Statistical Analysis Plan

Title: A Phase 2a, randomized, double-blind, placebo-controlled evaluation of PLN-74809 on type 1 collagen deposition using ^{68}Ga-CBP8 PET/MRI imaging in participants with idiopathic pulmonary fibrosis (IPF)

Protocol Number: PLN-74809-IPF-205

Protocol Version: Version 1.0 / Date 22 JUN 2021

Amendment 1 / Date 04 OCT 2021

SAP Version: Version 2.0, Date 25-Mar-2024

SAP Author: [redacted]

[redacted]

Previous SAP Versions

Version 1.0, Date 23-Jan-2024

SAP Amendments before database lock

Version	Issue Date	Section	Revision / Addition	Rationale
V 1.0	23-Jan-2024			First Version
V 2.0	20-Mar-2024	5.11.2.2	[redacted] updated for MMRM model.	For programming instruction
		11	TFL updates: Table 14.3.1.1 is updated to be presented by standard of care (Yes/No) Figures 14.2.1.1.3, 14.2.1.2.3, 14.2.1.3.3 are updated to lineplot, and footnote added.	Per Sponsor's request

REVIEW / APPROVAL SIGNATURES

Plan Author [redacted] Signature: [redacted]	**Plan Author** [redacted] Signature: [redacted]
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1 INTRODUCTION

This document details the planned statistical analyses for Pliant Therapeutics Inc, protocol "PLN-74809-IPF-205" study titled "A Phase 2a, randomized, double-blind, placebo-controlled evaluation of PLN-74809 on type 1 collagen deposition using ^{68}Ga-CBP8 PET/MRI imaging in participants with idiopathic pulmonary fibrosis (IPF)". The proposed analyses are based on the contents of Amendment 1 of the protocol (dated 04 Oct 2021). Any changes made from the planned analysis described in the protocol or after finalization of this SAP will be documented in the Clinical Trial Report (CTR).

This is a Phase 2a, single-center, randomized, double-blinded, placebo-controlled study to evaluate type 1 collagen deposition in the lungs following once-daily treatment with 160 mg PLN-74809 for 12 weeks in participants with IPF. The study consists of an up to 28-day screening period, a 12-week treatment period, and a 2-week (±3 days) post treatment follow-up period.

2 STUDY OBJECTIVES, ENDPOINTS, AND ESTIMANDS

2.1 Objectives

Primary objective:

- Quantification of type 1 collagen in the lung following 12 weeks of treatment with PLN-74809, as assessed by changes from baseline in ^{68}Ga-CBP8 positron emission tomography (PET)/ magnetic resonance imaging (MRI) tracer uptake patterns

Secondary objective:

- Assessment of the safety and tolerability of PLN-74809 in idiopathic pulmonary fibrosis (IPF) participants

Exploratory objectives:

- Relationships between PLN-74809 systemic exposure, PET imaging and biomarkers in IPF participants
- Forced vital capacity (FVC): absolute FVC volume and FVC as percent of predicted as assessed by spirometry
- Patient-reported outcome (PRO): a visual analog scale (VAS) for cough severity

2.2 Endpoints

2.2.1 Primary Endpoints

The primary pharmacodynamic endpoint of this study is the whole lung standardized uptake value (SUV).

2.2.2 Secondary Endpoints

The secondary safety endpoints are:

- Treatment emergent AEs and SAEs
- Clinical laboratory parameters, including hematology, serum chemistry, coagulation, and urinalysis
- ECG
- Vital signs measurements
- Concomitant medications

2.2.3 Exploratory Endpoints

Plasma PLN-74809 concentrations (total and unbound) and percent unbound PLN-74809 at each sampling time point will be presented in listings and summarized by day with descriptive statistics. Plasma PLN-74809 versus time profiles (with plasma concentrations on both a log and linear scale) will be plotted for each participant. In addition, the following PLN-74809 PK parameters will be estimated on Day 1:

- C_{max}: Maximum observed plasma concentration
- $AUC_{0\text{-}6h}$: Area under curve (AUC) from the time 0 to 6 hours postdose
- T_{max}: Time to reach C_{max}
- $C_{max,ub}$: Maximum observed unbound plasma concentration
- $AUC_{0\text{-}6h,ub}$: Unbound AUC from the time 0 to 6 hours postdose

The exploratory pharmacodynamic or efficacy endpoints are:

- Markers of fibrosis: Pro-peptide of Type III Collagen (PRO-C3), CTX-III_HP, and Integrin Beta 6(ITGB6)
- Absolute forced vital capacity (FVC) by volume (mL) and percent predicted (%)
- PRO: a VAS for cough severity

3 SAMPLE SIZE

The sample size of approximately 12 participants (8 participants receiving 160 mg PLN-74809 and 4 receiving placebo) is expected to provide a meaningful evaluation of PLN-74809 safety, tolerability and pharmacokinetics (PK) in the target population and add to the data of approximately 21 participants planned to be evaluated at this dose level in an ongoing multicenter, dose-ranging Phase 2a study (PLN-74809-IPF-202).

4 RANDOMIZATION

Approximately 12 eligible participants will be randomized in a 2:1 ratio (160 mg PLN-74809 vs placebo). Randomization will be stratified by use of standard-of-care IPF therapy (pirfenidone or nintedanib) (yes or no).

5 PLANNED ANALYSES

The Statistical Analysis Plan (SAP) and Table, Figure, Listing (TFL) Shells (and any amendments) must be approved prior to database lock. If, post database lock, additional statistical analyses or changes to the statistical analysis are required, then such additional analyses will be documented in a Post Database Lock Statistical Analysis Plan Addendum.

5.1 Analysis Sets

5.1.1 Screened Population

The screened population includes all participants screened who gave informed consent.

5.1.2 Intent-to-Treat Population

The intent-to-treat (ITT) population includes all randomized participants. Treatment assignment is by randomized treatment.

5.1.3 Safety Population

The safety population includes all randomized participants who received at least one dose of study drug. Treatment assignment is by actual treatment.

5.1.4 Pharmacokinetic (PK) Analysis Population

The PK analysis population includes all randomized participants who have sufficient PLN-74809 concentration data for PK calculation. Treatment assignment is by actual treatment.

5.1.5 Pharmacodynamic (PD) Population

The PD population includes all randomized participants who received any amount of study drug and who have results from baseline and from at least one post-baseline PET/MRI scan or PD assessment. Treatment assignment is by actual treatment.

5.2 Derived Data

This section describes the derivations required for statistical analysis. Unless otherwise stated, variables derived in the source data will not be recalculated.

5.2.1 Race

Where more than one race category has been selected for a participant, these race categories will be combined into a single category labelled "Multiple Race" in the summary tables. The listings will reflect the original selected categories.

5.2.2 Body Mass Index

Body mass index (BMI) will be calculated as follows:

BMI (kg/m^2) = Weight at Screening (kg) / [Height at Screening $(m)^2$]

5.2.3 GAP Index and Staging System

The GAP index and staging system is a multidimensional prognostic staging system derived from four commonly measured clinical and physiologic variables (Gender, Age and two lung physiology variables [FVC and DLCO]). Points are allocated to each clinical or physiological variable and points are summed to provide a total score (from 0 to 8). The total score is then used to assign a GAP stage (I, II, or III) as follows:

GAP Scoring

Predictor	Points Allocated
Gender	Female = 0 Male = 1
Age	≤ 60 = 0 61 – 65 = 1 > 65 = 2
Physiology - FVC, % Predicted	> 75 = 0 50 – 75 = 1 < 50 = 2
Physiology - DLCO, % Predicted	> 55 = 0 36 – 55 = 1 ≤ 35 = 2 [a]Cannot perform = 3
Total Point Score	**0-8**

[a] Cannot perform' is only assigned if symptoms or lung function prohibited performance of the DLCO maneuver. If DLCO is unavailable for a non-respiratory reason (eg, an operational reason), the GAP index and staging system cannot be applied.

GAP Staging System

Stage	I	II	III
Points	0-3	4-5	6-8

The screening assessments will be used to determine GAP stage.

5.2.4 Standardized Uptake Values

Standardized uptake values (SUVs) will be quantified, using MIMs software as specified in the protocol, for each lung (left and right) and by 6 regions (lower subpleural, lower central, middle subpleural, middle central, upper subpleural, and upper central) as well as whole lung, by the Imaging laboratory from the PET scans. Multiple SUV parameters will be provided for each region. The following parameters will be provided for each region, each lung, and for the whole lung:

- SUVmean: mean of the SUVs for each region in each lung
- SUVmax: maximum of the SUVs for each region in each lung
- SUVtopquartile: mean of the SUVs within the top quartile of each region in each lung

The mean of both lungs will be constructed as follows:

Region SUV metric = (left region SUV metric + right region SUV metric)/2

Whole lung SUV metric = (left whole lung SUV metric + right whole lung SUV metric)/2

5.2.5 Baseline and Change from Baseline

Baseline is defined as the last nonmissing value (either scheduled, unscheduled or repeat) before the participant received the first dose of study drug. The baseline value of the VAS is assumed to be collected in Visit 3 (Day 1). Change from baseline is defined as the difference between baseline and any post-baseline records.

