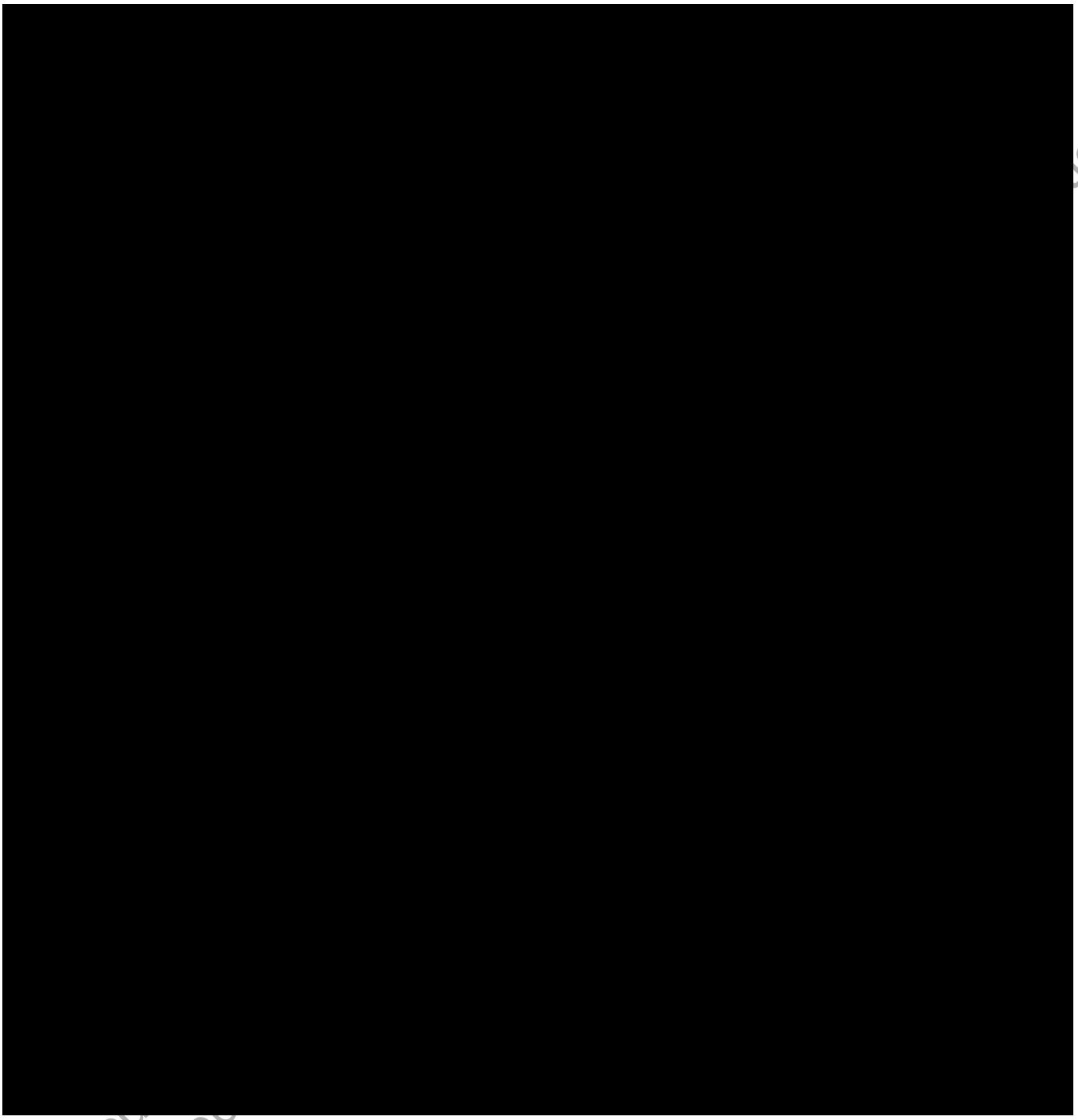

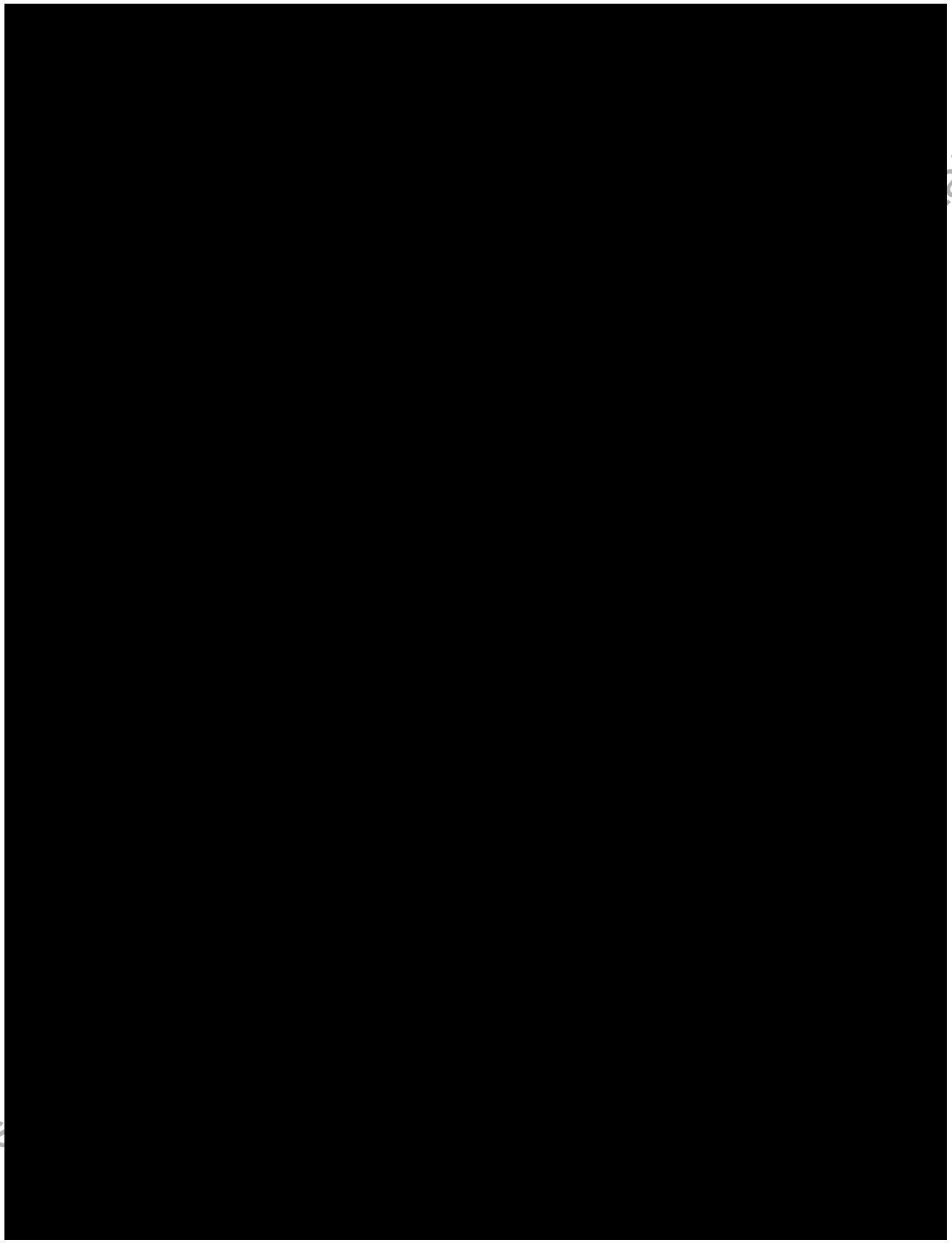

