NOVARTIS

Clinical Development

AIN457/ Secukinumab/Cosentyx®

CAIN457S12201 / NCT04300296

A proof of concept study to evaluate the efficacy, safety and tolerability of secukinumab 300 mg over 32 weeks in adult patients with biopsy-proven forms of lichen planus not adequately controlled with topical therapies - PRELUDE

Statistical Analysis Plan (SAP)

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Document History – Changes compared to previous final version of SAP

Date	Reason for update	Outcome for update	Section and title impacted (Current)
2020/7/17	Creation of final version	N/A - First version	NA
2021/11/23	To address comments during dry run preparation	• Amendment 1	[redacted] • Section 2.4.1: clarified the definition of duration of exposure. [redacted] • Section 2.6 [redacted]: specified the use of data after treatment discontinuation for secondary [redacted] endpoints. • Section 2.7.1: added analyses of exposure-adjusted incidence rate of AEs and risks. [redacted] • Section 5.4: clarified the description of the estimand framework. • Section 5.5.2: added the section “Multiple imputations for supplementary analysis: Hypothetical scenario”. • Section 5.6: Rule of exclusion criteria of analysis sets. Added a PD “M-INCL05-randomized in error” which causes subjects to be excluded from the Randomized set.
2021/12/14	To clarify endpoints and analyses following dry run completion	• Amendment 2	• Section 1.1 and 2.14: removed the descriptions no longer applicable after dry run. • Section 2.3.2: updated the disease history variables that would be summarized in the baseline characteristics table. • Section 2.6.1: added the analyses of Scalpdex by dimension.

2022/5/19	To add analysis for the final CSR	• Amendment 3	• Table 2-1: updated the treatment group labels. • Section 2.6.3: updated the BOCF imputation from treatment period 1 to the entire treatment period. [redacted]

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List of abbreviations

AE	Adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Classification
CLP	Cutaneous lichen planus
CSR	Clinical Study report
DLQI	Dermatology Life Quality Index
FAS	Full Analysis Set
eCRF	Electronic Case Report Form
EOT	End of treatment
[redacted]	[redacted]
IGA	Investigator's Global Assessment
LP	Lichen planus
LPP	Lichen planopilaris
LPPAI	Lichen Planopilaris Activity Index
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MLP	Mucosal lichen planus
NRS	Numeric Rating Scale
OLPSSM	Oral Lichen Planus Symptom Severity Measure
PBO	Placebo
[redacted]	[redacted]
[redacted]	[redacted]
PT	Preferred Term
[redacted]	[redacted]
PD	Pharmacodynamics
PRO	Patient-reported Outcomes
PSAD	Physician Assessment of Surface Area of Disease
Q2W	Once every 2 weeks

Q4W	Once every 4 weeks
RAP	Report and Analysis Process
RAS	Randomized Analysis Set
REU	Reticular Erythematous Ulcerative
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOC	System Organ Class

1 Introduction

Data will be analyzed by Novartis according to the data analysis [Section 12] of the study protocol that is available in [Appendix 16.1.1 of the CSR]. Important information is given in the following sections and details are provided, as applicable, in [Appendix 16.1.9 of the CSR].

This document covers statistical and analytical plans for the primary endpoint analysis i.e after all subjects have completed their Week 16 visit as well for the final analysis i.e after all subjects have completed the follow up period following the 32 week treatment period.

1.1 Study design

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial assessing the efficacy and safety of secukinumab 300 mg in two different dosing regimens in patients with biopsy-proven forms of lichen planus.

The study consists of three cohorts (one cohort per lichen planus subtype: cutaneous lichen planus (CLP), mucosal lichen planus (MLP) and lichen planopilaris (LPP)) and 4 study periods.

Patients are assigned to one of the three cohorts based on their **predominant** subtype and undergo a biopsy to confirm the clinical diagnosis at the screening visit:

- **Predominantly cutaneous** lichen planus
- **Predominantly mucosal** lichen planus
- **Lichen planopilaris**

Each cohort will follow the same study design across the 4 periods:

- **Screening Period**: up to 4 weeks prior to baseline
- **Treatment Period 1**: baseline to Week 16
- **Treatment Period 2**: Week 16 to Week 32
- **Follow-up**: 8 weeks after Week 32

Screening period:

A screening period of up to 4 weeks is used to assess patient´s eligibility for the trial and to washout/ adjust prohibited medications. The screening period covers the time from the signature of informed consent/screening visit (-4 weeks) to the randomization visit (Week 0).

Treatment Period 1:

Treatment Period 1 is placebo-controlled and covers the time from Week 0 (randomization visit) to Week 16. Patients who meet all eligibility criteria are randomized in a 2:1 ratio to one of the following two treatment arms **within** their cohort:

- **Secukinumab 300 mg every 4 weeks (Q4W) arm**: subjects receive a weekly induction treatment from baseline to Week 4 followed by secukinumab 300 mg every 4 weeks.

- **Placebo for 16 weeks followed by secukinumab 300 mg every 2 weeks (Q2W) arm:** subjects receive matching placebo injections.

Thirty-six patients will be randomized per cohort, 24 to active and 12 to placebo treatment, which means that the study will enroll approximately 108 subjects in total.

In Treatment Period 1 all subjects receive weekly subcutaneous injections of blinded study drug (either 300 mg secukinumab or placebo) at Weeks 0, 1, 2, 3 and 4. Thereafter the frequency of blinded study drug injections for all subjects is every 4 weeks up to Week 16. Home administration of study drug is **not** allowed during Treatment Period 1, except for the case of a pandemic. Subjects who complete Treatment Period 1 roll over to Treatment Period 2 at the Week 16 visit. The only exception are subjects from the placebo for 16 weeks followed by secukinumab 300 mg every 2 weeks arm, who achieve spontaneous remission at the Week 16 visit. Spontaneous remission is defined as an IGA of 0 or 1 at Week 16. These subjects do **not** proceed to Treatment Period 2 to avoid unnecessary treatment. Instead, they will directly enter the Follow-up Period after the Week 16 visit.

Treatment Period 2:

Treatment Period 2 starts at the Week 16 visit and covers the time until the Week 32 visit.

Depending on the treatment arm, subjects receive the following treatments:

- **Secukinumab 300 mg Q4W arm**: subjects receive continued treatment with secukinumab 300 mg every 4 weeks plus matching placebo injections to maintain treatment blinding.
- **Placebo for 16 weeks followed by secukinumab 300 mg Q2W arm**: subjects are switched to active treatment with secukinumab 300 mg **every 2 weeks** including a weekly induction starting from Week 16 to Week 20, with the exception of subjects achieving remission by Week 16.

The Week 16 injection is the first injection of Treatment Period 2.

Treatment remains blinded during Treatment Period 2. This means that starting at the Week 16 visit all subjects receive an induction consisting of weekly blinded study drug injections (either secukinumab 300 mg or placebo) at Weeks 16, 17, 18, 19 and 20, followed by blinded study drug injections every 2 weeks.

The last study drug injection is administered at Week 30. The end of Treatment Period 2 is Week 32. After Week 32, all subjects enter the Follow-up Period.

Subjects who discontinue study treatment prematurely for any reason other than withdrawal of informed consent should **not** be considered as discontinued from the study. Subjects should continue attending planned site visits and perform study assessments until the last visit of the treatment period during which they discontinue (Week 16 or Week 32).

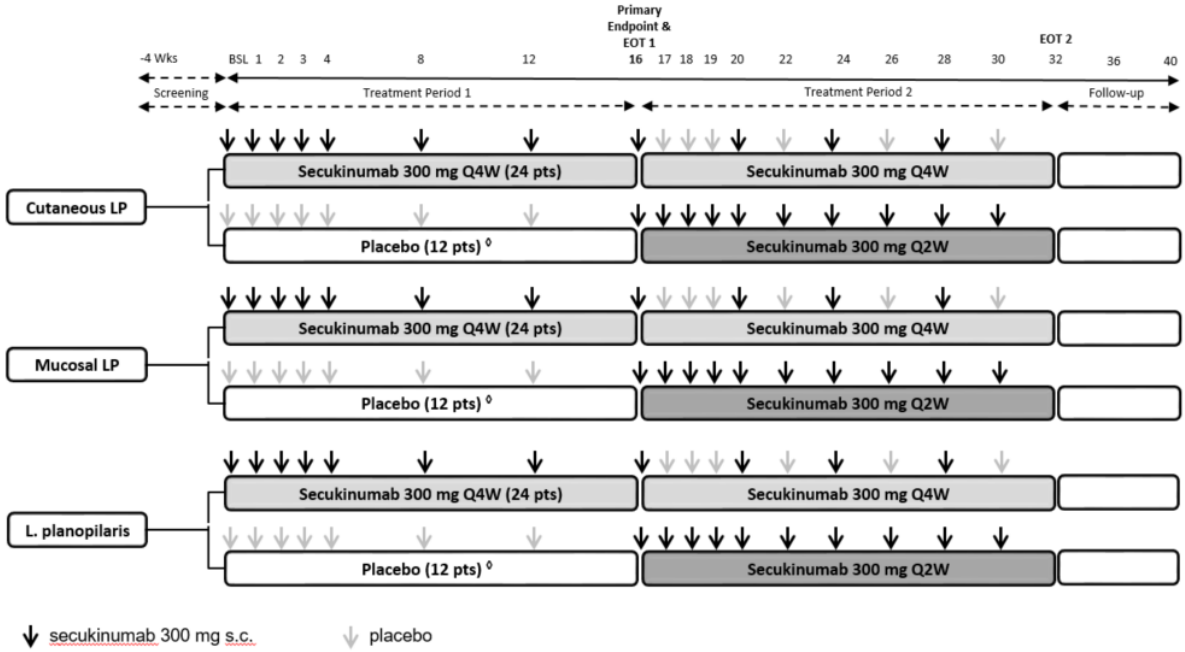
Subjects, whether they are willing to continue attending further study visits or not, should attend the End of Treatment visit (EOT) during which they discontinued (EOT 1 for discontinuation

during Treatment Period 1 and EOT 2 for discontinuation during Treatment Period 2). EOT 1 should be performed 4 weeks after the last dose of study drug, and EOT 2 should be performed 2 weeks after last dose of study drug.

Follow-up:

There is an 8-week Follow-up Period after Week 32. The End of Study (EOS) is reached at Week 40. If a subject discontinues study during Follow-up period, visit Week 40 has to be performed.

Figure 1-1 Study design



◊ Patients in the placebo treatment arms roll over to a Q2W dosing regimen after Week 16, except for patients who achieved an IGA of 0 or 1 at Week 16. These patients directly enter the Follow-up Period after Week 16. **EOT** End of Treatment, **LP** Lichen planus, **pts** patients, **Q4W** every 4 weeks, **Q2W** every 2 weeks

The primary endpoint will be evaluated at Week 16, where Week 16 represents a widely used and well-accepted timing for the assessment of key endpoints in several inflammatory skin diseases such as psoriasis, hidradenitis suppurativa or atopic dermatitis, as well as an established timepoint to detect the efficacy of secukinumab. The total study duration, up to 32 weeks of treatment, allows the collection of long-term efficacy and safety data beyond 16 weeks of treatment. Subjects who have been on placebo treatment in Treatment Period 1 are switched to active treatment with secukinumab 300 mg every 2 weeks (starting with the regular weekly induction). This enables placebo treated patients to receive active treatment during the trial as well. Furthermore, it allows the assessment of efficacy and safety of the 2-weekly dosing regimen in lichen planus.

The purpose of this primary endpoint analysis is to assess whether secukinumab shows efficacy and safety in the selected lichen planus subtypes at an early time point (proof of concept). This

enables planning of further clinical development of secukinumab in lichen planus. At the end of the study, a final analysis will be performed once all patients have completed their last study visit. All patients, investigators and site personnel will remain blinded until the final database lock.

Further analyses are currently not planned. However, an unscheduled analysis could be conducted if a compelling reason arises, for example, if requested by health authorities.

1.2 Study objectives and endpoints

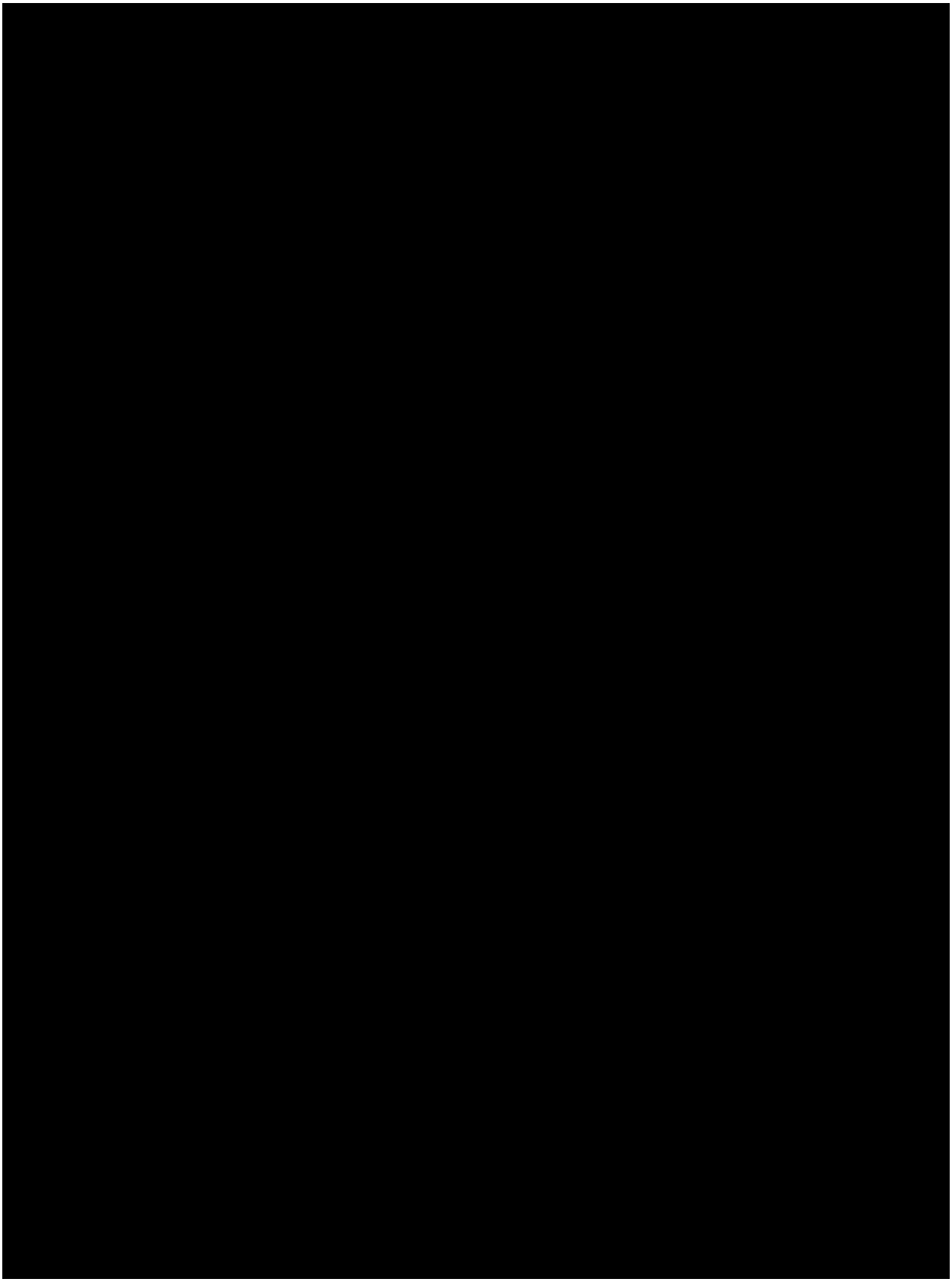
The purpose of this proof of concept study is to elucidate the efficacy of secukinumab in the treatment of adult patients with biopsy-proven lichen planus not adequately controlled by topical therapies and to assess the safety and tolerability over 32 weeks.