5.2.6 Percent Change from Baseline

Percent change from baseline will be calculated as change from baseline multiplied by 100 then divided by the baseline value.

5.2.7 Early Terminations Assessments

Early Termination (ET) assessments will not be summarized unless the ET visit falls on a scheduled visit. ET assessments will be listed only.

5.2.8 Unscheduled Visits

Only scheduled post-baseline values will be tabulated unless otherwise stated. Post-baseline repeat / unscheduled assessments will be included in all listings in the relevant appendices of the CTR.

5.2.9 Duration / Study Day / Time

Study day will be calculated as the number of days from first dose of study drug

- date of event – date of first dose of study drug + 1, for events on or after first dose
- date of event – date of first dose of study drug, for events before first dose

5.2.10 Conventions for Missing and Partial Dates

Dates (historical or during study conduct) will only be imputed if a full date is needed for a calculation or to support a definition.

All dates presented in the individual participant listings will be presented as recorded on the electronic case report form (eCRF).

Missing / Partial Start / Stop Date of Adverse Events, Medical History and Concomitant Medication

Missing and partial start dates will be imputed solely for the purpose of determining whether an AE is treatment-emergent, medical history is ongoing at screening, or a medication is concomitant to study drug.

Partial or missing stop date will be imputed as follows:

If the stop date is completely missing and the event has resolved, or the participant has stopped taking the concomitant medication, the stop date will be imputed as the date of the participant's last clinic visit in the study.

- If only the year is known, the stop date will be imputed as "31-Dec" of that year or as the date of the participant's last clinic visit in the study if in the same year.
- If the month and year are known, the stop date will be imputed as the last day of that month unless the stop date corresponds to the same month as the participant's last clinic visit in which case the date of participant's last clinic visit in the study will be used instead.

Missing start date will be imputed as follows:

- If the stop date occurs on or after the start of study drug or the event / concomitant medication is ongoing, the start date will be imputed as the date of the first dose of study drug.
- If the stop date occurs before the start of study drug, the start date of the event / concomitant medication will be imputed as the participant's screening date or the stop date of the event / concomitant medication whichever the earlier.

Partial start date (year present, but month and day missing)

- If the stop date occurs on or after the start of study drug or the event / concomitant medication is ongoing, and the year is the same as the year of first dosing, the start date will be imputed as the date of the first dose of study drug. If the year is different from the year of first dosing, "01-Jan" will be used.
- If the stop date occurs before the start of study drug, the start date of the event / concomitant medication will be imputed as the "01-Jan" of the same year.

Partial start date (month and year present, but day missing)

- If the stop date occurs on or after the start of study drug or the event / concomitant medication is ongoing, the start date will be imputed as the first day of the same month and year unless this partial start date is in same month as the first dose of study drug in which case the date of first dose of study drug will be used.

- If the stop date occurs before the start of study drug, the start date will be imputed as the first day of the month and year of the partial stop date.

If the start time is missing it will be imputed only in the case where the start date of the concomitant medication / event corresponds to the date of the first dose of study drug. The time will be imputed as the same time as the first dose of study drug. In all other cases the time will not be imputed.

Missing Date of Last Dose

If date of last dose is not present, the date of completion/termination will be imputed as the date of last dose for the calculation of study drug exposure.

5.2.11 Exposure to Study Drug

Exposure to study drug will be calculated as follows:

date of last dosing - date of first of dosing + 1

The exposure calculation will not take into account breaks in therapy.

5.2.12 Study Drug Compliance

Study drug compliance will be calculated by comparing the amount of drug dispensed and drug returned for each participant as follows:

Number of tablets taken = Total dispensed – Total returned (if the number returned is missing, a value of 0 will be used).

Expected number of tablets = Number of days on study (calculated as per Section 5.2.9 for duration of exposure) × Number of tablets for the treatment group (per the table below).

PLN-74809	2 × 80-mg tablets per day
Placebo	2 tables per day

Compliance (%) = (Number of tablets taken / Expected number of tablets taken) × 100.

5.2.13 Inexact Values

In the case where a variable is recorded as "> x", "≥ x", "< x" or "≤ x", a value of x will be taken for analysis purposes.

5.2.14 Electrocardiogram Data

For electrocardiogram (ECG) data recorded on continuous scales, if replicate (ie, triplicate) values are recorded at a time point, the mean of the replicates rounded to the nearest integer will be used for summarization. For overall interpretation, if more than one value is recorded, the most severe (worst case) of the respective readings will be taken.

Only ECG data for specified visits and time points will be summarized. All ECG data will be presented in listings.

5.2.15 Electrocardiogram Abnormalities

Any QTcF interval (ms) result meeting the following criteria will be identified as an ECG abnormality:

Grade	Abnormality
1	Postbaseline value >450 and ≤480 msec
2	Postbaseline value >480 and ≤500 msec or postbaseline increase >30 and ≤60 msec
3	Postbaseline value >500 msec or postbaseline increase >60 msec
4	Incidence of Torsade de pointes, Ventricular tachycardia, Arrhythmia

In addition, a listing of abnormal QTc results, as identified above, will be provided with the associated grade assigned per the above table. The abnormality will be flagged as 'Confirmed' if the abnormality was observed in 2 consecutive assessments.

5.2.16 Vital Signs

For blood pressure and pulse rate, the orthostatic changes will be calculated as standing minus supine readings.

Temperatures reported in Fahrenheit will be converted to Celsius for reporting using the following formula:

Celsius = (Fahrenheit – 32)/1.8

5.2.17 Pharmacokinetic Parameters

Concentration-time data for total and unbound PLN-74809 will be analysed using noncompartmental methods in [redacted][1] in conjunction with the internet-accessible implementation of [redacted][2]

During the PK analysis, concentrations below the limit of quantitation (BLQ) up to the time of the first quantifiable concentration will be treated as zero. Embedded (values between 2 quantifiable concentrations) and terminal BLQ concentrations will be treated as "missing". PK analysis will be performed using actual time relative to dosing. AUC will be calculated using the linear-up log-down method.

The following PK parameters will be calculated for PLN-74809 on Day 1:

- C_{max}: Maximum observed plasma concentration
- AUC_{0-6h}: AUC from the time 0 to 6 hours postdose
- T_{max}: Time to maximum observed plasma concentration
- $C_{max,ub}$: Maximum observed unbound plasma concentration
- $AUC_{0-6h,\ ub}$: Unbound AUC from the time 0 to 6 hours postdose

PK parameters will be summarized using descriptive statistics.

5.3 Conventions

5.3.1 Medical Coding

Adverse events and medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 26.1. Conditions will be assigned to a system organ class and preferred term based on the Investigator-reported verbatim term.

Any medications taken (other than study drug) will be coded using the World Health Organization Drug Dictionary (WHO Drug), Version B3 Sep 2023. Medications (both prior and concomitant) will be assigned to an Anatomical Therapeutic Chemical (ATC) Level 4 drug classification and preferred name based on the medication name reported on the eCRF.

5.3.2 Data Handling

All clinical data programming will be performed using [redacted])[3]Error! Reference source not found. and based on Clinical Data Interchange Standards Consortium (CDISC) data standards.

Study Data Tabulation Model (SDTM) programming will follow SDTM version 1.7 together with SDTM implementation guide 3.3. Analytical Data Model (ADaM) programming will follow ADaM implementation guide 1.1. Specifications for SDTM and ADaM datasets are described in a separate document.

5.3.3 Summary Statistics

Continuous variables will be summarized using an 8-point summary, the number of nonmissing observations, mean, standard deviation, median, interquartile range (Q1, Q3), minimum, and maximum.

PK concentration-time data and PK parameters will be summarized using a 7-point summary, the number of nonmissing observations (n), arithmetic mean (mean), standard deviation (SD), median, minimum (min), maximum (max), and coefficient of variation (CV%).

Categorical variables will be summarized by presenting the frequency and percent. Percentages will be based on the number of nonmissing observations for the participant population, unless otherwise specified. For each variable, all categories will be shown. Zero frequencies (but not the percent) within a category will be presented.