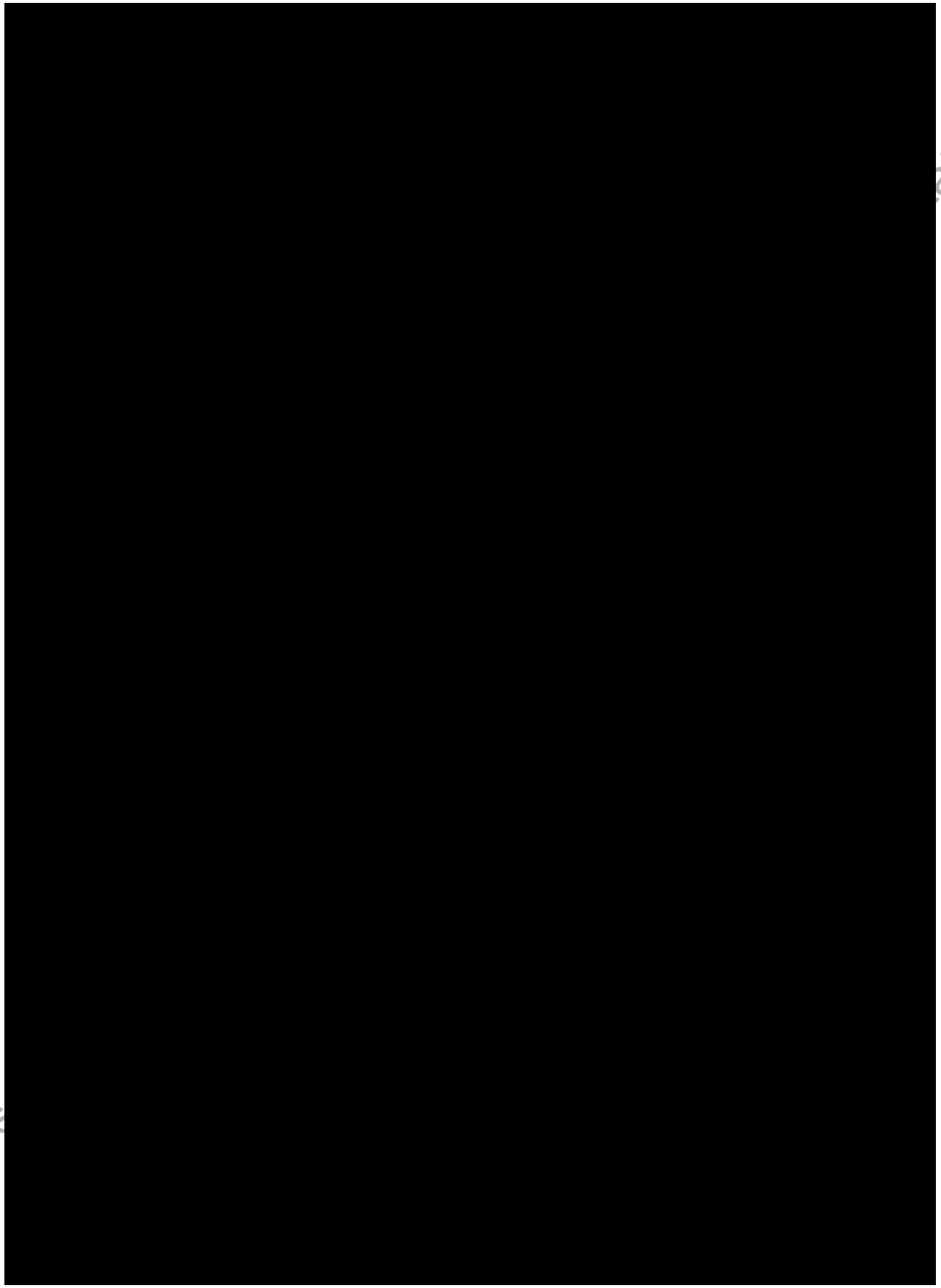

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14 AMENDMENT(S) TO THE STATISTICAL ANALYSIS PLAN (SAP)