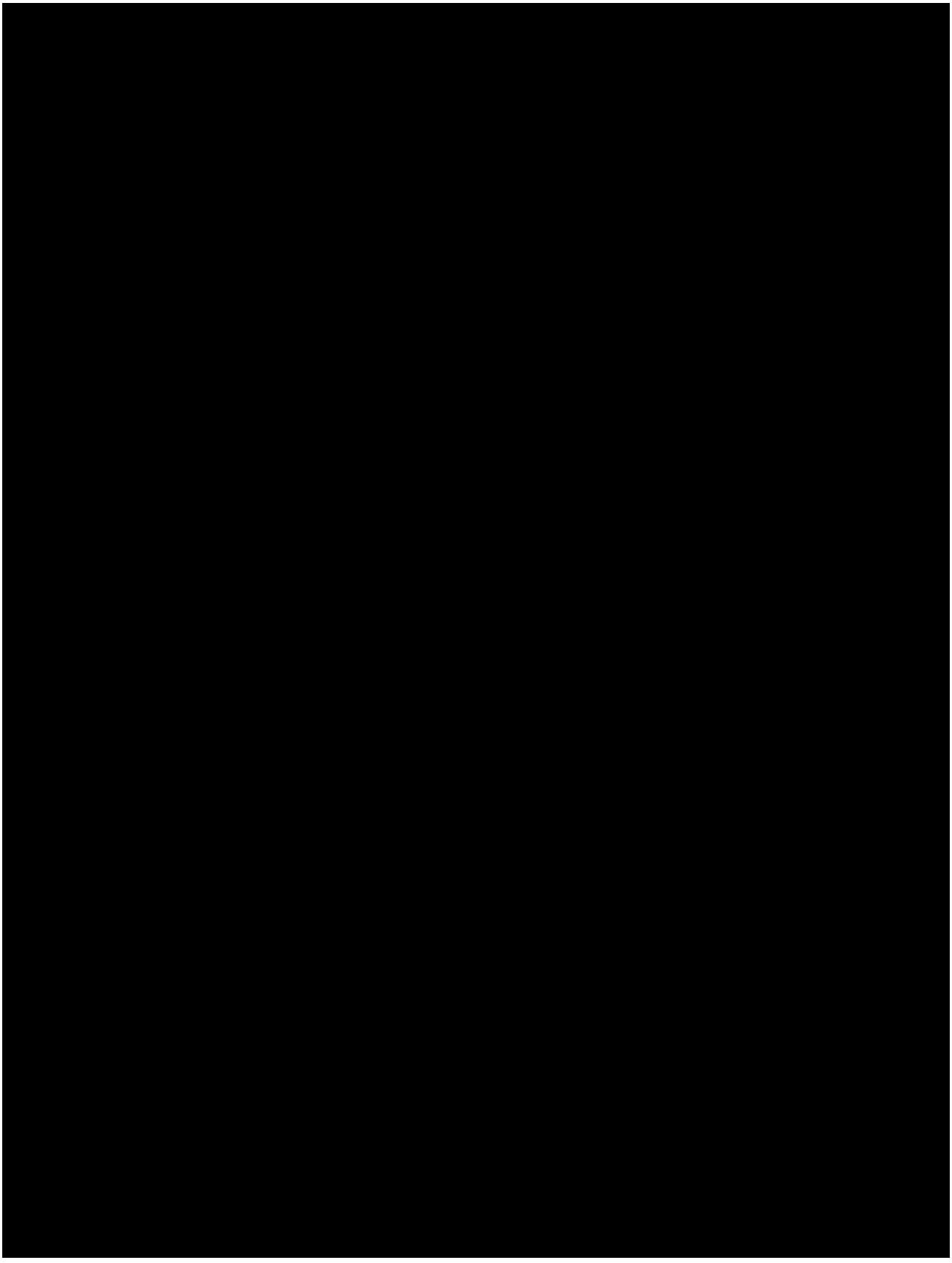
Table 1-1 Objectives and related endpoints.

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To demonstrate the clinical efficacy of secukinumab 300 mg every 4 weeks (Q4W) in subjects with cutaneous lichen planus (CLP), mucosal lichen planus (MLP), or lichen planopilaris (LPP) inadequately controlled by topical therapies, with respect to improvement in Investigator's Global Assessment (IGA) response by Week 16, compared to placebo.	• Achievement of IGA response at Week 16 *Patients diagnosed with biopsy-proven forms of CLP, MLP or LPP will be considered responders if they achieve an absolute IGA score ≤2 at Week 16*
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• The secondary objectives of this trial comprise the following: - evaluate the efficacy of secukinumab 300 mg Q4W compared to placebo throughout 16 weeks in Treatment Period 1; - evaluate the long term efficacy of secukinumab 300 mg Q4W throughout 32 weeks in Treatment Period 2; - evaluate the efficacy of secukinumab 300 mg Q2W in Treatment Period 2; - evaluate the safety profile of secukinumab 300 mg throughout the duration of the study. Detailed assessments are described the next section.	
All subtypes Investigator's Global Assessment (IGA)	• Achievement of at least 2 points improvement from baseline in the IGA score at Week 16 and 32, and throughout the duration of the study • Achievement of IGA 0/1 score at Week 16 and 32, and throughout the duration of the study

Objective(s)	Endpoint(s)
• Dermatology Life Quality Index (DLQI)	• Absolute and relative change in DLQI from baseline to Week 16 and 32, and throughout the duration of the study
	• Achievement of DLQI 0/1 score at Week 16 and 32, and throughout the duration of the study, among the subset of subjects with DLQI ≥2 at baseline
• Patient assessment of itch (NRS)	• Absolute and relative change in NRS from baseline to Week 16 and 32, and throughout the duration of the study
• Patient assessment of pain (NRS)	• Absolute and relative change in NRS from baseline to Week 16 and 32, and throughout the duration of the study
• To assess the safety and tolerability of secukinumab in subjects with lichen planus.	• Adverse events, laboratory values, vital signs
Cutaneous Lichen Planus (CLP)	
• Physician Assessment of Surface Area of Disease (PSAD) for Skin Disease	• Absolute and relative frequencies in PSAD from baseline to Week 16 and 32, and throughout the duration of the study
Mucosal Lichen Planus (MLP)	
• Reticular Erythematous Ulcerative (REU) score	• Absolute and relative change in REU score from baseline to Week 16 and 32, and throughout the duration of the study
• Oral Lichen Planus Symptoms Severity Measure (OLPSSM) score	• Absolute and relative change in OLPSSM score from baseline to week 16 and 32, and throughout the duration of the study
Lichen Planopilaris (LPP)	
• LPP Activity Index (LPPAI)	• Absolute and relative change in LPPAI score from baseline to Week 16 and 32, and throughout the duration of the study
• SCALPDEX Questionnaire	• Absolute and relative change in SCALPDEX Questionnaire score from baseline to Week 16 and 32, and throughout the duration of the study

[redacted]





2 Statistical methods

2.1 Data analysis general information

Novartis will be performing the analysis. Statistical software SAS version 9.4 or later will be used.

All data will be analyzed separately for each cohort (predominantly CLP, predominantly MLP, LPP), unless specified otherwise.

Summary statistics for continuous variables will include N, mean, standard deviation, minimum, lower quartile, median, upper quartile, maximum. Summary statistics for discrete variables will be presented in contingency tables and will include absolute and relative frequencies.

All listings will be presented by cohort and treatment groups.

Footnotes in the outputs will be kept to a minimum.

Footnotes will generally be provided for

- abbreviations used in the output; abbreviations used on several outputs, e.g. for listings in [Appendix 16.2] can be presented on a separate page and do not have to be repeated as footnotes on each listing
- sorting order of categories, e.g. for sorting within MedDRA (Medical Dictionary for Regulatory Activities) hierarchy levels
- MedDRA version used for reporting of MedDRA coded data

Footnotes will generally NOT be given for

- units displayed on the output
- interpretation of results (e.g. “odds ratio larger 1 favors active treatment”)
- information that can be retrieved from the statistical section of the clinical study report (CSR) unless it is not identifiable from the output, e.g.
  - explanation of analysis model used unless results of more than one model are displayed in an output
  - derivations of variables (e.g. BMI will not be explained in a footnote)
- information that will be provided in the clinical study protocol and/or methods section of the CSR (e.g. baseline definition if this is specified in the statistical section of the CSR)

2.1.1 General definitions

2.1.1.1 Study Day 1 and other study days

The first day of administration of randomized study treatment (first dose) is defined as *Study*

Day 1 or *Day 1*.

All other study days will be labeled relative to Day 1. For event dates on or after Day 1, study day for an event date is calculated as Date of event – [Day 1] + 1, i.e., Day 2, Day 3, etc., will be one day, two days, etc., after Day 1, respectively. For event dates before Day 1, study day for an event date is calculated as Date of event – [Day 1], i.e., Day -1, Day -2, etc., will be one day, two days, etc., before Day 1, respectively. Duration of an event will be calculated as (Event end date – Event start date + 1).

The descriptor "Day 0" will not be used.

2.1.1.2 Screening, baseline and post-baseline definitions

Screening refers to any procedures (e.g., checking inclusion and exclusion criteria) performed prior to the first dose of study treatment. Per protocol, subject informed consent must be obtained prior to performing any study related activity. The date of signing informed consent is the start date of screening period. Any assessment obtained during the screening period will be labeled screening assessment. Assessments made on Day 1 may occur before or after the first dose.

For *efficacy* analyses, baseline is the last assessment (including unscheduled visits) obtained on or before the randomization day. All assessments obtained after randomization are considered as post-baseline unless otherwise specified.

For *safety* analyses, baseline is the last assessment (including unscheduled visits) obtained (on or) before the first dose (day) of study treatment. All assessments obtained after the first dose (day) of study treatment are considered as post-baseline unless otherwise specified.

Of note, baseline will be derived based on randomization day or first dose day, exact randomization or dosing time is not considered.

2.1.1.3 Day of last dose of study treatment

The date of last dose will be collected via the CRF. The subject's exposure will be calculated considering the end of study period visit (including follow-up visits F4, F8) or last dose day +84 days whichever occurs earlier.

2.2 Analysis sets

The following analysis sets will be used for the data analysis. Rules of exclusion criteria of analysis are detailed in Section 5.6.

The **Randomized Analysis Set (RAS)** consists of all randomized subjects. Subjects will be analyzed according to the treatment assigned at randomization.

The **Full Analysis Set (FAS)** comprises all subjects to whom study treatment has been assigned. Subjects will be analyzed according to the treatment assigned to at randomization. Mis-randomized subjects (mis-randomized in IRT) will be excluded from FAS. Mis-randomized subjects are defined as cases where IRT contacts were made by the site either prematurely or

inappropriately prior to confirmation of the subject's final randomization eligibility and no study medication was administered to the subject.

The **Safety Set** includes all subjects who received at least one dose of study treatment. Subjects will be analyzed according to the study treatment received, where treatment received is defined as the randomized/assigned treatment if the subject took at least one dose of that treatment or the first treatment received if the randomized/assigned treatment was never received.

The summary statistics analyses in this study will be performed according to domains with respective specifications of analyses sets, analyses period and treatment groups (Table 2-1).

Table 2-1 Summary statistics specifications

Domains	Analyses sets	Analysis Period	Treatment group labels for each analysis period
Patient disposition, Demographics, Other baseline characteristics*	RAS	Treatment Period 1	Secukinumab 300 mg Q4W Placebo Total
		Treatment Period 2 Follow up (only for disposition tables)	Secukinumab 300 mg Q4W Secukinumab 300 mg Q2W Total
Efficacy endpoints	FAS	Treatment Period 1	Secukinumab 300 mg Q4W Placebo
		Entire treatment period	Secukinumab 300 mg Q4W Placebo Placebo-Secukinumab 300 mg Q2W
Safety data (Number of doses, duration of exposure, prior and concomitant therapies, concomitant medical procedures, significant non-drug therapies, laboratory data, AEs, etc.)	Safety set	Treatment Period 1	Secukinumab 300 mg Q4W Placebo
		Entire treatment period	Secukinumab 300 mg Q4W Secukinumab 300 mg Q2W Placebo Any Secukinumab

* Treatment groups for protocol deviations for entire treatment period: AIN457 300 mg Q4W, AIN457 300 mg Q2W, Any AIN457 300 mg, Placebo, Total

2.2.1 Subgroup of interest

The efficacy endpoints will be evaluated by subgroups in an RShiny app. Subgroups of interest may include gender, age, Hepatitis C infection, weight, smoking history, previous systematics therapy for lichen planus, time since diagnosis, baseline IGA score and oral/genital affection in MLP.

2.3 Patient disposition, demographics and other baseline characteristics

The analyses of patient disposition, demographics and other baseline characteristics will be based on the randomized set.

Summary analyses in this section 2.3 will be shown by treatment groups as specified in Table 2-1.

2.3.1 Patient disposition

The number of subjects screened will be presented. In addition, the reasons for screen failures will be provided. The number and percentage of subjects in the randomized set who completed Treatment Period 1, Treatment Period 2 and Follow up Period, and who discontinued the study prematurely (including the reason for discontinuation) will be presented by study period for each treatment group.

For each protocol deviation, the number and percentage of subjects for whom the deviation applies will be tabulated by treatment group.

2.3.2 Demographics and other baseline characteristics

Common background and demographic variables will be analyzed in the randomized set.

For three lichen planus subtype cohorts (predominant subtype), summary statistics for these variables will be analyzed for each cohort (Section 2.1) and for each treatment group (Table 2-1) according to the type of variables as continuous or discrete. Summary statistics could be analyzed across three cohorts.

Lichen planus specific baseline characteristics and history of disease will be summarized for three cohorts (predominant subtypes) as follows.