Incidences of AEs, medical history, and concomitant medications will be reported at the participant level. Participants will only be counted once within each preferred term and system organ class under the highest severity and relationship to study drug. Percentages will be calculated using the number of participants in the treatment group for the safety population.

5.3.4 Decimal Places

For summary statistics, n will be reported as a whole number. Means, medians, and percentiles will be displayed to 1 more decimal place than the data, dispersion statistics (eg, standard deviation) will have 2 more decimal places than the data, and the minimum and maximum will be displayed to the same number of decimal places as reported in the raw data.

Where appropriate, less decimal places may be used on a case-by-case basis as denoted in the table shells.

Percentages will be displayed with 1 decimal place. All data presented in the individual participant listings will be presented as recorded on the eCRF.

5.3.5 *P*-values

P-values will be displayed to 4 decimal places. *P*-values <0.0001 will be presented as p<0.0001.

5.3.6 Data Displays

All TFLs will be generated as individual Rich Text Format (.rtf) files. Data summaries and graphical analyses will be reported within Section 14 of the CTR and individual participant data listings within Appendix 16.2 of the CTR.

Participant disposition, baseline characteristics, and demographics, will be presented by treatment group (PLN-74809 or placebo) and overall. Other summaries will be presented by treatment group (PLN-74809 or placebo) only.

Treatment group labels will be displayed as follows:

PLN-74809 160 mg (N=XX)	Placebo (N=XX)	Overall (N=XX)

Listings will be sorted in the following order: treatment group, participant, parameter, and visit unless otherwise stated. All data will be listed and participants who were not randomized will be displayed after the randomized treatment groups.

5.4 Participant Disposition

The overall total number of participants in the screened population will be summarized. The number of participants randomized will be summarized by treatment group and overall.

Participant disposition will be summarized by treatment group and overall for the safety population, as follows:

- The number of participants in each analysis population (screened, safety, ITT, PK, and PD Populations).
- The number of participants who complete the study drug.
- The number of participants who complete the study.
- The number of participants who early terminated from the study and the reason for early termination.

5.5 Protocol Deviations

Protocol deviations will be summarized by classification (major, minor, and total) and reason by treatment group and overall for the safety population. A listing of protocol deviations will be provided within Appendix 16.2 of the CTR.

5.6 Baseline Comparability

The comparability of treatment groups with respect to participant demographics and baseline characteristics will be assessed in a descriptive manner, but no formal statistical testing will be performed.

Standard continuous or categorical variable summaries will be presented by randomized treatment group for the following variables based on the safety population.

Demographic characteristics include:

- Age at Informed Consent (years)
- Sex
- Fertility Status for Women
- Ethnicity
- Race
- Weight at screening (kg)
- Height at screening (cm)
- Body Mass Index at screening (kg/m^2)
- Duration of IPF diagnosis (months), defined as the number of months from start date of first date reported for medical history preferred term 'idiopathic pulmonary fibrosis' to first dose of study drug
- Participant taking nintedanib or pirfenidone at screening
- Duration of nintedanib or pirfenidone use (months), defined as the number of months from start date of usage of nintedanib or pirfenidone to first dose of study drug
- GAP stage

A listing of demographic characteristics at baseline will be provided.

5.7 Medical History

A summary of previous and ongoing conditions at screening will be presented by randomized treatment group and overall for the safety population. All reported medical history data will be listed. Non-pharmacological procedures will be provided as a separate listing.

5.8 Prior and Concomitant Medications

Separate tabulations will be produced for prior and concomitant medications presented by randomized treatment group and overall for the safety population. Prior medications are defined as all medications started and stopped before the date of the first dose of study drug. Concomitant medications are defined as medications taken on or after the date of the first dose of study drug.

Both prior and concomitant medication verbatim terms (as recorded on the eCRFs) will be mapped to ATC Level 4 and Drug Reference Names using the WHO dictionary (version B3 Mar 2022). Prior and concomitant medications will be summarized using ATC Level 4.

5.9 Exposure to Study Drug

Extent of exposure (number of days of exposure to study drug) will be presented by randomized treatment group for the safety population.

5.10 Treatment Compliance

Treatment compliance will be summarized using descriptive statistics based on the classification in Section 5.2.12 by actual treatment group for the safety population.

5.11 Efficacy Analyses

All statistical tests will be performed using a two-tailed 5% overall significance level, unless otherwise stated. All comparisons between treatments will be reported with 95% confidence intervals for the difference.

5.11.1 Primary Endpoint

The primary endpoint is the change from baseline to week 12 in the top quartile mean SUV for the whole lung (average of the right and left lungs).

Whole lung and by lung region top quartile SUVs will be summarized using descriptive statistics by treatment groups and visit for the PD Population.

In addition, an analysis of covariance (ANCOVA) model will be used to summarize the primary endpoint. The model will include terms for baseline top quartile mean SUV and treatment group. The LS means, corresponding SEs, and 95% CI for each treatment group will be obtained from the model. An estimate for the LS mean difference (PLN-74809 vs. placebo), corresponding SE, 95% CI, and *P*-value for each dose group will also be presented.

Example [redacted] for ANCOVA model is provided below, [redacted] may be added or adjusted for ease of output and interpretation:

[redacted]

Where

base	is value at baseline
chg	is change of from baseline
socyn	is the participant's use of standard of care at baseline (Yes or No)
trt	is the dose group

Whole lung and by region metric SUVs will be presented as a box plots by treatment group (side-by-side) with all regions on the same figure.

5.11.2 Exploratory Efficacy Analysis

5.11.2.1 Other SUV metrics

The other SUV endpoints, SUVmean and SUVmax, will be summarized in a similar manner as the primary endpoint including observed change, LS mean and box plots.

5.11.2.2 Forced Vital Capacity (FVC)

Observed absolute FVC volume and observed FVC percent predicted will be summarized using descriptive statistics by treatment group and visit in the ITT population. Change from baseline in absolute FVC volume and FVC percent predicted will be assessed at Week 4, Week 8, and Week 12.

A mixed model repeated measures (MMRM) will be utilized to assess the difference between treatment groups with respect to change from baseline to Week 4, Week 8, and Week 12 of absolute FVC volume. The change of absolute FVC volume from baseline will be considered as outcome variable, whereas treatment group, visit, treatment*visit interaction, standard of care (pirfenidone or nintedanib; yes or no) status, and baseline FVC will be included as fixed effects. An unstructured covariance (UN) will be utilized as the within-participant covariance structure and, in the event that the model fails to converge, a compound symmetry structure will be used.

The MMRM model will be applied to the change from baseline in the FVC percent predicted except the outcome variable will be change from baseline in FVC percent predicted, and baseline variable will be the baseline FVC percent predicted.

The LS means, corresponding SEs, and 95% CI for each treatment group will be obtained from the model. An estimate for the LS mean difference (PLN-74809 vs. placebo), corresponding SE, 95% CI, and *P*-value for each dose group will also be presented.

Example [redacted] for MMRM model is provided below, [redacted] may be added or adjusted for ease of output and interpretation:

[redacted]

Where

base is value at baseline
chg is change of from baseline
socyn is the participant's use of standard of care at baseline (Yes or No)

trt is the dose group
visit is the visit number

5.11.2.3 Patient-Reported Outcome (PRO): a VAS for Cough Severity

Observed cough VAS score and change from baseline in cough VAS score will be summarized using descriptive statistics by treatment groups and visit for the ITT Population. All collected VAS data will be listed.

5.11.3 Exploratory Pharmacokinetic/Pharmacodynamics Analysis

5.11.3.1 Pharmacokinetics

Blood samples for determination of total and unbound PLN-74809 concentrations will be collected at predose (0 h), and at 2, 4, and 6 hours post dose on Day 1 and at predose and at least 2 hours postdose on Weeks 4 and 12. Concentration-time data will be tabulated by Day/Week and nominal time using descriptive statistics. All BLQ values will be presented as "BLQ" in the concentration listings. For presentation of the individual data and summary statistics, concentrations BLQ will be set to zero.

Individual participant and mean plasma concentration-time data will be presented graphically on linear and semi-logarithmic scales. Mean data will be plotted using nominal sample times, and individual data will be plotted using actual times. Concentrations collected outside the sampling time window will be excluded from PK analysis and may be excluded from summary statistics.

PK parameters for PLN-74809 (total and unbound) will be calculated as described in Section 5.2.17 and summarized using descriptive statistics.

5.11.3.2 Biomarker Change from Baseline

Biomarker results, PRO-C3, CTX-III_HP, and ITGB6, will be summarized using descriptive statistics by treatment group and visit for each parameter. Actual biomarker concentration at each visit, the change from baseline and percent change from baseline will be presented. The result adjusted for dilution factor will be used in summaries and listings. Samples that were hemolyzed, received ambient or with a note indicating improper storage will be excluded from summaries and listed only. If a sample has been excluded, then the change from baseline for that sample will not be calculated.