14.1 Amendment 1

Rationale for the Amendment

The SAP has been amended for the following reasons:

- To update the protocol amendment version to v2.0 dated June 2021
- To clarify that data from participants withdrawing from the study early at end of treatment (EOT) visits will be mapped to the next scheduled visit per assessment
- To indicate that if a Baseline measurement is missing and there are multiple Screening lab values, then the most recent lab value prior to Baseline will be considered as the Baseline value. Unscheduled lab measurements taken before Baseline will be labelled as Screen Re-test values
- To clarify that the assessment of cumulative corticosteroid (prednisone equivalent) doses by visit will be limited to medications for a SLE indication only. Corticosteroid doses for indications other than SLE are considered for escape treatment interventions

[redacted]

- To describe the presentation and analysis of data for the regular IDMC meetings

[redacted]

- To add a listing for study participants who were re-screened (using the ES)
- To clarify which Baseline PRO characteristics will be assessed
- To add a sensitivity analysis to exclude those participants who were either unblinded or potentially unblinded to the investigator and/or study team from the FAS
- To clarify the groups of participants considered for Supplementary analysis 3
- To update the supportive analysis for the change from Baseline in SLEDAI-2K at Week 48
- To define the severe, moderate, and mild SFI flare categories across body systems

- To update the Pharmacokinetics (PK) section in accordance with standardized UCB text. Changes include updates to analyses of immunogenicity (ie, ADA and Nab sample and participant status), and correlation of ADA with PK, PD and/or efficacy
- To define antiphospholipid (aPL) single, double, and triple positivity
- To include an analysis on the incidence of TEAEs by intensity, and incidence of TEAEs excluding adverse events related to COVID-19 vaccines as determined by the investigator
- To define the calculation of planned and actual dose received
- To update the planned dose as when SL0043 initially began, the planned infusion volume was 150mL. This was later changed to 200mL. Sites adopted the change from 150mL to 200mL infusions between Oct 2020 and April 2021
- To include an output summarizing the impact of COVID-19 due to confirmed or suspected COVID-19 infection (including impact category and visit (ie, timepoint)) by treatment arm using the FAS
- To clarify what will happen if BILAG SLE-relatedness is missing post-Baseline
- To define the EULAR/ACR classification criteria
- To define the EQ-5D total score across the 5 individual items and the VAS (denoted as the EQ-5D UK Tariff)
- To include the revised definition of DORIS
- To state the mapping of each country to the respective region and pooled region used for analysis
- To update the CTCAE grade version from 4.3 to 5.0
- To add BMI in vital signs analyses
- To add tertiary endpoint “Change from Baseline in Clinical SLEDAI-2K by visit”
- To update the analysis of tertiary endpoint BILAG worsening from handling with NRI to observed cases
- To update the analyses of prednisone equivalent dose from probability plot to cumulative distribution function plot

In addition, a few clarifications, inconsistencies, acronyms, and typographical errors have been made/defined/corrected within the SAP text.

14.2 Amendment 2

Rationale for the Amendment

The primary reasons for this amendment are to reduce the sample size and consequently remove the interim analysis, and to change the population-level summary of the primary efficacy estimand from an odds ratio for the proportion achieving BICLA response at Week 48 in each treatment group to the difference in proportion achieving BICLA response at Week 48. Other updates have been incorporated for reasons including addressing regulatory feedback, removing multiple imputation for data impacted by COVID-19, providing further clarity and correcting

errors. In addition to the changes listed below, correction of minor typographical errors, inconsistencies, acronyms, and formatting/stylistic changes have been made within the SAP text.