Table 2-2 Demographics and other baseline characteristics

Variable(s)	Cohorts applied
Demographics	
Continuous	CLP, MLP, LPP, All
Age	
Height	
Weight	
Body mass index (BMI)	
Categorical	
Age categories (<65 years, 65 years and older)	

Variable(s)	Cohorts applied
Gender	
Race	
Ethnicity	
Smoking status at baseline	
Lichen planus specific baseline characteristics	
Continuous	
Patient Assessment of Itch (by each of the three questions)	CLP, MLP, LPP, All
Patient Assessment of Pain (by each of the three questions)	
Dermatology Life Quality Index (DLQI)	
Time since diagnosis of predominant lichen planus	
Reticular Erythematous Ulcerative score (REU)	MLP
Oral Lichen Planus Symptom Severity Measure (OLPSSM)	MLP
Lichen Planopilaris Activity Index (LPPAI)	LPP
Scalpdex	LPP
Categorical	
IGA score (at least moderate and severe)	CLP, MLP, LPP, All
Hepatitis C infection	
Previous exposure to biological systemic medication for lichen planus (yes, no)	
Previous exposure to non-biologic systemic medication for lichen planus (yes, no)	
Current use of topical medications (excluding ultrahigh or high potency corticosteroids, as per WHO classification) (yes, no)	
Percentage of patients with concomitant MLP	CLP
Baseline IGA score of concomitant MLP (at least mild, moderate, and severe)	CLP
Anatomical location of concomitant MLP (Oral, Genital, Esophageal)	CLP, MLP, All
Percentage of patients with concomitant CLP	MLP
Baseline IGA score of concomitant CLP (at least mild, moderate, and severe)	MLP

Body Mass Index (*BMI*) will be calculated using the following formula:

$$\text{BMI} = (\text{body weight in kilograms}) / (\text{height in meters})^2$$

For BMI, height and body weight of the last value prior to first dose will be used as a baseline value. If there is no weight or height recorded prior to taking the study treatment, BMI will be missing.

Time since diagnosis of the lichen planus (predominant subtypes) will be calculated using the following formula:

- Time since diagnosis of predominant lichen planus= (inform consent date – diagnosis date of the predominant lichen planus (from medical history CRF page) + 1)/365.25

Any condition entered on the relevant medical history / current medical conditions CRF will be coded using the MedDRA dictionary. They will be summarized by System Organ Class (SOC) and Preferred Term (PT) of the MedDRA dictionary.

2.4 Treatments (study treatment and concomitant medications)

The analysis of study treatment data will be based on the safety set.

2.4.1 Study treatment / compliance

The number of secukinumab and placebo injections doses will be summarized for Treatment Period 1 and entire treatment period by treatment group using contingency tables as specified in Table 2-1.

The duration of exposure to study treatment will be summarized as the number of subjects with exposure of at least certain time thresholds, displayed using the following categories: “any exposure”, “≥1 week”, “≥2 week”, “≥3 week” , “≥4 weeks”, “≥8 weeks”, “≥12 weeks”, “≥16 weeks”, “≥24 weeks”, “≥32 weeks. The results will be presented by analyses periods and treatment groups as specified in Table 2-1.

Duration of exposure will be defined as the time from first dose of study medication to the last dose plus 84 days or last visit (including follow-up visits) whichever occurs earlier. For subjects who discontinued or have their last visit earlier than last dose plus 84 days, the end of study treatment exposure will be the date of the last study visit in the follow-up period or in the corresponding treatment period.

Duration of exposure (days) = min (“end of study” date, last dose date +84) – first dose date +1

Duration of exposure (years) = duration of exposure (days) / 365.25

2.4.2 Visit windows

Visit windows will be used for the data that is summarized by visit; they are based on the study evaluation schedule and comprise a set of days around the nominal visit day. For any assessment, there are protocol defined scheduled visits around which visit windows were created to cover the complete range of days within the study. For subjects randomized to Placebo group to secukinumab 300 mg every 2 weeks arm, the day of taking the first secukinumab dose will also need to be taken into visit window consideration. The visit windows are shown in Table 2-3. In this table, the days are counted since the first dose of study treatment (study days) for safety assessments and the days are counted since the date of randomization for efficacy assessments. These visit windows apply to measurements taken at every visit. For assessments collected less often different visit windows will be applied as detailed below.

When visit windows are used, all visits will be re-aligned, i.e. they will be mapped into one of the visit windows. E.g., if the Week 4 visit of a subject is delayed and occurs on Day 60 instead of on Day 29, it will be re-aligned to visit window Week 8. In the case of major deviations from the visit schedule, or due to unscheduled visits, several assessments of a subject may fall in a particular visit window (either scheduled or unscheduled). Statistical approaches to handle multiple assessments in a given visit window are specified in Section 2.4.3.

Table 2-3 Assessment windows for scheduled visits

Analysis Visit	Week	Scheduled Day	Visit Window
Baseline	BSL	1	-28 days to Day 1*
Week 2	2	15	Day 2-22
Week 4	4	29	Day 23-43
Week 8	8	57	Day 44-71
Week 12	12	85	Day 72-99
Week 16	16	113	Day 100-127
Week 20	20	141	Day 128-155
Week 24	24	169	Day 156-183
Week 28	28	197	Day 184-211
Week 32	32	225	Day 212-239
Week 36	36	253	Day 240-267
Week 40	40	281	Day 268-295

* Day 1 is the date of the first drug administration for safety assessments and the date of the randomization for efficacy assessments.

For parameters which are not collected at every visit (e.g. laboratory, Lichen Planopilaris Activity Index), visit windows defined in Table 2-3 will be combined. The following rules are used to determine the visit window for an applicable visit post baseline: “Lower limit” = “upper limit of prior applicable visit” + 1. “Upper limit” = “target day of current visit” + integer part of (“target day of next applicable visit” – “target day of current visit”)/2. For example, if a parameter is measured at Week 12 and Week 28 only, Week 12 visit window will extend from Day 2 to Day 141 (combining Week 1 to Week 20 visit windows), Week 28 will extend from Day 142 to Day 295 (combining Week 21 to Week 40). If more than one assessment falls into the interval, the rules defined in Section 2.4.3 below are applied.

The analysis visit will be used for listing of visit and period for both safety and efficacy data. If a visit falls after the last visit window (after Day 295) it is not assigned an analysis visit and will be listed under label “After Week 40”.

2.4.3 Multiple assessments within visit windows

When there are *multiple assessments* in a particular visit window, the following rules are applied to select one value “representing” the subject in summary statistics in a visit window (Table 2-4).

For baseline assessment definition, see Section 2.1.1.2. For post-baseline visit windows the

following applies (unless otherwise specified):

- for *quantitative variables*, the *closest* to the actual visit is chosen (if two assessments have the same distance, then the earlier one will be chosen);
- in case qualitative variables are based on quantitative variables, the visit will be assigned to the quantitative variable, and this visit will be used for the derived qualitative variable.

Table 2-4 Rules for selecting values for analysis within a given visit window

Timing of measurement	Type of data	Rule
Baseline	All data	See Section 2.1.1.2
Post-baseline efficacy	All data except for PRO (e.g., IGA)	The measurement closest to the target day will be used. In the event two measurements are taken equally apart (e.g., 1 day before target date and 1 day after), the results from the earlier visit will be used. If two measurements are taken on the same day, then select the first one using eCRF visit number. If two measurements have been taken on the same day and same visit then select the worst.
	PRO data	The measurement closest to the target day will be used. In the event two measurements are taken equally apart (e.g., 1 day before target date and 1 day after), the earlier one will be used. If two measurements have been taken on the same day, select the worst. If two measurement have the same value, select the first one using eCRF visit number.
Post-baseline safety	Summary visit information (e.g. laboratory values, vital signs, etc.)	The (non-missing) measurement closest to the target day will be used. In the event two measurements are taken equally apart (e.g. 1 day before target date and 1 day after) the first one will be used. If two measurements are taken on the same day then select the first one (using the time). If two measurements are taken on the same date/time then use the first visit number (assuming this is the planned visit). If two measurements are taken on the same date/time/eCRF visit number then use the average of two assessments.
Post-baseline safety	Notable abnormalities for laboratory values	The most extreme measurement in the window will be used. Note this means a subject can have a notably high and notably low measurement within an analysis period.

2.4.4 Prior, concomitant and post therapies

Medications will be identified using Novartis Drug and Therapy Dictionary (NovDTD) including Anatomical Therapeutic Chemical (ATC) code. Prior and concomitant treatments will be summarized by Treatment Period 1 and entire treatment period and by respective treatment groups (Table 2-1).

Prior medications are defined as drugs taken and stopped prior to the first dose of study treatment. Any medication given at least once between the day of first dose of study treatment, and within 84 days after last dose will be a concomitant medication, including those that were started before first dose of study treatment and continued into the Treatment Period.

Prior or concomitant medication will be identified based on recorded or imputed start and end dates of medication taken (see Section 5.1.3).

Medications will be presented in alphabetical order, by ATC codes and grouped by anatomical main group (the 1st level of the ATC codes). Tables will also show the overall number and percentage of subjects receiving at least one drug of a particular ATC code and at least one drug in a particular anatomical main group.

In addition, medical procedures and significant non-drug therapies as coded in MedDRA will be summarized.

2.5 Analysis of the primary objective

The primary aim of the study is to demonstrate the efficacy of secukinumab (300 mg Q4W) with respect to IGA responder status after 16 weeks of treatment compared to placebo.

2.5.1 Primary endpoint

The primary endpoint of the study is the proportion of IGA responders within each cohort at Week 16, where IGA response is defined as achieving an absolute IGA score less than or equal to 2. Each cohort (CLP, MLP and LPP) of the study will have its own primary efficacy endpoint analyzed separately.

The analysis of the primary endpoint will be based on the FAS.

2.5.2 Statistical hypothesis, model, and method of analysis

The primary endpoint of IGA response at Week 16 is a binary (yes/no) outcome; it will be analyzed by a Bayesian method based on the Beta-Binomial model. Bayesian inference based on the non-informative prior of Beta (1/3, 1/3) for each treatment group will be used to obtain the posterior distribution of the treatment difference between secukinumab and placebo for the three subtypes, respectively.

The Bayes PoC criteria to be assessed for the primary endpoint are:

1) the posterior probability of the treatment difference greater than zero ($\delta>0$) is greater than 90%;

$$\Pr(\delta(\text{secukinumab, placebo}) > 0 \mid \text{data}) > 90\% \textbf{ and}$$

2) the posterior probability of the treatment difference exceeding half of the target effect of 0.30 ($\delta>0.15$) is greater than 50%

$$\Pr(\delta(\text{secukinumab, placebo}) > 0.15 \mid \text{data}) > 50\%$$

where δ denotes the treatment difference between secukinumab and placebo with respect to the

IGA response at Week 16.

Bayesian model

The statistical model used will include a fixed factor for treatment (secukinumab or placebo).

It is assumed that the number of responder patients is a random variable following a binomial distribution Binomial (n_k, p_k) where n_k is the sample size and p_k is the true underlying proportion of responder patients. Given the prior of Beta (1/3, 1/3) for each treatment group, the posterior of p_k is also a Beta distribtion as following:

$$p_k \,|s_k \sim \text{Beta}(1/3+s_k,\ 1/3+n_k-s_k)$$

where s_k is the observed number of patients who have responded among the n_k patients observed.

Estimates of the posterior probabilities of the difference of the IGA responder rate between the secukinumab 300 mg treatment and placebo groups at Week 16 will be presented together with two sided 95% credible intervals (2.5% to 97.5%). Estimates of the posterior probabilities of the efficacy criteria (criteria 1 and 2) being met will be provided.

The posterior beta density function of the estimated proportion of responders will be displayed graphically.

2.5.3 Handling of missing values/censoring/discontinuations.

Subjects who discontinue treatment before Week 16 will be considered failures (i.e., non-responder). Missing values not related to treatment discontinuation will be analyzed as observed.

2.5.4 Supplementary analyses

Two supplementary analyses are planned.

2.5.4.1 Hypothetical strategy

A supplementary analysis will evaluate the treatment effect assuming that patients would not discontinue study drug for the intended duration of 16 weeks (hypothetical strategy). Data after study treatment discontinuation will be replaced by multiple imputed data using the MAR (missing at random) assumption. Detail information could be found in the Estimand charter (Section 5.4 and Section 5.5.2).

[redacted]

[redacted]

2.6 Analysis of secondary objectives

2.6.1 Secondary endpoints

Secondary efficacy endpoints will be analyzed separately for each independent cohort (CLP, MLP, LPP) or for one specific cohort, as specified in Table 2-5. Treatment groups for summary statistics are summarized in Table 2-1.

[redacted]

- **Endpoints for each independent cohort**

Investigator's Global Assessment (IGA)

The following IGA related endpoints are considered:

- **IGA ≥2 points improvement response**: defined as achieving an ≥2 IGA score decreasing compared with baseline (thus at least achieving an IGA score of ≤ 2).
- **IGA 0 or 1 response**: defined as achieving an IGA score of 0 or 1 (thus at least achieving an IGA ≥2 points improvement)

For IGA ≥2 points improvement response and IGA 0 or 1 response from Week 1 to Week 16, comparisons between the 300 mg Q4W treatment regimen and placebo groups will be conducted using the Fisher exact test. Estimates of the difference of response rates between the 300 mg Q4W treatment regimen and placebo groups together with 95% confidence intervals will be presented.

Summary statistics for IGA ≥2 points improvement and IGA 0 or 1 response by visit from baseline up to the end of study for each treatment group will be presented in contingency tables with the number and percentage of subjects in each category.

Dermatology Life Quality Index

Seven scores will be derived from the DLQI: the total score of each of the six dimensions and the total score over all items. The higher the score, the more quality of life is impaired. The DLQI total score over all items will be calculated by summing the score of each question resulting in a maximum score of 30 and a minimum score of 0.

For the total DLQI score and each of the seven total item scores, summary statistics will be provided for the absolute and percentage change from baseline by visit up to the end of study for each treatment group.

Achievement of DLQI total score of 0 or 1 among subjects with baseline DLQI score ≥2 will be considered as a DLQI 0/1 responder. The number and proportion (%) of DLQI responders will be presented by visit up to the end of study for each treatment group. Between-treatment differences for the proportion of DLQI responder from Week 1 to Week 16 together with 95% confidence intervals will be presented.

Patient Assessment of Itch (NRS)

Itch is assessed with three questions about an overall severity, severity at the worst moment and the overall degree of bother, respectively. Each of the question will be answered using a numeric rating scale (NRS, ranging from 0 to 10).

For each of the three questions, summary statistics will be provided for the absolute and percentage change from baseline by visit up to the end of study for each treatment group.

Patient Assessment of Pain (NRS)

Pain is assessed with three questions, each answered using a numeric rating scale (NRS, ranging from 0-10).

For each of the three questions, summary statistics will be provided for the absolute and percentage change from baseline by visit up to end of study for each treatment group.