Actual biomarker concentrations will be presented as a line plot showing the mean (± SD) concentration at each visit by treatment group for each parameter.

Absolute change from baseline and percentage change from baseline will be presented as a line plot showing baseline (0) and the mean (± SD) concentration at each post-dose visit by treatment group for each parameter.

Change from baseline to each visit will also be analysed for all biomarkers using an MMRM in the same manner as described in Section 5.11.2.1, except the factor for standard of care use (Y/N) will be excluded. LS means (±SE) for each treatment group and estimates for treatment difference compared to placebo, with corresponding SE, 95% CI and *P*-value, will be provided.

5.11.3.3 MRI Parameters

MRI parameters, contrast wash-in rate (kwashin), contrast wash-out rate (kwashout), maximum or peak enhancement (ME), and area under the curve at 60 seconds (AUC_{60}) will be summarized descriptively by treatment groups and visit for observed value and change from baseline.

5.11.3.4 Relationships Between Endpoints

The Spearman correlation will be utilized to assess the correlations between the following endpoints in each treatment group. The Spearman correlation coefficient will be presented with the *P*-value for each pair of endpoints.

- By region SUV to by region SUV using change from baseline in top quartile SUV
- Change from baseline in whole lung top quartile SUV, change from baseline in PRO-C3, change from baseline in CTX-III_HP, change from baseline in ITGB6, change from baseline in FVC (mL), change from baseline in FVC percent predicted (%), and observed PLN-74809 Week 12 pre-dose concentration (total and unbound).

Sample [redacted] for Spearman correlation:

[redacted]

5.12 Safety Analyses

The safety analyses will be presented by the treatment received for the safety population.

5.12.1 Adverse Events

AE analyses will be presented by the treatment received for the safety population. Tabulations will be presented overall and by standard of care (Yes, No).

AEs will be collected from the time of informed consent through completion of the participant's last study visit.

A treatment emergent adverse event (TEAE) is defined as:

- Any AE that has an onset on or after the first dose of study drug through completion of the last study visit.

- Any pre-existing AE that has worsened in severity on or after the first dose of study drug through completion of the last study visit.

AEs occurring prior to first dose are considered nontreatment emergent and will be listed only.

The Investigator will determine the relationship of the AE to treatment (related, not related). A study drug-related AE is defined as an AE as being possibly or probably related to the study drug. If an AE has missing relationship it is assumed to be related to the study drug for analysis purposes. Same rule is applied to study procedure-related AE.

Severity of the AE will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) grading system (Version 5.0): Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (Severe), Grade 4 (Life-Threatening), Grade 5 (Fatal). Grade 3 (Severe) will be assumed for an AE with missing grade.

An overall summary of AEs (incidence and number of events) will be presented by treatment group and overall, for the following:

- TEAEs
- TEAEs Related to Study Drug
- TEAEs Related to a Study Procedure
- Serious TEAEs
- Serious TEAEs Related to Study Drug
- TEAEs of CTCAE Grade 3 or Higher
- TEAEs of CTCAE Grade 3 or Higher Related to Study Drug
- TEAEs Leading to Interruption of Study Drug
- TEAE Leading to Early Discontinuation of Study
- TEAEs Leading to Early Termination from Study
- TEAEs Leading to Death

Summaries of TEAEs (by participant incidence) will be presented by system organ class and preferred term, by treatment group and overall, for the following:

- TEAEs
- TEAEs Related to Study Drug
- Serious TEAEs
- Serious TEAEs Related to Study Drug
- TEAEs Related to a Study Procedure
- TEAEs of CTCAE Grade 3 or Higher
- TEAEs of CTCAE Grade 3 or Higher Related to Study Drug
- TEAEs Leading to Interruption of Study Drug

- TEAEs Leading to Early Discontinuation of Study Drug (action taken with study treatment as 'Drug Withdrawn' or 'Drug Interrupted Permanently')
- TEAEs Leading to Early Termination from Study
- TEAEs Leading to Death
- TEAEs by System organ class, Preferred term and Maximum Grade (incidence only)
- ECG-Related or Potentially Cardiac-Related TEAEs (incidence only)

In addition, TEAEs by preferred term will also be summarized.

In addition, listings of all reported AEs and SAEs will be provided in Appendix 16.2.7 of the CTR:

- AEs
- TEAEs Leading to Early Discontinuation of Study Drug
- TEAEs Leading to Early Termination from Study
- TEAEs Leading to Death
- Serious AEs

System organ class will be presented in descending order of frequency in the PLN-74809 group and then alphabetically. Preferred terms will be displayed in descending order of frequency in the PLN-74809 group and then alphabetically.

For the summary by severity, participants reporting more than one AE per system organ class and preferred term will only be counted once for the most severe event.

5.12.2 Electrocardiogram-related/Potentially Cardiac-related Treatment-emergent Adverse Events

Participants who have TEAEs with any of the following preferred terms will be identified and reported on a separate summary:

- Electrocardiogram QT prolonged
- Syncope
- Seizure
- Torsade de pointes
- Ventricular tachycardia
- Ventricular fibrillation
- Ventricular flutter
- Ventricular arrhythmia
- Sudden death

5.12.3 Laboratory Data

Descriptive statistics of the observed values and change from baseline (continuous data) will be presented by treatment group and visit for each hematology, coagulation, urinalysis, and serum chemistry parameter. Each measurement (continuous data) will be classed as below, within, or above the normal range, based on normal ranges supplied by the laboratory used. Shift tables in relation to the normal range from baseline to each follow-up visit will be presented. A summary table showing the numbers of participants with at least one abnormal result at any time post-baseline will be presented by laboratory parameter.

Clinical laboratory test parameters will be listed, using the CTCAE grading scale, for individual participants, with values outside the reference ranges flagged. Summary statistics will be calculated for each parameter and summarized by treatment group.

All laboratory data will be listed. Pregnancy test data will be listed only. Abnormal laboratory data will also be listed separately.

5.12.4 Vital Signs

Descriptive statistics for observed values and changes from baseline in the following vital signs will be presented by treatment group and visit:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Heart rate (bpm)
- Temperature (degrees Celsius)
- Body weight (kg)
- Pulse oximetry (%)

5.12.5 Electrocardiogram Data

Descriptive statistics for observed values and changes from baseline in the following ECG variables will be tabulated at each follow-up:

- Heart rate (bpm)
- PR interval (ms)
- RR interval (ms)
- QRS complex (ms)
- QT interval (ms)
- QTc interval (ms) [Fridericia's formula - QTcF]

Shift tables in relation to the overall interpretation (Normal, Abnormal NCS, and Abnormal CS) from baseline to each follow-up visit will be presented.

A summary table showing the numbers of participants by ECG grades (Section 5.2.15), at any time, will be presented.

All ECG data will be listed.

5.12.6 Physical Examination

Details of clinically significant physical examination findings will be listed.

6 MULTIPLICITY

No multiplicity testing is planned.

7 INTERIM ANALYSIS

No interim analyses are planned.

8 DATA SAFETY MONITORING BOARD ANALYSIS

No data safety monitoring board (DSMB) analyses are planned.

9 CHANGES TO PLANNED PROTOCOL ANALYSIS

The following are changes to planned protocol analyses:

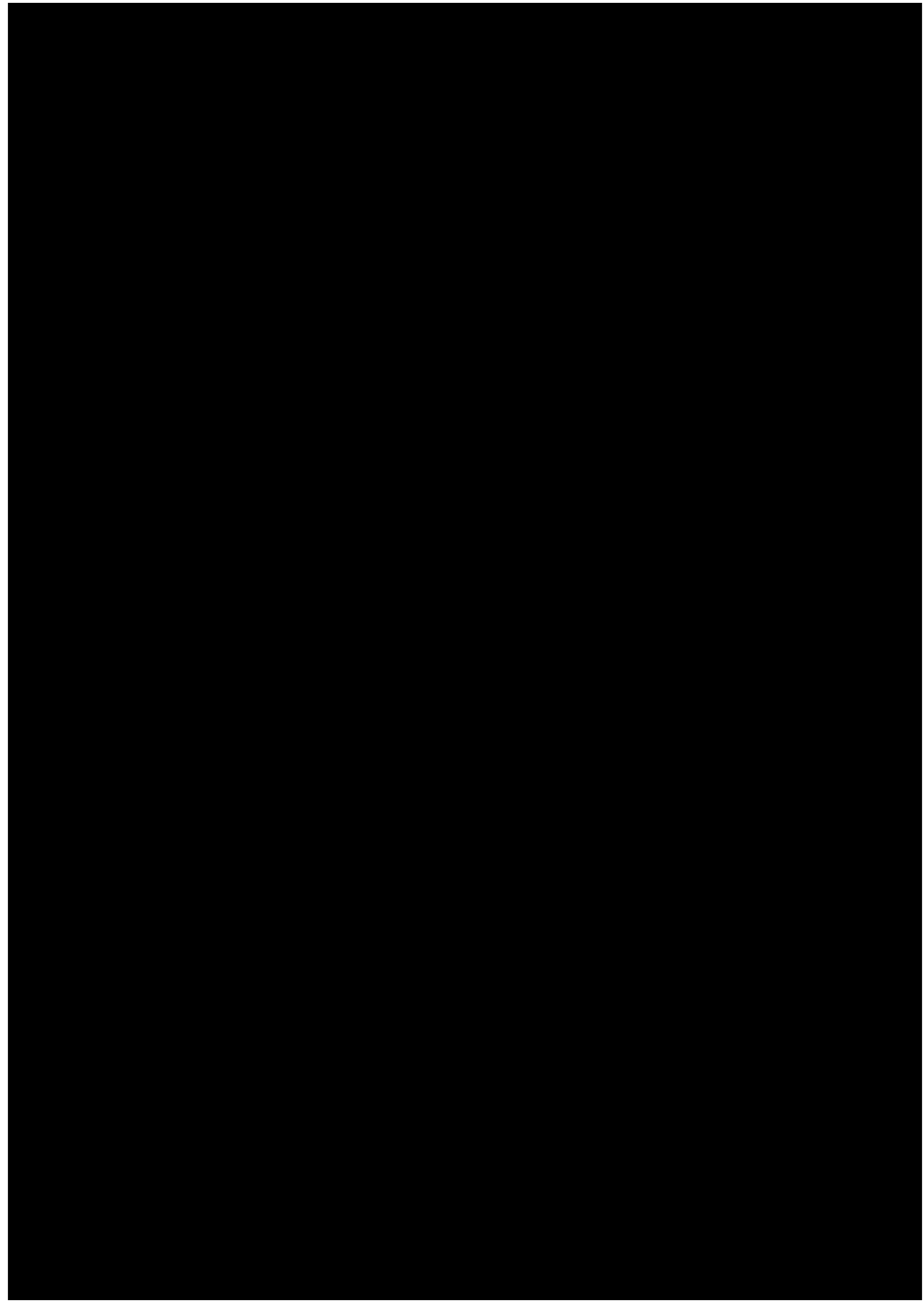
- Clarification that the primary endpoint is the standardized up take value for the whole lung.
- The set of biomarkers to be analysed in the Protocol Section 7.10.3 was changed to only PRO-C3 based on evidence from clinical studies completed post protocol finalization.
- New biomarkers, CTX-III_HP and ITGB6, were added based on evidence from clinical studies completed post protocol finalization.
- Baseline FVC values will be assessed pre-dose only and not an average of screening and pre-dose.
- End of study FVC (average of Week 12 (on-treatment) and Week 14 (off-treatment) will not be reported as this metric was identified as uninformative in clinical studies completed post protocol finalization.
- Grading of laboratory assessments, not identified as AEs, will not be conducted.