- To update the protocol amendment version to v4.0 dated 16 March 2023 in Section 1.
- To update the power calculation for the reduced sample size in Section 2.4.
- To clarify that data from participants withdrawing from the study early at end of treatment (EOT) visits will be mapped to the next scheduled visit per assessment for purpose of analyses and inclusion in summary tables but will be presented in terms of nominal visit in listings in Section 3.2.
- To define the baseline values for SLEDAI-2K assessments when a lab component for SLEDAI is missing at Baseline in Section 3.4.
- To remove COVID-19 impacted data as a special case of missing data and modify the analyses accordingly due to rare occurrence of missed visits due to COVID-19 impact in Section 4.3 and 8.
- To update the multiple imputation steps for CMH test in Section 4.3.3, 8.3.1 and 8.3.2.
- To add the strategy of handling data impacted by COVID-19 in Section 4.4, if data is missing due to COVID-19 it will be treated the same as other missing data.
- To clarify that if a treatment change represents an intercurrent event in the category of escape treatment intervention 1, it will be confirmed by a blinded independent adjudicator in Section 4.5.
- To update the definition of escape treatment intervention 2 per EULAR guidance in Section 4.5.2.
- To indicate that there will be no interim analysis since sample size is reduced in Section 4.6.2 and to remove appendices of Interim Futility Analysis Outputs and Choice of Endpoint for SL0043 Futility Assessment.
- To update the number of sites for the study since sample size is reduced in Section 4.7.
- To remove some subgroup analyses due to low numbers in the subgroup or due to redundancy with other subgroups in Section 4.9.1.
- To display additional demographics information from subjects recruited in the USA in Section 6.1.
- To update the primary analysis from using logistic regression model to CMH based on regulatory feedback and to remove COVID-19 impacted data as an intercurrent event in Section 8.
- To update the definition of observed cases in Section 8.2.1.
- To remove the primary efficacy endpoint sensitivity analysis of GEE and add sensitivity analysis to evaluate the impact of partially available data (ie, one component missing) being imputed via multiple imputation rather than carrying forward the component value from prior visit in Section 8.3.1.

- To update sensitivity analysis 2 (tipping point) for CMH given the change in the primary estimand in Section 8.3.1.
- To add a sensitivity analysis overview (forest plot) in Section 8.3.1.1.
- To update supplementary analysis 4 of BICLA using odds ratio via a logistic regression model given the change in the primary estimand to analysis of the difference between proportions in Section 8.3.2.
- To clarify the definition of the additional analyses in Section 8.3.2.
- To clarify that BILAG flares will be adjudicated and that worsening of symptoms after the Baseline Visit will only be considered as a flare if there was at least 1 post-Baseline Visit, prior to the worsening, where the symptom remained the same or improved in Section 8.4, 8.5 and 13.2.1.
- To specify the analysis of achievement of severe BILAG flare free through Week 48 endpoint in Section 8.4.
- To remove the supportive analysis of change from Baseline in SLEDAI-2K at Week 48 and add sensitivity analyses of the endpoint per regulatory feedback in Section 8.4.1.
- To remove the analysis of BILAG grades and shifts from Baseline corresponding to the Neuropsychiatric domain in Section 8.6.1.3 and 13.19.
- To specify that two definitions of the LAMDA score will be computed in Section 8.6.1.4.
- To update the immunogenicity analysis per latest standard in Section 9.2.
- To state that Nab analysis will not be included in the study CSR but in a separate report in Section 9.2.2.
- To clarify the use of narrow or broad AE SMQ in Section 10.1 and 13.19.
- To clarify the definition of SLEDAI-2K and S2K RI-50 in Section 13.3.

14.3 Amendment 3

Rationale for the Amendment

[redacted]

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

This document has been reviewed and approved per the Review and Approval of Clinical Documents Standard Operating Procedures. Signatures indicate that the final version of the Statistical Analysis Plan (SAP) or amended SAP is released for execution.

Approval Signatures

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