- **Endpoint for CLP**

Physician Assessment of Surface Area of Disease (PSAD) for Skin Disease

PSAD evaluates the extent of cutaneous lesions. PSAD ranges from 0 to 5, with lower scores corresponding to lower percentages of surface area with disease.

The number and percentage of subjects in each category will be presented by visit up to the end of study for each treatment group.

- **Endpoints for MLP**

Reticular erythematous Ulcerative (REU) score

The REU score was developed as a semi-quantitative scale, measuring disease severity based on 3 dimensions: reticulation, erythema and ulceration. Scores for each of the 3 clinical dimensions will add up to a total weighted score (REU score).

Summary statistics for the REU score will be provided for absolute and percentage change from baseline by visit up to end of study for each treatment group.

Oral Lichen Planus Symptom Severity Measure (OLPSSM)

OLPSSM was a PRO-based assessment of the symptom experience of subjects with oral lichen planus in clinical studies, ranging from 0 to 28, with higher scores indicating worse severity.

Summary statistics will be provided for absolute and percentage change from baseline of OLPSSM score by visit up to end of study for each treatment group.

- **Endpoints for LPP**

LPP Activity Index (LPPAI)

LPPAI is a numeric score to quantify the signs and symptoms of LPP (Chiang, 2010). Subjects with an LPPAI reduction greater than 85% over pretreatment values were considered responders, with 25% to 85% reduction were considered partial responders, and with less than 25% reduction were considered non-responders.

Summary statistics will be provided for absolute and percentage change from baseline of LPPAI score by visit up to the end of study for each treatment group.

The number and proportion of LPPAI responders and partial responders will be presented by visit up to the end of study for each treatment group.

Scalpdex

Scalpdex is a self-administered, health-related quality of life instrument originally developed for scalp dermatitis. This survey includes 23 items, each item scored on a scale of 0-100, where 0=never, 25=rarely, 50=sometimes, 75=often and 100=all the time. The 23 items are mapped into 3 major domains that affect patient quality of life: symptoms, functioning, and emotions. The Scalpdex will be evaluated both as a total score, calculated as the mean of all 23 items, and by 3 dimensions, calculated as the mean of the item scores pertaining to each domain (Chen, 2002).

Summary statistics will be provided for absolute and percentage change from baseline of Scalpdex total score and scores of 3 domains by visit up to end of study for each treatment group.

Table 2-5 Overview of analysis methods for secondary efficacy variables

Variable(s)	Cohorts applied	Summary statistics for discrete data	Statistical analyses	Summary statistics for continuous data	Graphs*
IGA response over time[a]	CLP, MLP, LPP	X	Fisher exact test @ Week 1- 16		X
DLQI 0/1 response over time	CLP, MLP, LPP	X			X
DLQI total score and item score overtime	CLP, MLP, LPP			X	X[b]
Patient Assessment of Itch (NRS) over time (3 questions)	CLP, MLP, LPP			X	
Patient Assessment of Pain (NRS) over time (3 questions)	CLP, MLP, LPP			X	
PSAD over time	CLP	X			X[c]
REU over time	MLP			X	X[d]
OLPSSM over time	MLP			X	
LPPAI responder and partial responder over time	LPP	X			
LPPAI score over time	LPP			X	X[d]
Scalpdex over time	LPP			X	

*Line plots. The graphs may only be presented in the Rshiny app where appropriate.
[a]IGA responses include: 1) IGA ≥2 points improvement response and 2) IGA= 0 or 1 response.
[b]Total DLQI score change from baseline by cohort.
[c]Ploted as a categorical variable.
[d]Time course of percent change from baseline.

2.6.2 Statistical hypothesis, model, and method of analysis

Not applicable

2.6.3 Handling of missing values/censoring/discontinuations

Data collected after treatment discontinuation by Week 32 will be replaced with the baseline value of the patients for all secondary endpoints above. Missing values not related to treatment discontinuation will be analyzed as observed.

2.7 Analyses of safety endpoints

All safety analyses will be based on the safety set. Only those visits that were pre-planned in the protocol will be reported in tables for safety variables.

Analysis of adverse events will be based on treatment emergent events, which are defined as events started on or after the first dose of study treatment or events present prior to the first dose of study treatment but increased in severity based on preferred term and on or before last dose + 84 days.

Other safety variables including LAB, Vitals will be evaluated based on on-treatment events, which are defined as any events that happened after first dose of study treatment and on or before last dose +84 days.

Safety analysis will be performed on actual treatment, for patients in any of the three cohorts and in each of the three cohorts, respectively. Analyses will be presented by Treatment Period 1 and entire treatment period and by treatment groups as specified in Table 2-1.

2.7.1 Adverse events (AEs)

For adverse events and other binary safety variables, crude incidences and exposure-adjusted incidence rate (EAIR) will be derived as described below and summarized in Table 2-6. The crude incidence of treatment emergent adverse events will be summarized by primary SOC and PT.

All AEs and serious adverse events (SAEs) will be listed with "treatment emergent" flag displayed.

Table 2-6 Overview of analyses on some safety endpoints

Analysis period	AEs & SPP risks	SAEs	AEs by severity	Study treatment related AEs, death & other significant AEs	Notables (lab/vitals)
Treatment Period 1	• crude incidence	• crude incidence	• crude incidence	• crude incidence	• crude incidence
Entire study period	• crude incidence • exposure-adjusted incidence rate	• crude incidence • exposure-adjusted incidence rate	• crude incidence	• crude incidence • exposure-adjusted incidence rate	• crude incidence

AEs will be summarized by presenting, for each cohort and each treatment group, the number and percentage of subjects having at least one AE, having at least one AE in each primary SOC and having each individual AE (preferred term). Summaries will also be presented for AEs by severity. If a particular AE 'severity' is missing, this variable will be listed as missing and treated as missing in summaries. If a subject reported more than one AE with the same PT, the AE with the greatest severity will be presented. If a subject reported more than one AE within the same primary SOC, the subject will be counted only once with the greatest severity at the SOC level, where applicable. AEs by severity will be provided by SOC and AEs by severity and PTs may be provided if required at ad-hoc basis.

The most common AEs reported (at least two cases in any treatment group by SOC and PT) will be presented in descending frequency according to its incidence in AIN457 300 mg Q4W group starting from the most common event. Here the threshold value is set to at least two cases in any treatment group by PT but it may be updated.

Separate summaries will be provided for deaths, SAEs, and other significant AEs leading to discontinuation.

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on treatment AEs which are not SAEs with an incidence greater than 5% and on treatment SAEs and SAE

suspected to be related to study treatment will be provided by SOC and PT on the safety set population.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

Algorithms for AE date imputations will be provided in Section 5.1.2.

2.7.2 Deaths

Separate summary and listing will be provided for deaths. The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

2.7.3 Laboratory data

The summary of laboratory evaluations will be presented for two groups of laboratory tests (hematology and serum chemistry). Descriptive summary statistics for the change from baseline to each study visit will be presented. These descriptive summaries will be presented by cohort, test group, laboratory test and treatment group. Change from baseline will only be summarized for subjects with both baseline and post baseline values. In addition, Summary of notable abnormalities of key laboratory tests will be provided by treatment group. Detail on notable abnormalities derivations will be specified in Section 5.3.

2.7.4 Other safety data

2.7.4.1 Vital signs

Analysis of the vital sign measurements using summary statistics for the change from baseline for each post-baseline visit will be performed. These descriptive summaries will be presented by cohort, vital sign and treatment group. Change from baseline will only be summarized for subjects with both baseline and post-baseline values.

The number and percentage of subjects with newly occurring notable vital signs will be presented. Criteria for notable vital sign abnormalities are provided in Table 2-7 below. A listing of subjects with newly occurring notably abnormal vital signs will be provided.

Table 2-7 Criteria for notable vital sign abnormalities

Vital sign (unit)	Notable abnormalities
Systolic blood pressure (mmHg)	>= 140 mmHg or < 90 mmHg
Diastolic blood pressure (mmHg)	>=90 mmHg or <60 mmHg
Pulse (bpm)	> 100 bpm or <60 bpm

[redacted]

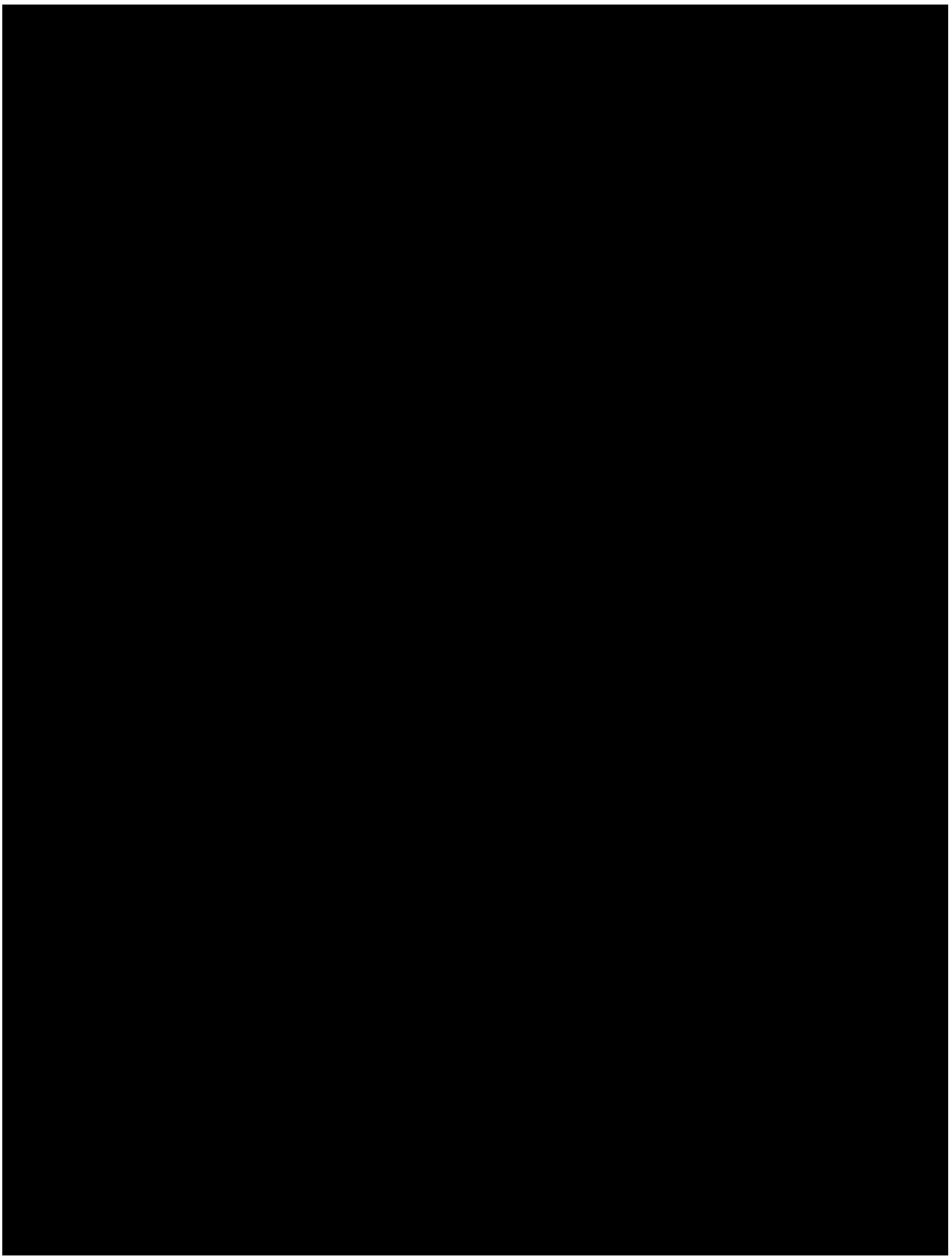
2.9 PD and [redacted]/PD analyses

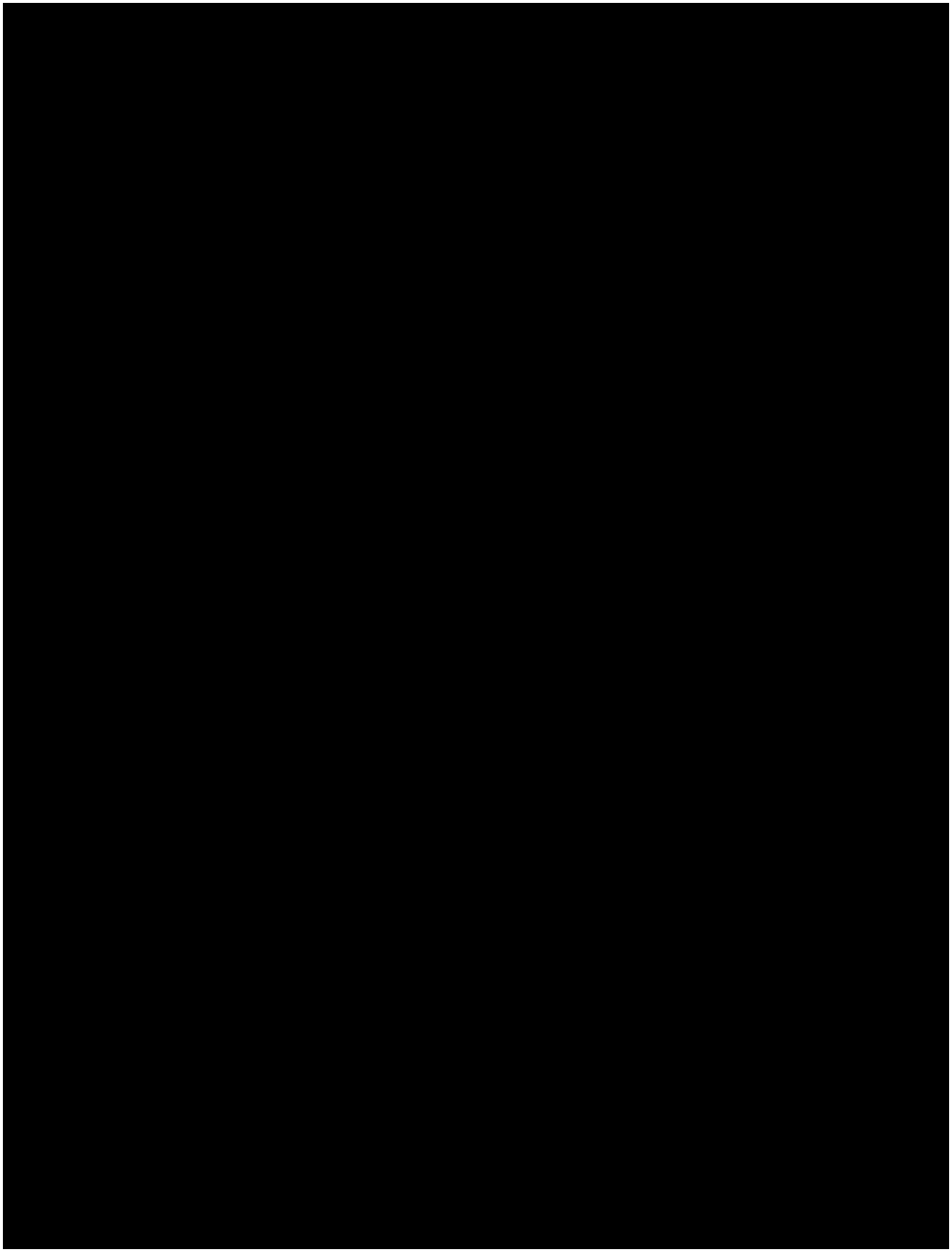
The [redacted] other clinically important endpoints, such as PSAD, REU, LPPAI will be investigated if appropriate.