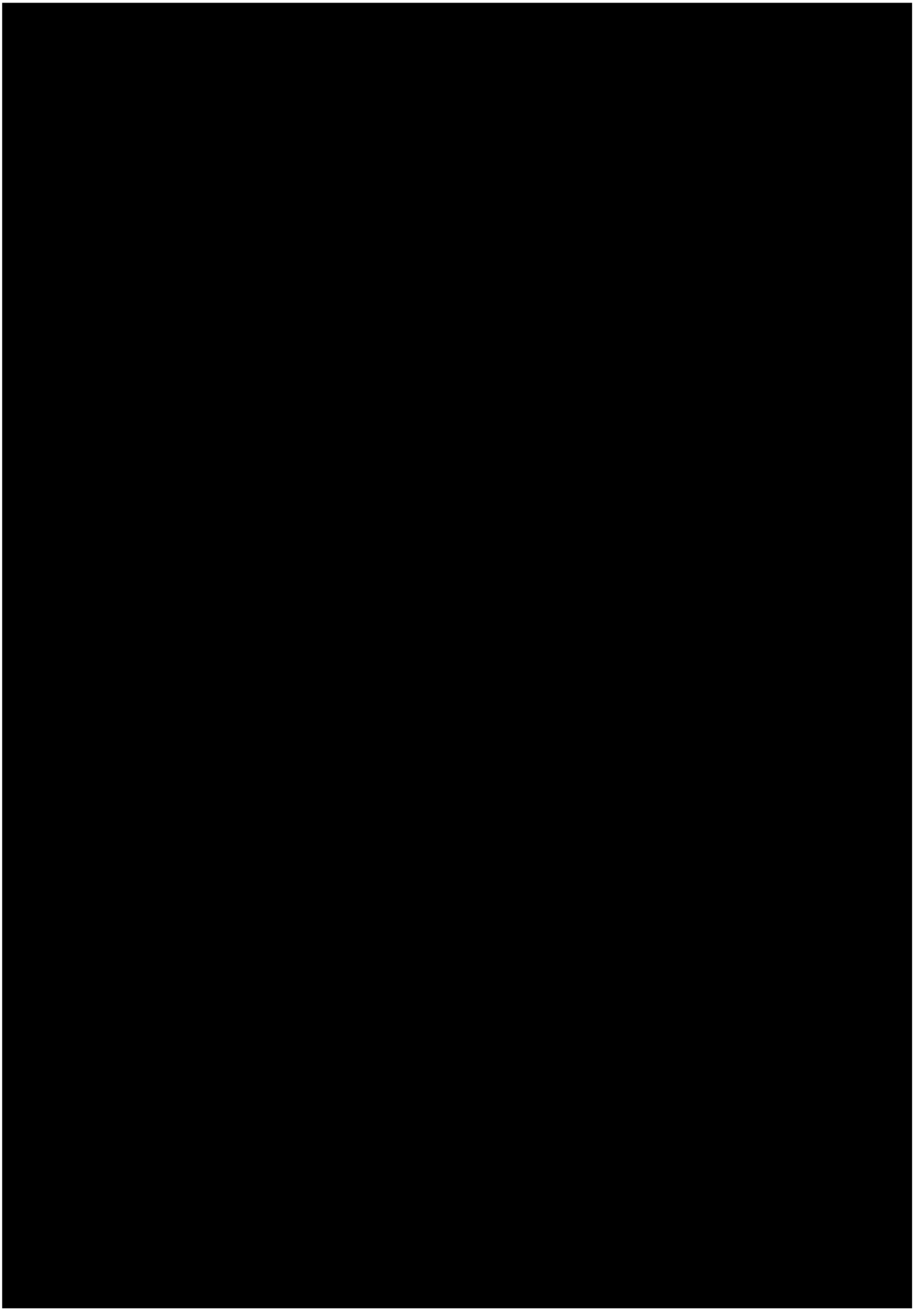
10 REFERENCES

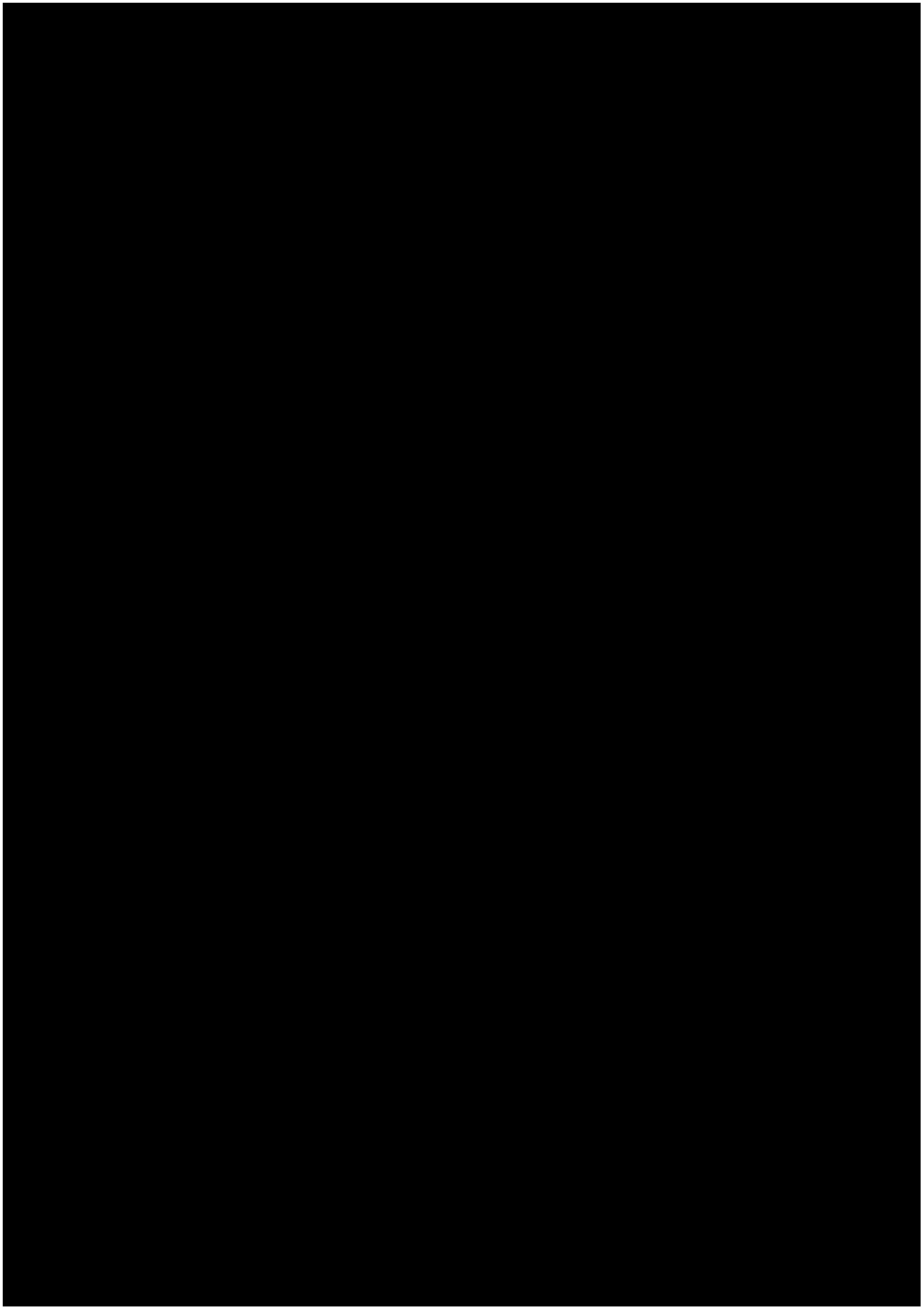
1. [redacted]
2. [redacted]
3. [redacted]

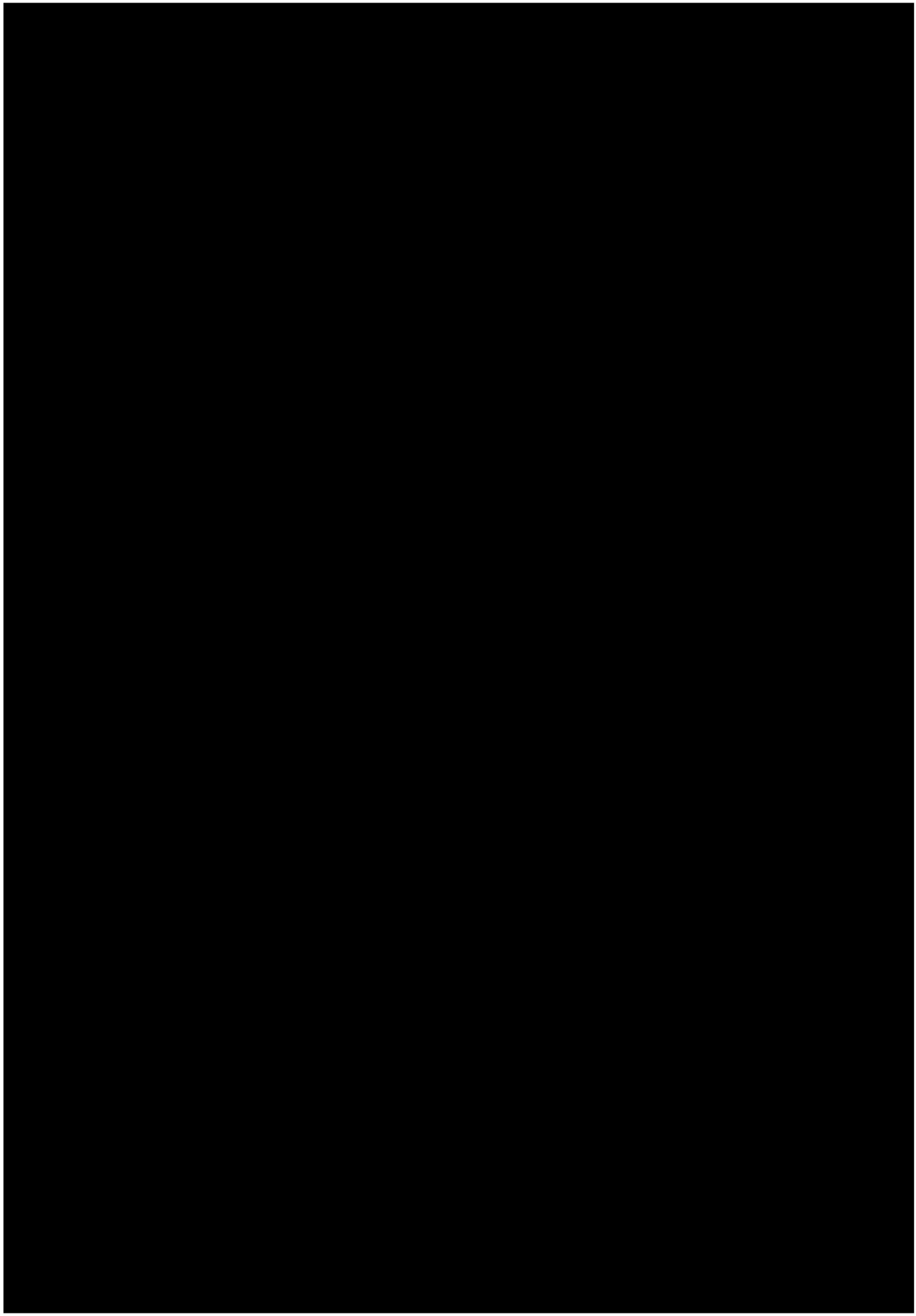