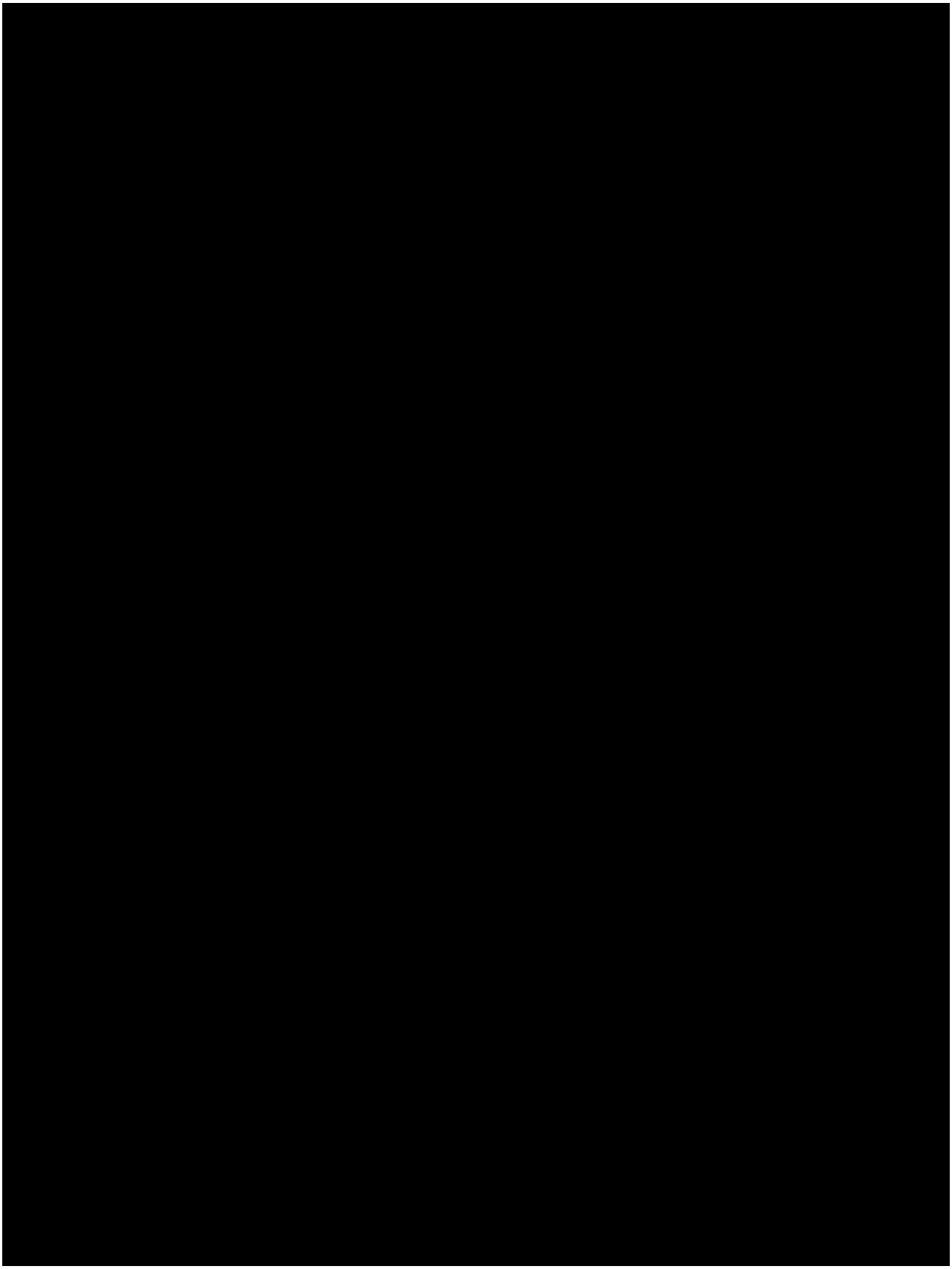
[redacted]

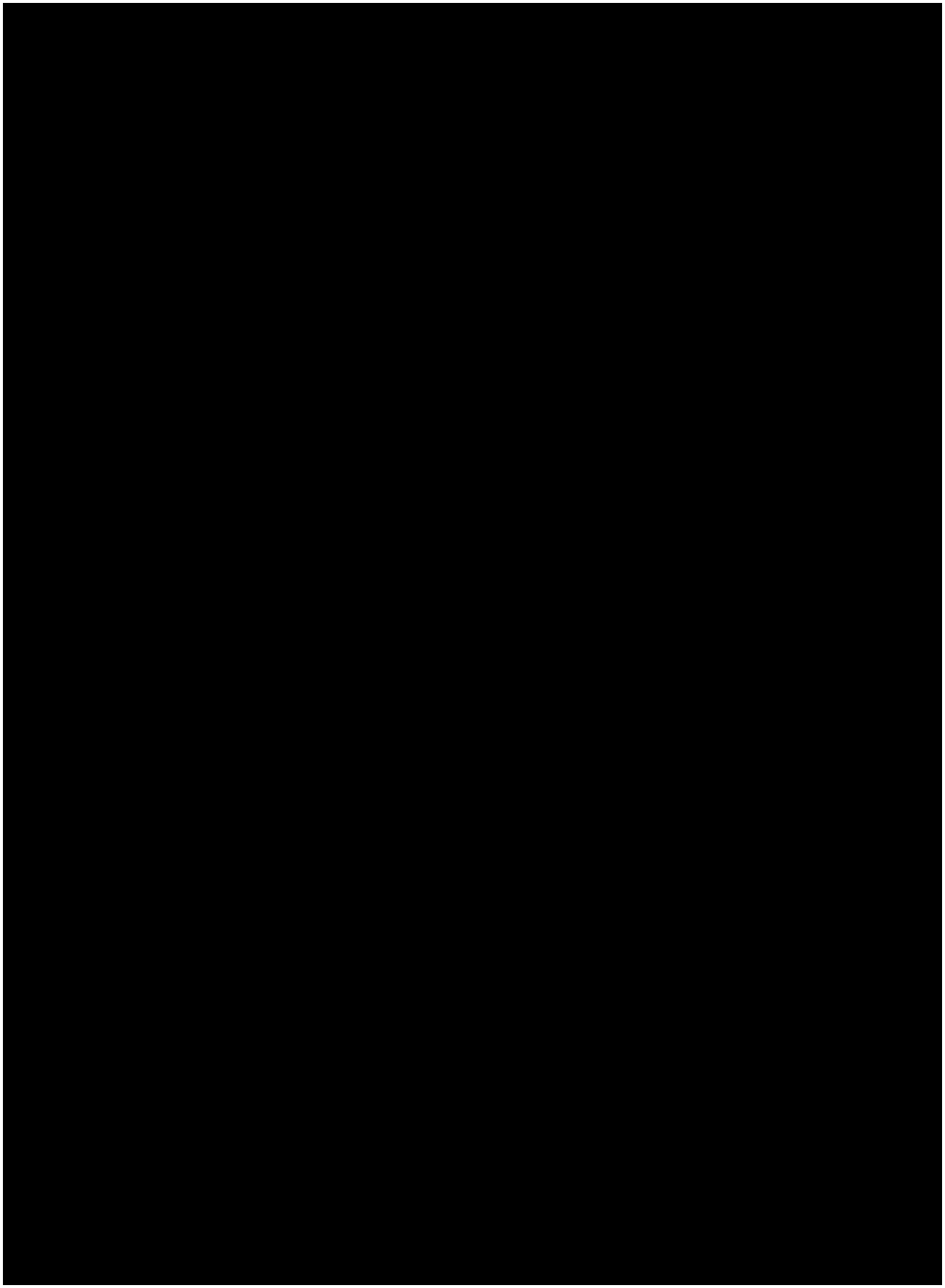
2.11 Patient-reported outcomes

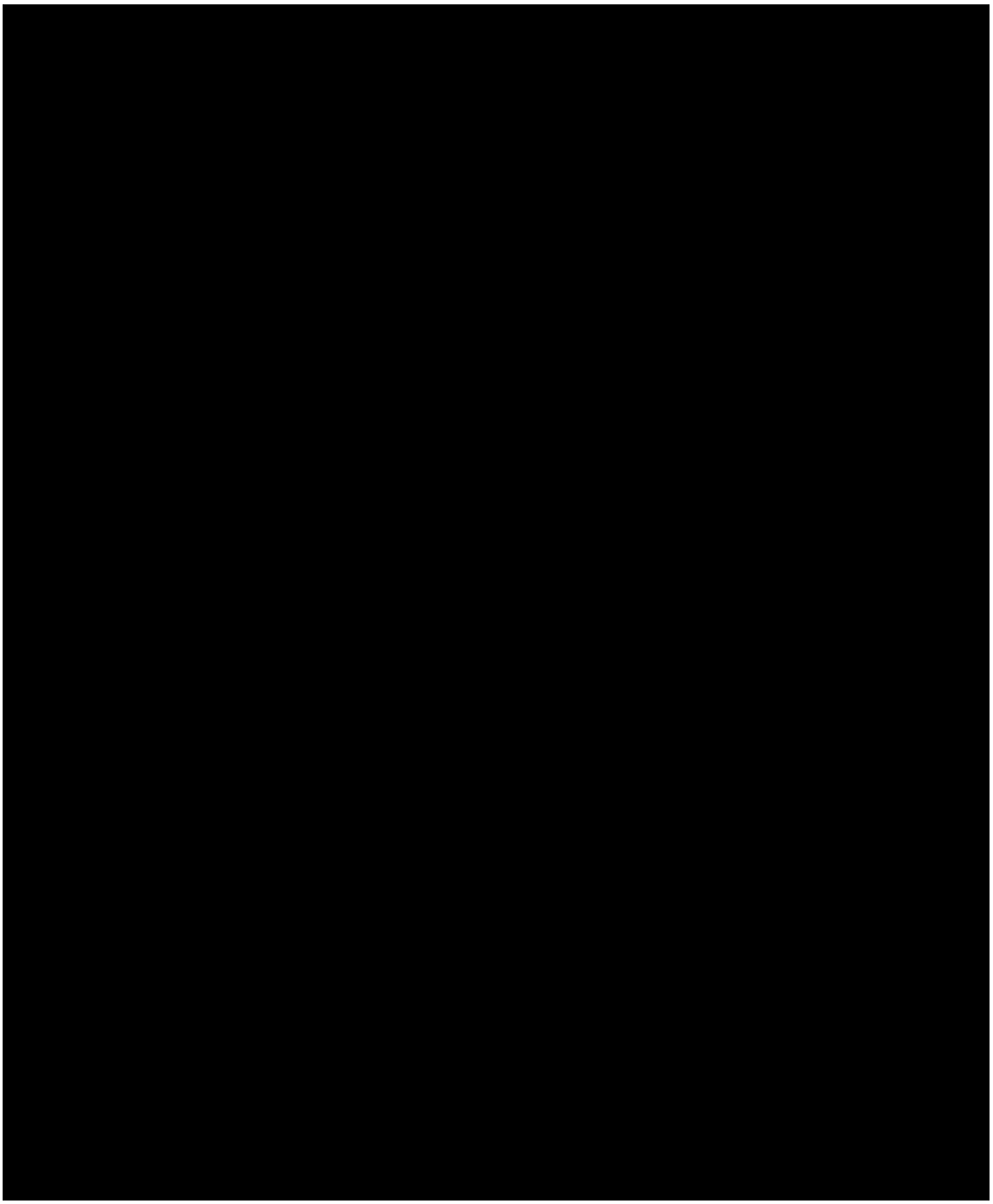
Please refer to Section 2.6 and Section 2.13 for the analysis method of Patient-reported outcomes.











2.14 Interim analysis

Primary endpoint analysis will be performed after all subjects have completed Week 16 visit. Additional analyses may be performed to support health authority interactions as necessary. At the End of Study, a final analysis will be performed when all subjects have completed the

last study visit.

3 Sample size calculation

Total sample size planned for this study is 108 with 36 subjects in each subtype.

For each subtype, 24 secukinumab 300 mg Q4W treatment regimen subjects and 12 placebo subjects assures the 71% probability to claim positive PoC results, based on the assumptions that the placebo IGA responder rate is 20% and secukinumab 300 mg Q4W placebo difference (delta) of the IGA responder rates is at least 30%.

For different response rate assumptions on the secukinumab 300 mg Q4W and placebo dose regimens, Figure 3-1 and Table 3-1 reported below show that there is no substantial difference in the probability of claiming a successful PoC results between randomization ratios 1:1 and 2:1. Considering the absence of previous lichen planus secukinumab data, randomization 2:1 is chosen for this study, to assure the collection of more efficacy and safety data on lichen planus secukinumab subjects, while limiting the number of subjects exposed to placebo. Figure 3-1 and Table 3-1 also show that the probability of claiming positive PoC results being around 70% when the secukinumab 300 mg Q4W and placebo difference (delta) of the IGA responder rates is 30% in any scenario, and greater than 85% when the secukinumab 300 mg Q4W and placebo difference (delta) of the IGA responder rates is 40% in any scenario.

Figure 3-1 Operating Characteristics on different randomization ratio and different response rate assumption

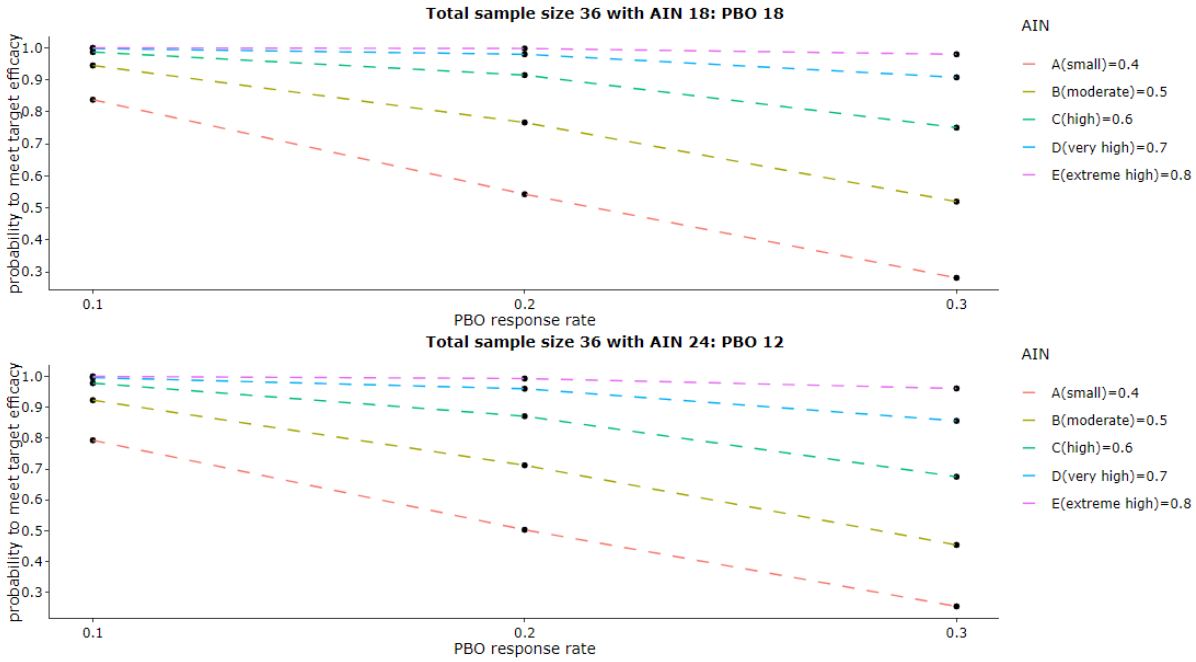


Table 3-1 Operating Characteristics on different randomization ratio and different response rate assumption

Secukinumab response rate	Placebo response rate	Probability to meet target efficacy with AIN 18: PBO 18	Probability to meet target efficacy with AIN 24: PBO 12
A(small)=0.4	0.1	0.838	0.793
B(moderate)=0.5	0.1	0.945	0.923
C(high)=0.6	0.1	0.987	0.978
D(very high)=0.7	0.1	0.998	0.996
E(extreme high)=0.8	0.1	1.000	1.000
A(small)=0.4	0.2	0.543	0.503
B(moderate)=0.5	0.2	0.767	0.712
C(high)=0.6	0.2	0.915	0.871
D(very high)=0.7	0.2	0.980	0.960
E(extreme high)=0.8	0.2	0.998	0.993
A(small)=0.4	0.3	0.282	0.255
B(moderate)=0.5	0.3	0.520	0.454
C(high)=0.6	0.3	0.751	0.675
D(very high)=0.7	0.3	0.908	0.856
E(extreme high)=0.8	0.3	0.980	0.961

*Calculation for Operating Characteristics was based on QTD version 3.0.0

[redacted]

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

Any partial dates will be imputed as follows:

The earlier day will be taken from below

- The last day in the month and
- The end day of the corresponding Treatment Period

5.1.2 AE date imputation

Impute AE end date:
1. If the AE end date 'month' is missing, the imputed end date should be set to the earliest of the (min (last visit date, last dose date + 84 days), 31DECYYYY, date of death).
2. If the AE end date 'day' is missing, the imputed end date should be set to the earliest of the (min (last visit date, last dose date + 84 days), last day of the month, date of death).
3. If AE 'year' is missing or AE is ongoing, the end date will not be imputed.
Impute AE start date:
Before imputing AE start date, find the AE start reference date.
1. If the (imputed) AE end date is complete and the (imputed) AE end date < treatment start date then AE start reference date = min(informed consent date, earliest visit date).
2. Else AE start reference date = treatment start date
1. If the AE start date 'year' value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL.
2. If the AE start date 'year' value is less than the treatment start date year value, the AE started before treatment. Therefore:
    a. If AE 'month' is missing, the imputed AE start date is set to the mid-year point (01JULYYYY).
    b. Else if AE 'month' is not missing, the imputed AE start date is set to the mid-month point (15MONYYYY).
3. If the AE start date year value is greater than the treatment start date year value, the AE started after treatment. Therefore:
    a. If the AE month is missing, the imputed AE start date is set to the year start point (01JANYYYY).
    b. Else if the AE month is not missing, the imputed AE start date is set to the later of

(month start point (01MONYYYY), AE start reference date + 1 day).

4. If the AE start date year value is equal to the treatment start date year value:
   a. And the AE month is missing the imputed AE start date is set to the AE reference start date + 1 day.
   b. Else if the AE month is less than the treatment start month, the imputed AE start date is set to the mid-month point (15MONYYYY).
   c. Else if the AE month is equal to the treatment start date month or greater than the treatment start date month, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

If complete (imputed) AE end date is available and the imputed AE start date is greater than the (imputed) AE end date, then imputed AE start date should be set to the (imputed) AE end date.

5.1.3 Concomitant medication date imputation

Impute CM end date:

1. If CM end day is missing and CM month/year are non-missing then impute CM day as the minimum of treatment end date and the last day of the month.
2. If CM end day/month are missing and CM year is non-missing then impute CM day as the minimum of treatment end date and the end of the year (31DECYYYY).
3. If imputed CM end date is less than the CM start date, use the CM start date as the imputed CM end date.

Impute CM start date:

1. If the CM start date year value is missing, the imputed CM start date is set to one day prior to treatment start date.
2. If the CM start date year value is less than the treatment start date year value, the CM started before treatment. Therefore:
   a. If the CM month is missing, the imputed CM start date is set to the mid-year point (01JULYYYY).
   b. Else if the CM month is not missing, the imputed CM start date is set to the mid-month point (15MONYYYY).
3. If the CM start date year value is greater than the treatment start date year value, the CM started after treatment. Therefore:
   a. If the CM month is missing, the imputed CM start date is set to the year start point (01JANYYYY).
   b. Else if the CM month is not missing, the imputed CM start date is set to the month start point (01MONYYYY).
4. If the CM start date year value is equal to the treatment start date year value:
   a. And the CM month is missing or the CM month is equal to the treatment start date month, then the imputed CM start date is set to one day prior treatment start date.
   b. Else if the CM month is less than the treatment start date month, the imputed CM start date is set to the mid-month point (15MONYYYY).
   c. Else if the CM month is greater than the treatment start date month, the imputed CM start date is set to the month start point (01MONYYYY).

If complete (imputed) CM end date is available and the imputed CM start date is greater than the (imputed) CM end date, then imputed CM start date should be set to the (imputed) CM end date.

5.1.4 Medical history date imputation

1. If the medical history date day/ month are missing and the year is non-missing:
    a. If the year part of the date is equal to the year part of the inform consent date, then the imputed date is set to the year start point (01JANYYYY).
    b. Otherwise the imputed date is set to the mid-year point (01JULYYYY).
2. If the medical history day is missing and the month/year are non-missing:
    a. If the month and year part of date is equal to the month and year part of the inform consent date, then the imputed date is set to the month start point (01MONYYYY).
    b. Otherwise the imputed date is set to the mid-month point (15MONYYYY).

5.1.5 Other imputations

For laboratory test values below Lower Level of Quantification (LLQ) or above Upper Level of Quantification (ULQ) will be imputed as LLQ or ULQ value, respectively. The numerical part of the reported result will be treated as the actual LLQ or ULQ. These laboratory values will be displayed in listings using the standard unit with the reported sign ("<" or ">")."

5.2 AEs coding/grading

AEs will be coded according to MedDRA dictionary. The MedDRA version used for reporting the adverse events will be described in a footnote.

5.3 Laboratory parameters derivations

The following criteria will be used to define expanded limits and clinically notable abnormalities of key laboratory tests.

Liver Function and Related Variables

Alanine transaminase (ALT) (SGPT): > 3 x Upper Limit of Normal (ULN)

Aspartate transaminase (AST) (SGOT): > 3 x ULN

Total bilirubin: > 2 x ULN

Alkaline phosphatase: > 2.5 x ULN

Renal Function

Creatinine (serum): > 1.5 x ULN

Hematology

Hemoglobin: ≥ 20 g/l decrease from baseline

Platelet count: < Lower Limit of Normal (LLN)

White blood cell count: < 0.8 x LLN

Neutrophils: < 0.9 x LLN

Eosinophils: > 1.1 x ULN

Lymphocytes: > 1.1 x ULN

5.4 Estimand Charter

5.4.1 Introduction

Secukinumab is being explored as a treatment for lichen planus, and studied in subjects with biopsy-proven forms of lichen planus not adequately controlled with topical therapies in the proof of concept trial CAIN457S12201.

This section describes the estimands and corresponding estimation procedures for the primary endpoint, in line with the latest discussions of the forthcoming ICH E9 (R1) addendum.

An estimand defines in detail what needs to be estimated to address a specific scientific question of interest. A description of an estimand includes five attributes:

- The population, that is, the patients targeted by the scientific question;
- The variable (or endpoint), to be obtained for each patient, that is required to address the scientific question;
- The treatment of interest. The test treatment of interest and the control treatment to which comparison will be made (if applicable).
- The specification of how to account for intercurrent events to reflect the scientific question of interest;
- The population-level summary for the variable that provides, as required, a basis for a comparison between treatment conditions.

This section focuses in particular on the management of intercurrent events (for example, discontinuation of assigned treatment, use of an additional or alternative therapy). Other aspects of the estimand like the population, the variable, the treatment of interest and the population-level summary for the variable are presented, but are not the focus of this document.

5.4.1.1 Purpose of the CAIN457S12201 study

The purpose of this proof of concept study is to explore the efficacy of secukinumab in the treatment of adult patients with biopsy-proven lichen planus not adequately controlled with topical therapies, and to assess the safety and tolerability over 32 weeks. The primary objective

of the study is to demonstrate the efficacy of secukinumab (300 mg Q4W) with respect to IGA response (i.e., achievement of IGA score ≤ 2) after 16 weeks of treatment compared to placebo.

5.4.1.2 Different types of intercurrent events

1. Changes in the dose of allowed concomitant medications for topical therapy: patients entering the trial are not allowed to use any topical therapies except for the allowed concomitant topical medications (described in Section 6.2.1 of the protocol). Patients must have reached a stable dose and application frequency of these allowed topical treatments at least 2 weeks prior to randomization and the administration should remain stable regarding dose and application frequency during first 16 weeks treatment.
2. Other concomitant medications: medications that are not explicitly prohibited by the protocol (e.g., antibiotics or NSAIDs, or supplements).
3. Prohibited medications: medications that are prohibited by the protocol (described in Section 6.2.2 of the protocol) and that have a potential confounding effect on the efficacy of secukinumab (e.g. immunosuppressive agents such as methotrexate, cyclosporin or systemic glucocorticoids).
4. Discontinuation of study treatment.

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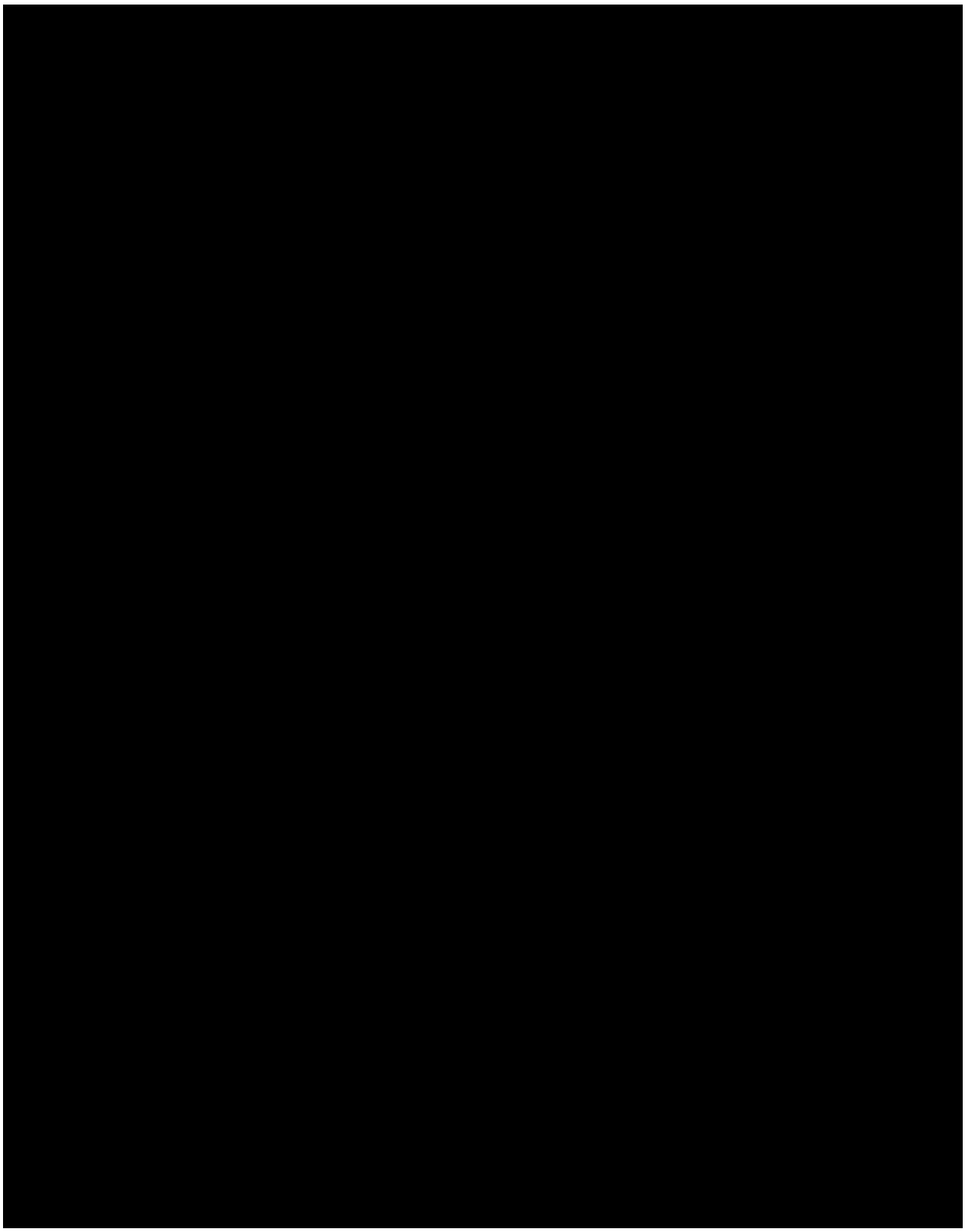