[redacted]	**Controlled Quality Management Document**	
[redacted]	Sponsor:	Pliant Therapeutics Inc
	Protocol Number:	PLN-74809-IPF-205
STATISTICAL ANALYSIS PLAN		

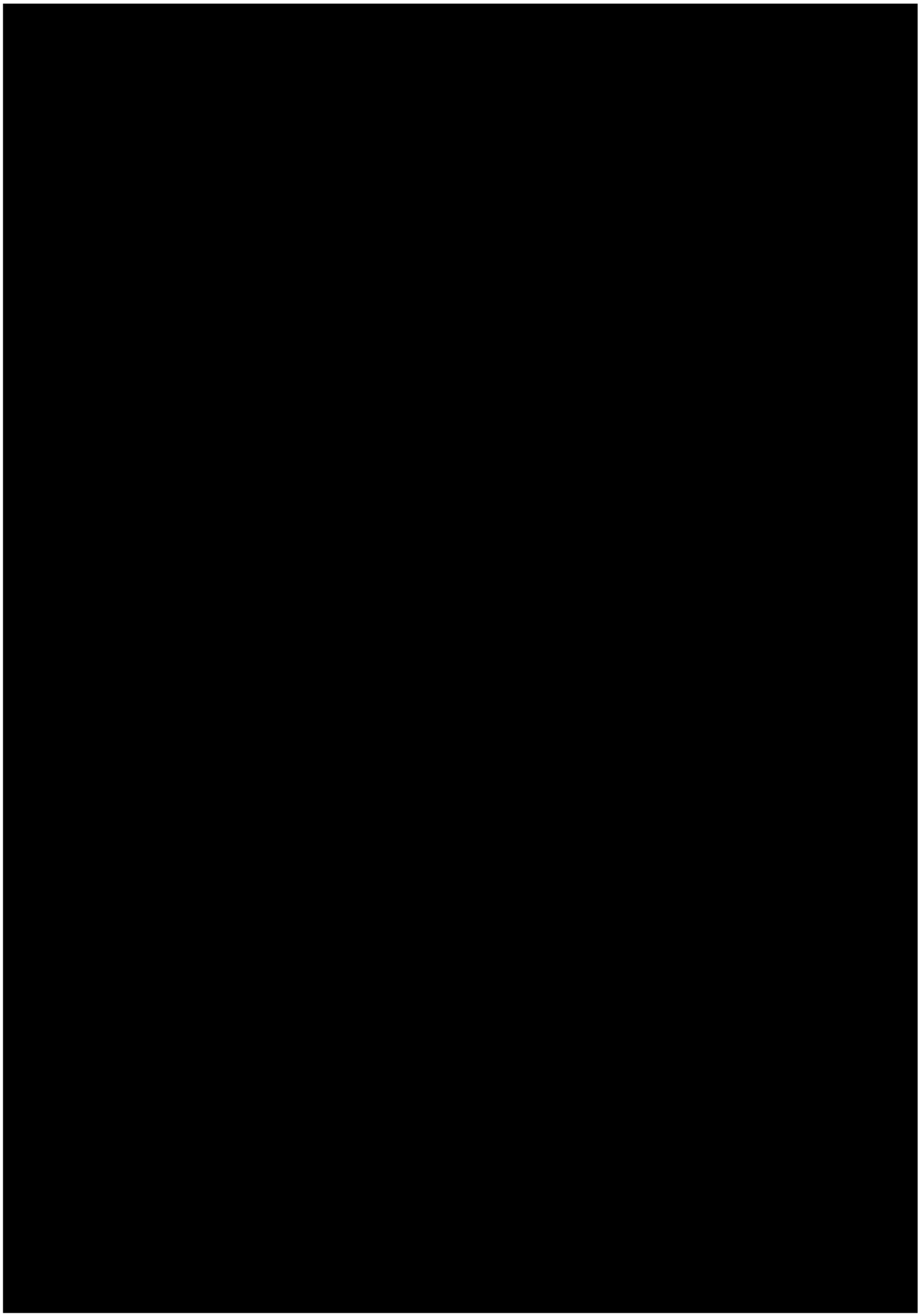
[redacted]