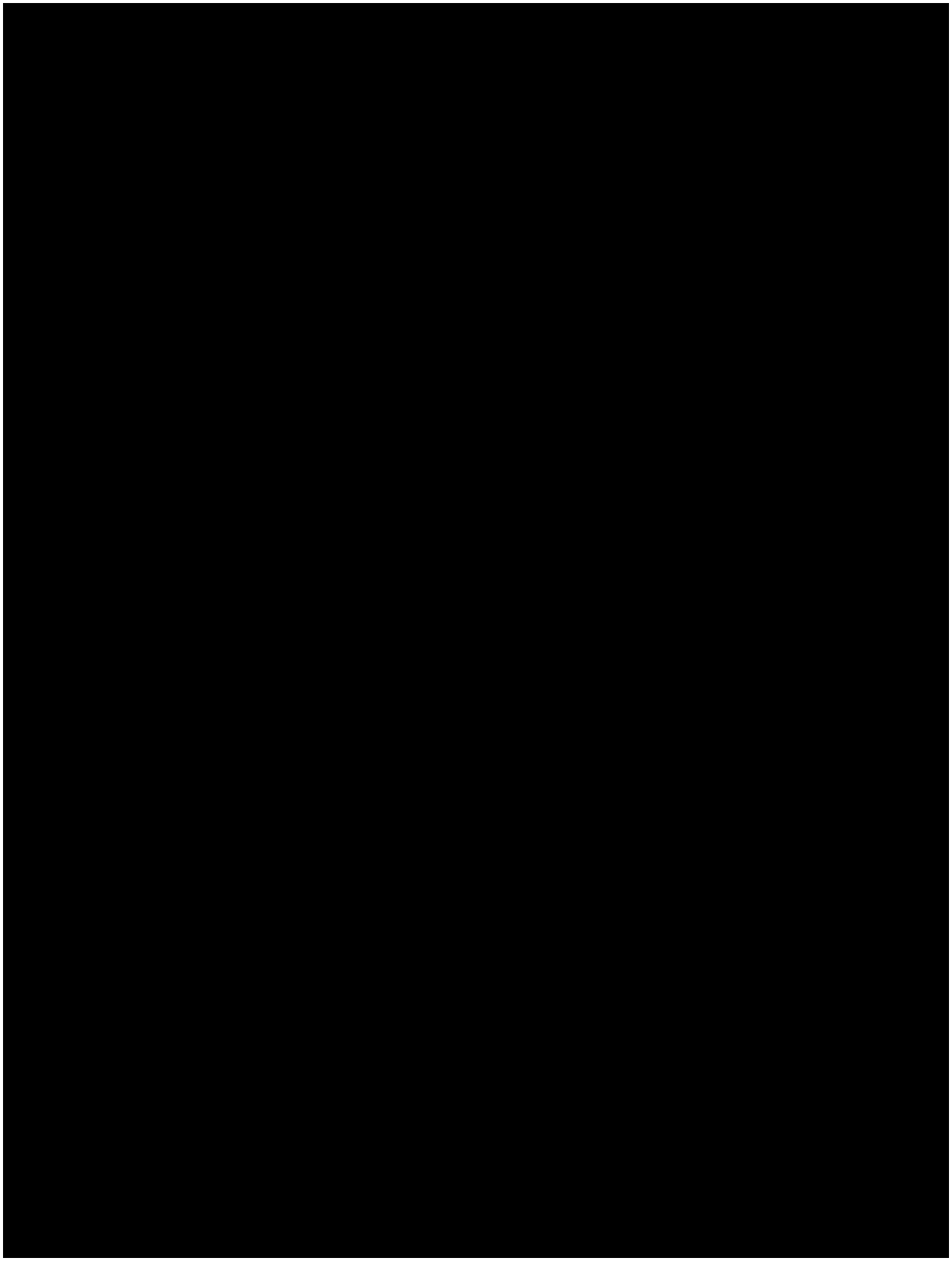

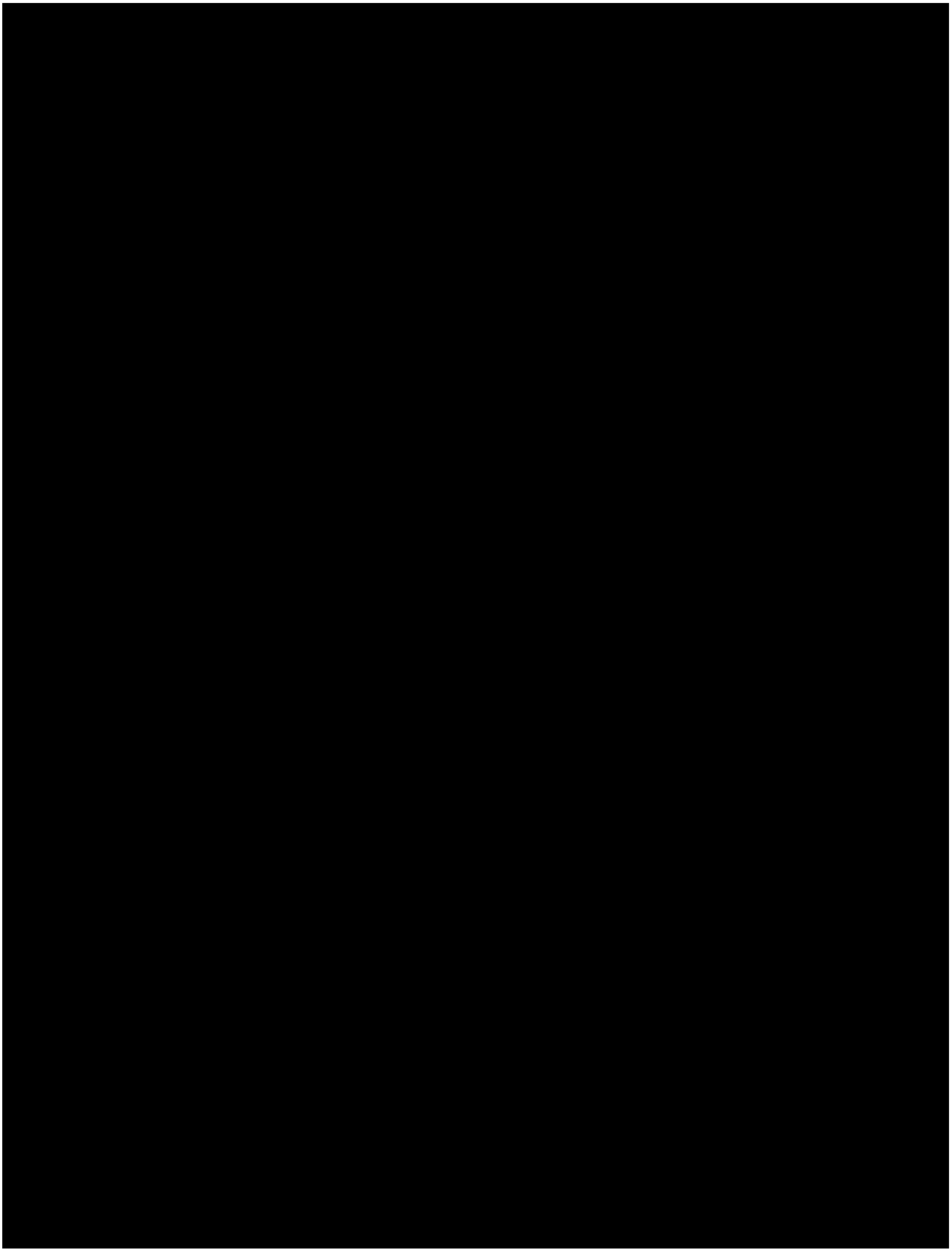

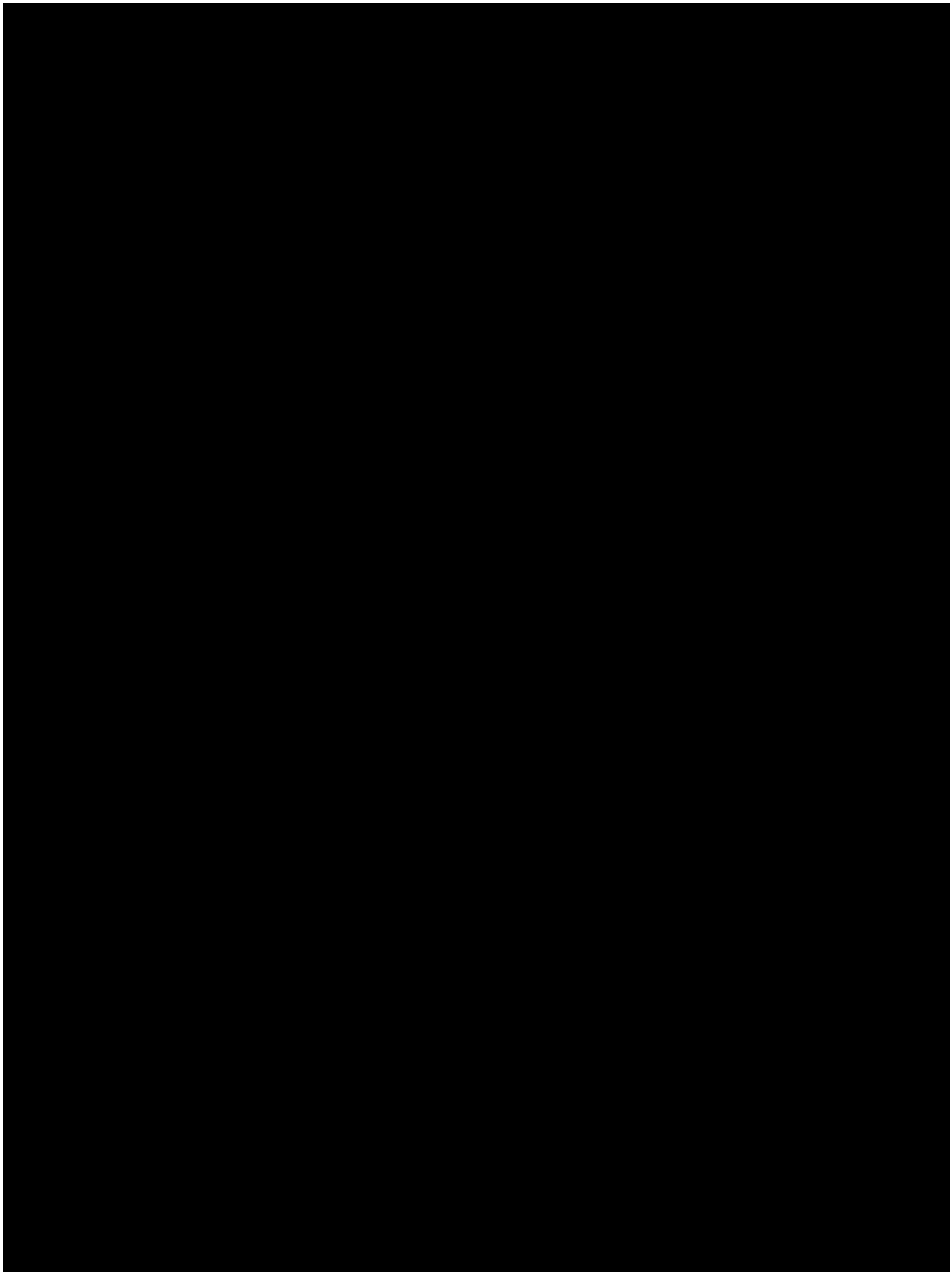

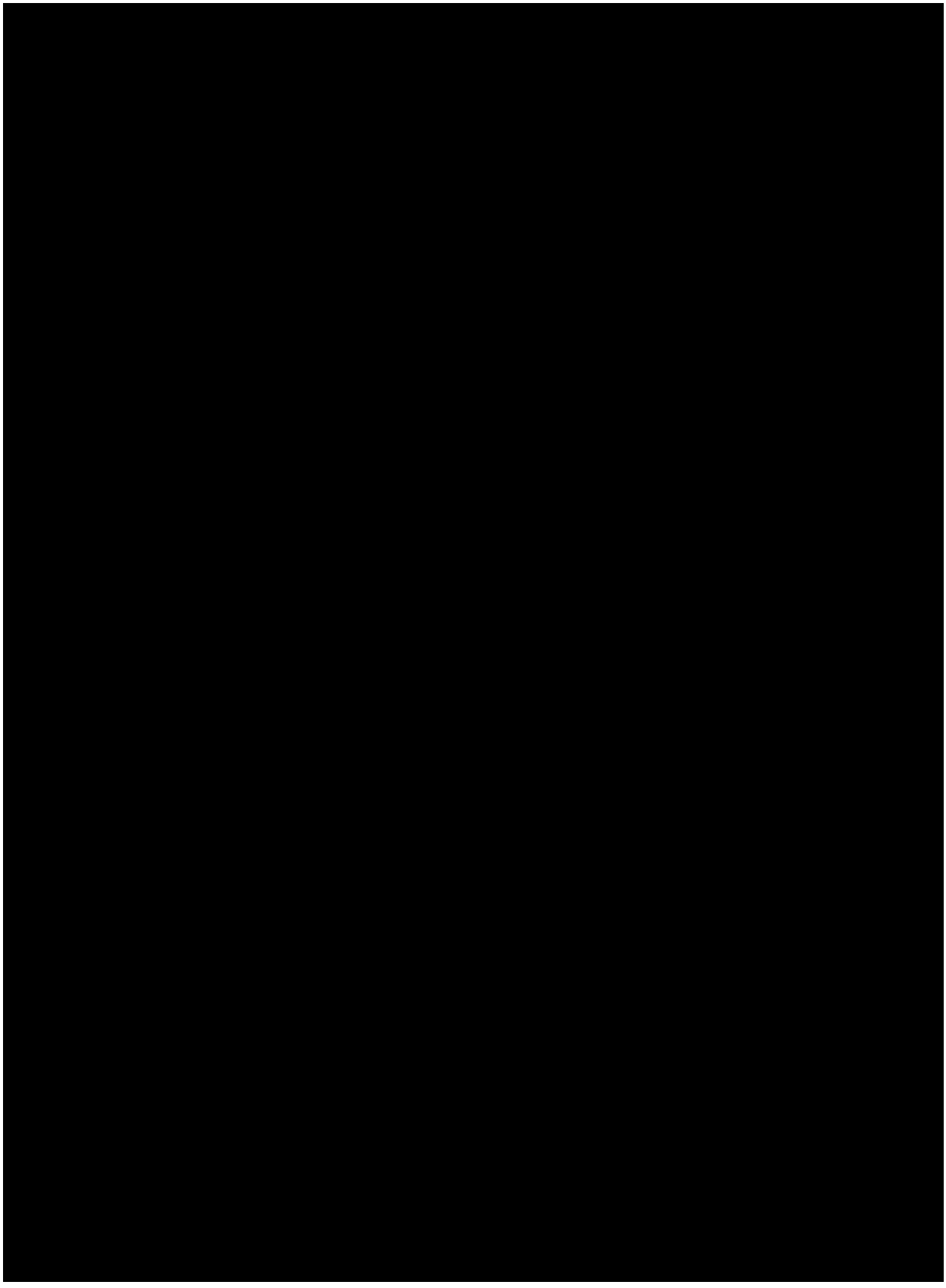