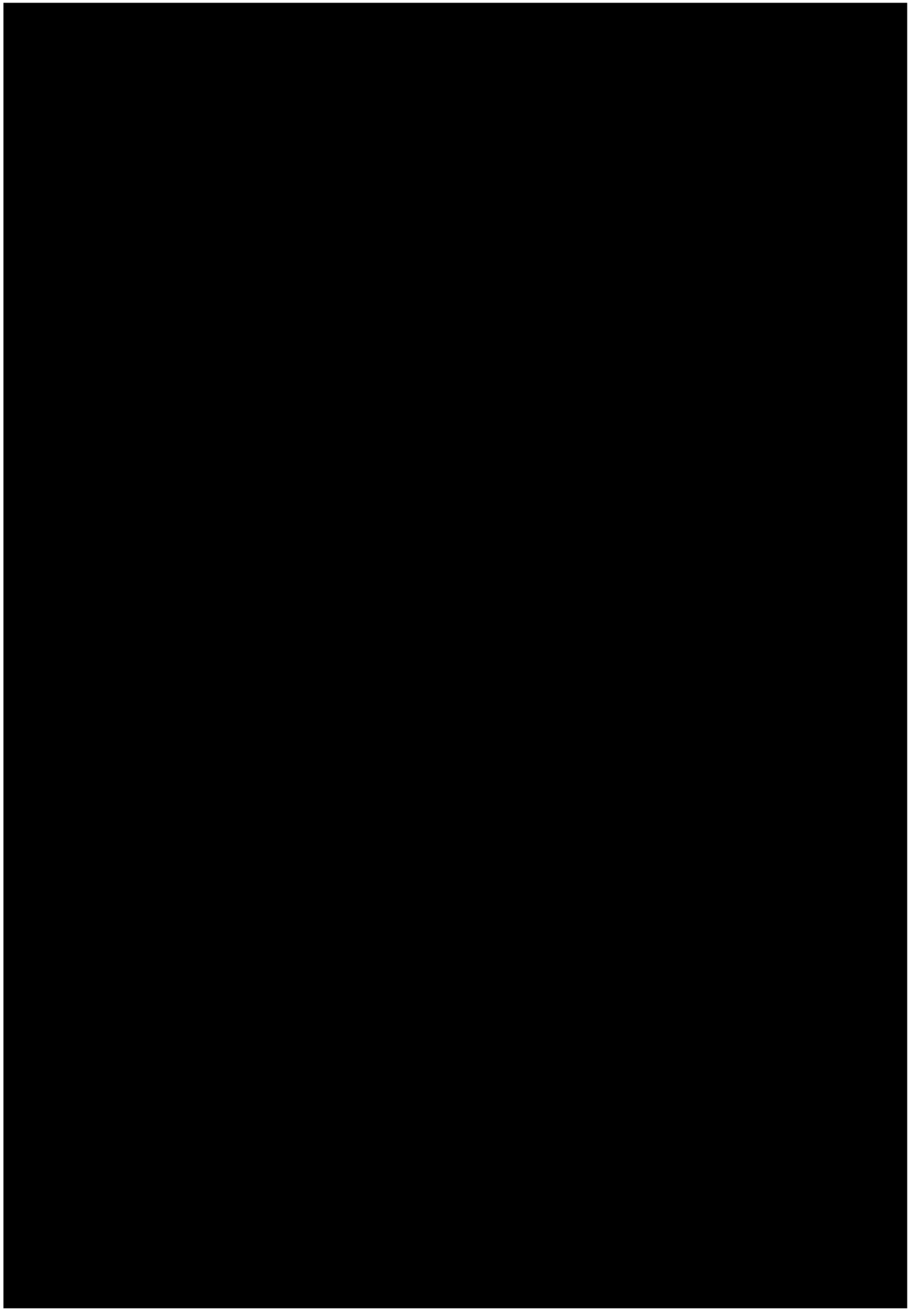


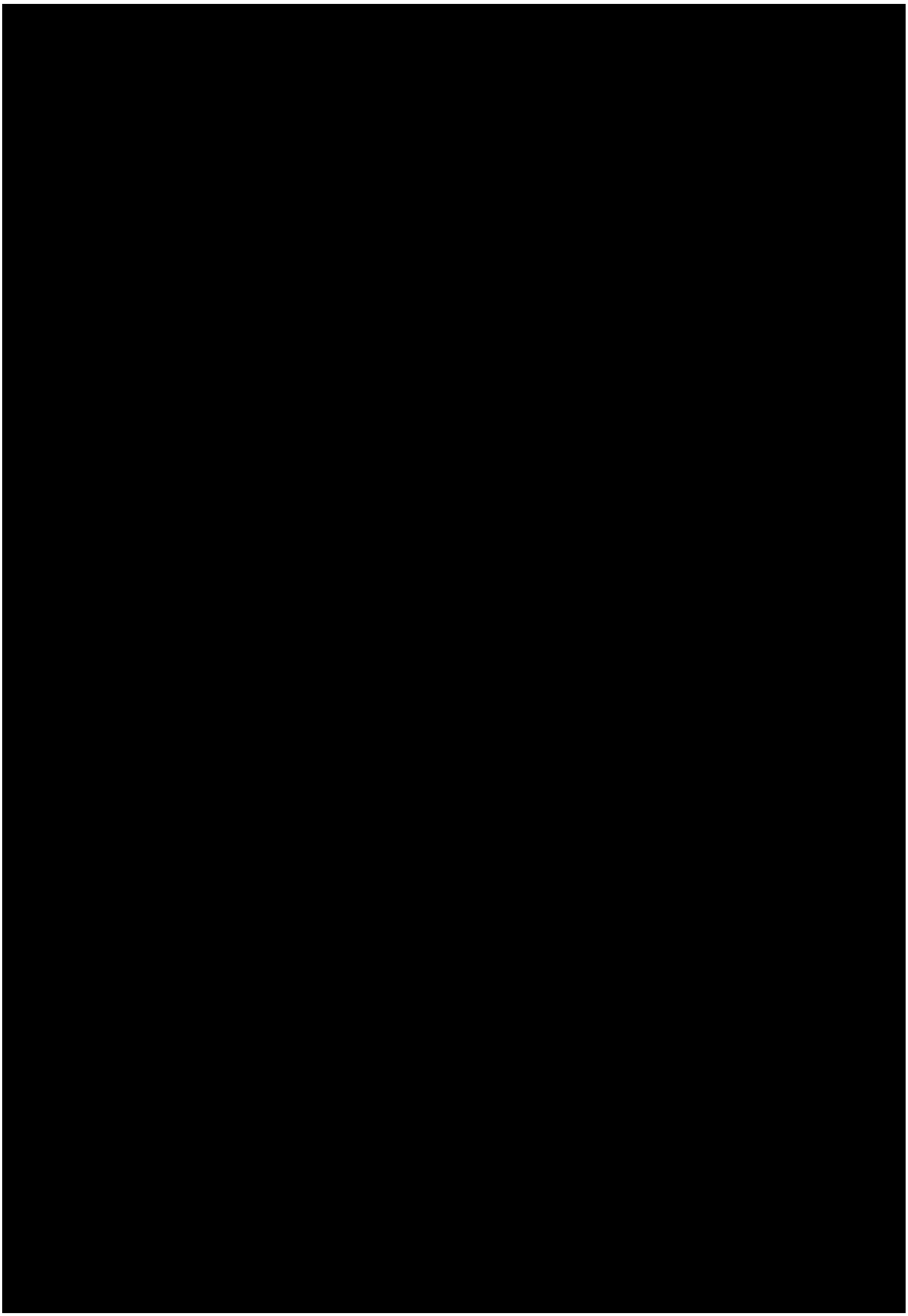


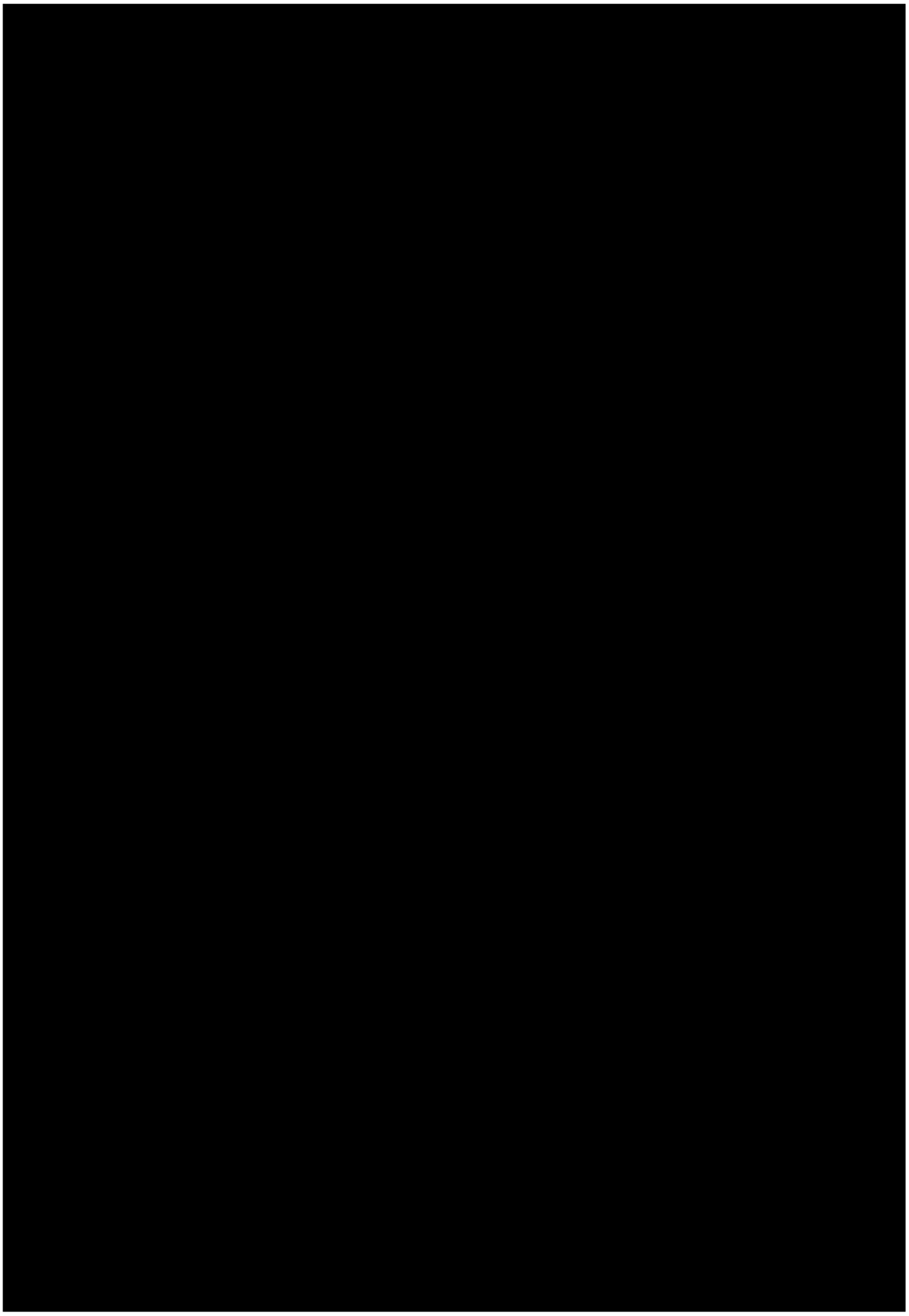


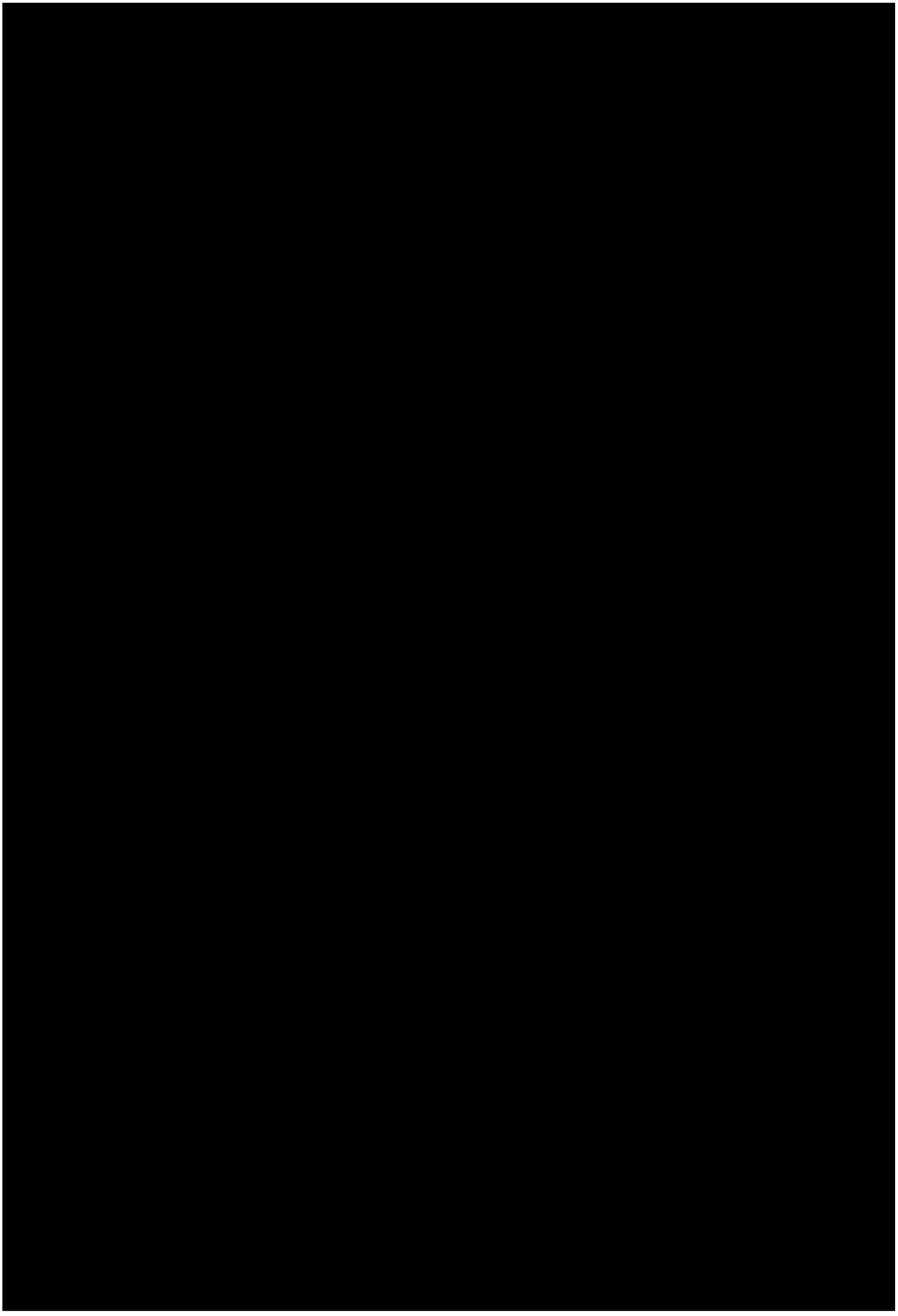












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