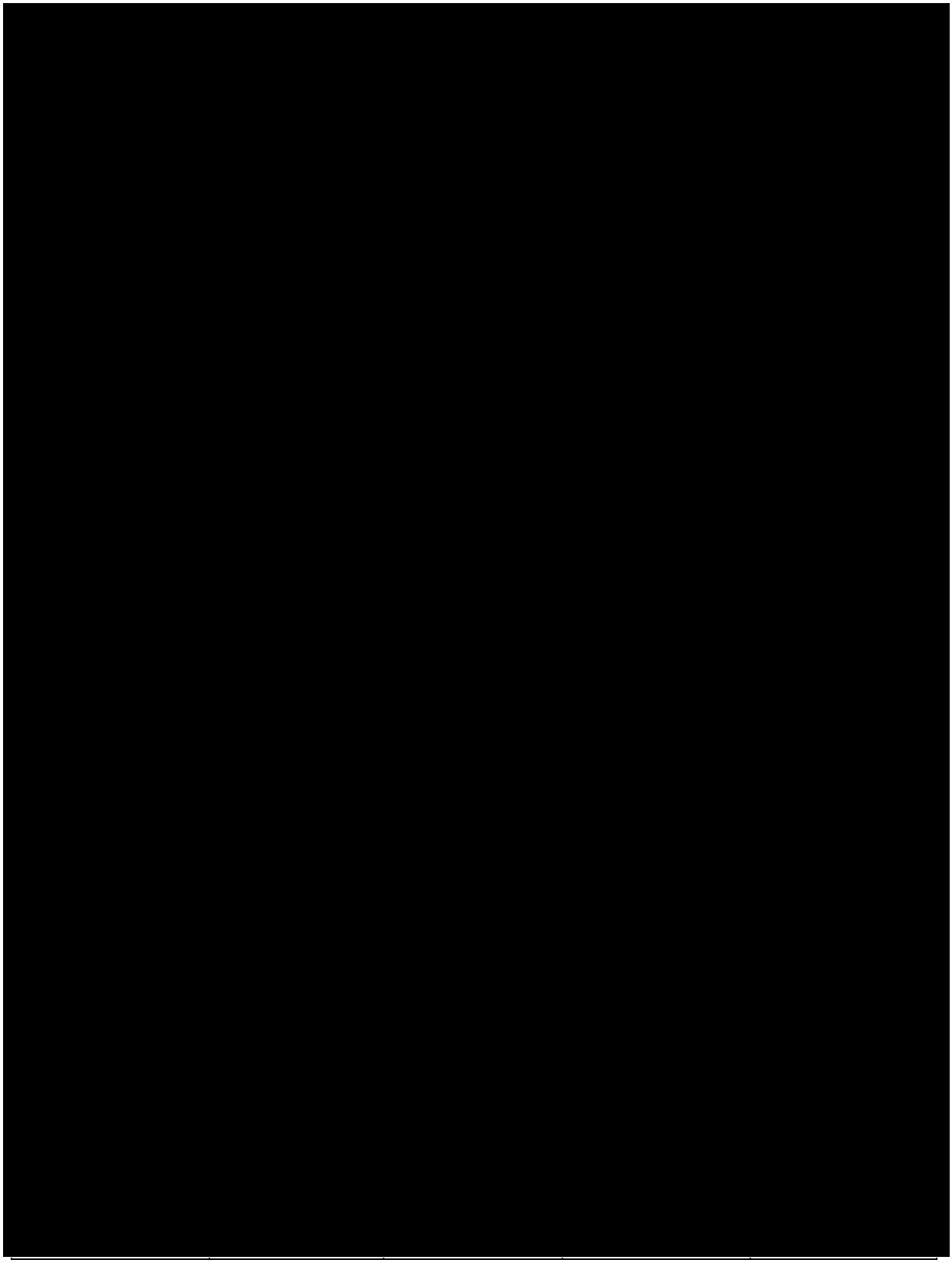

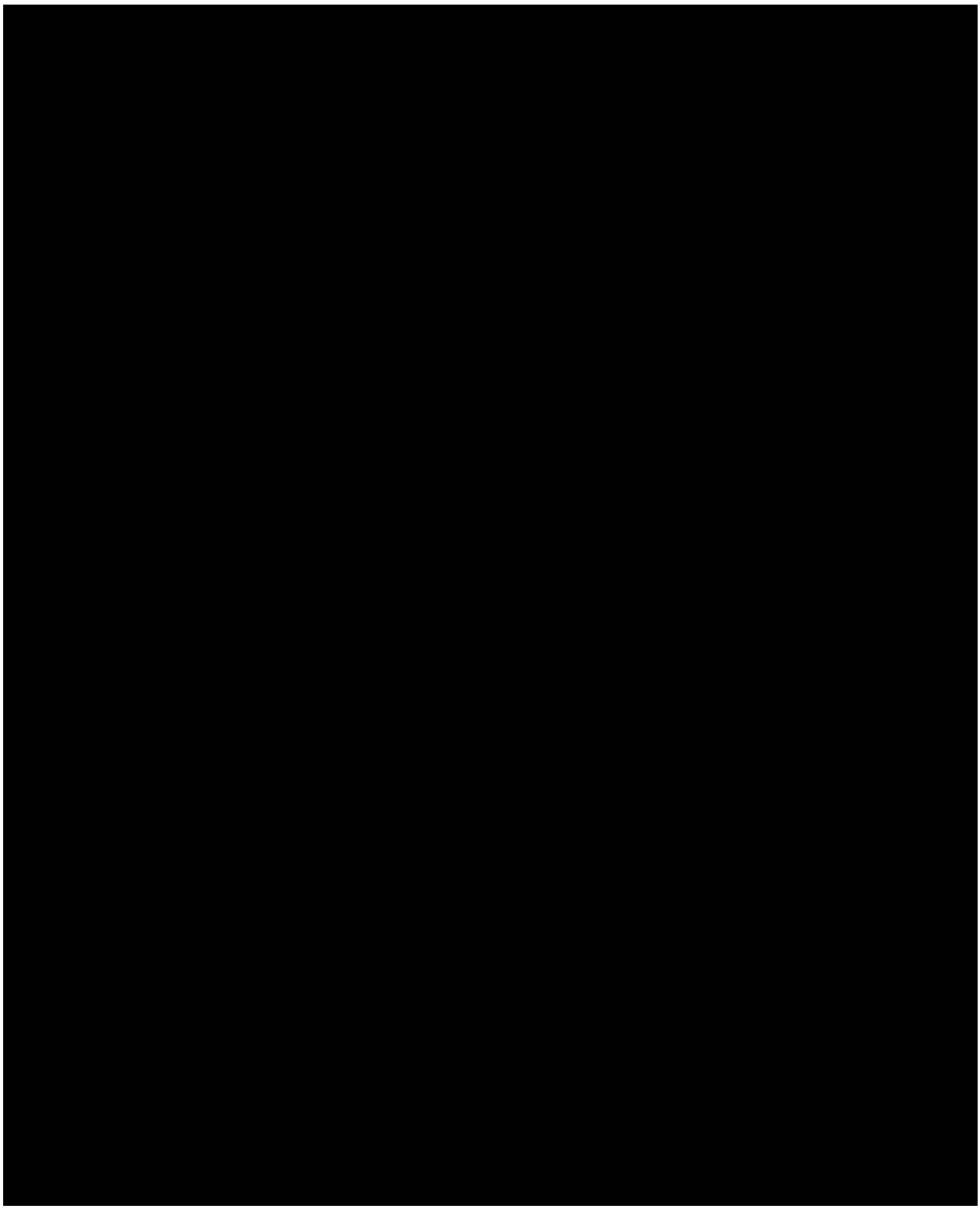

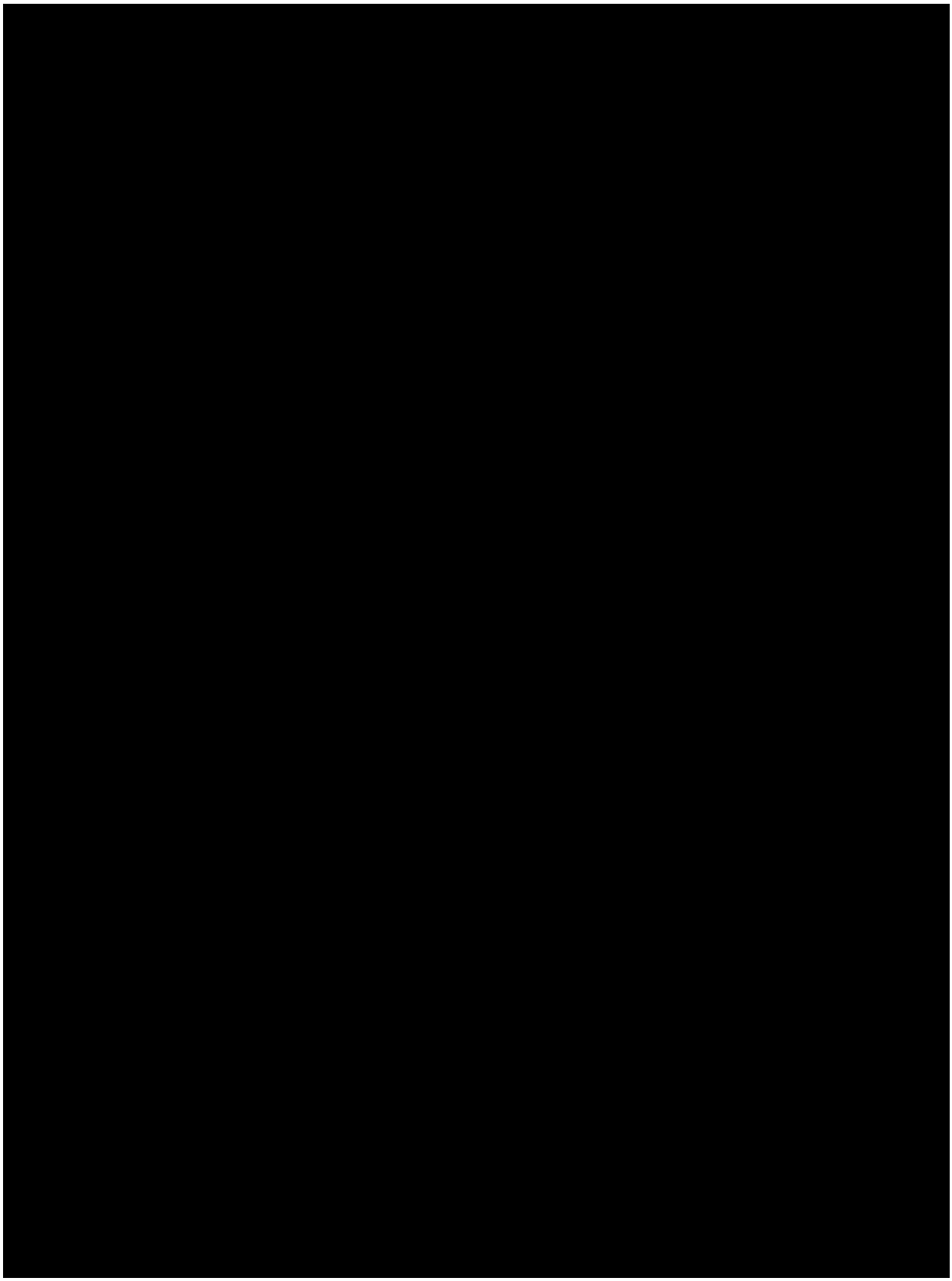

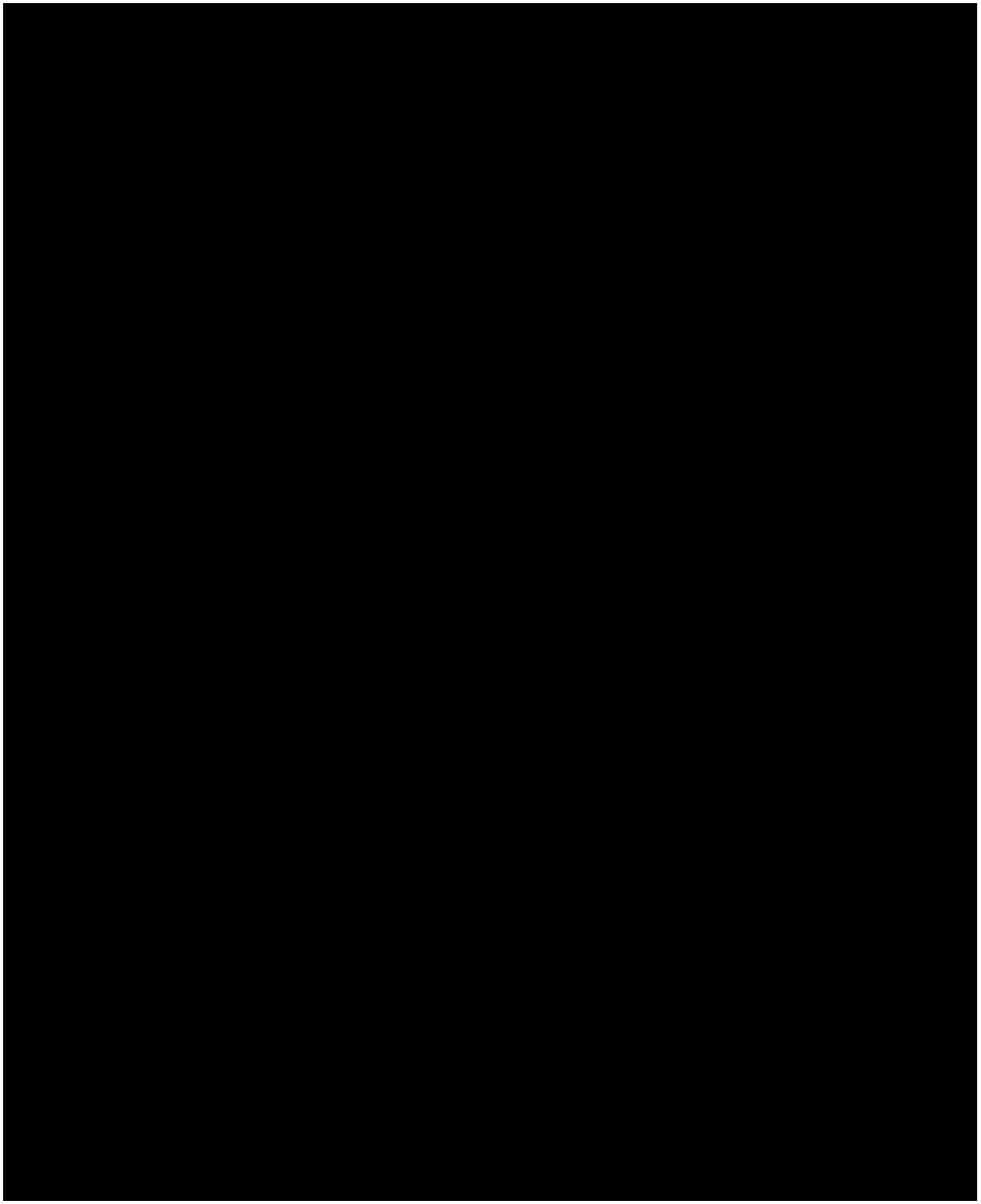

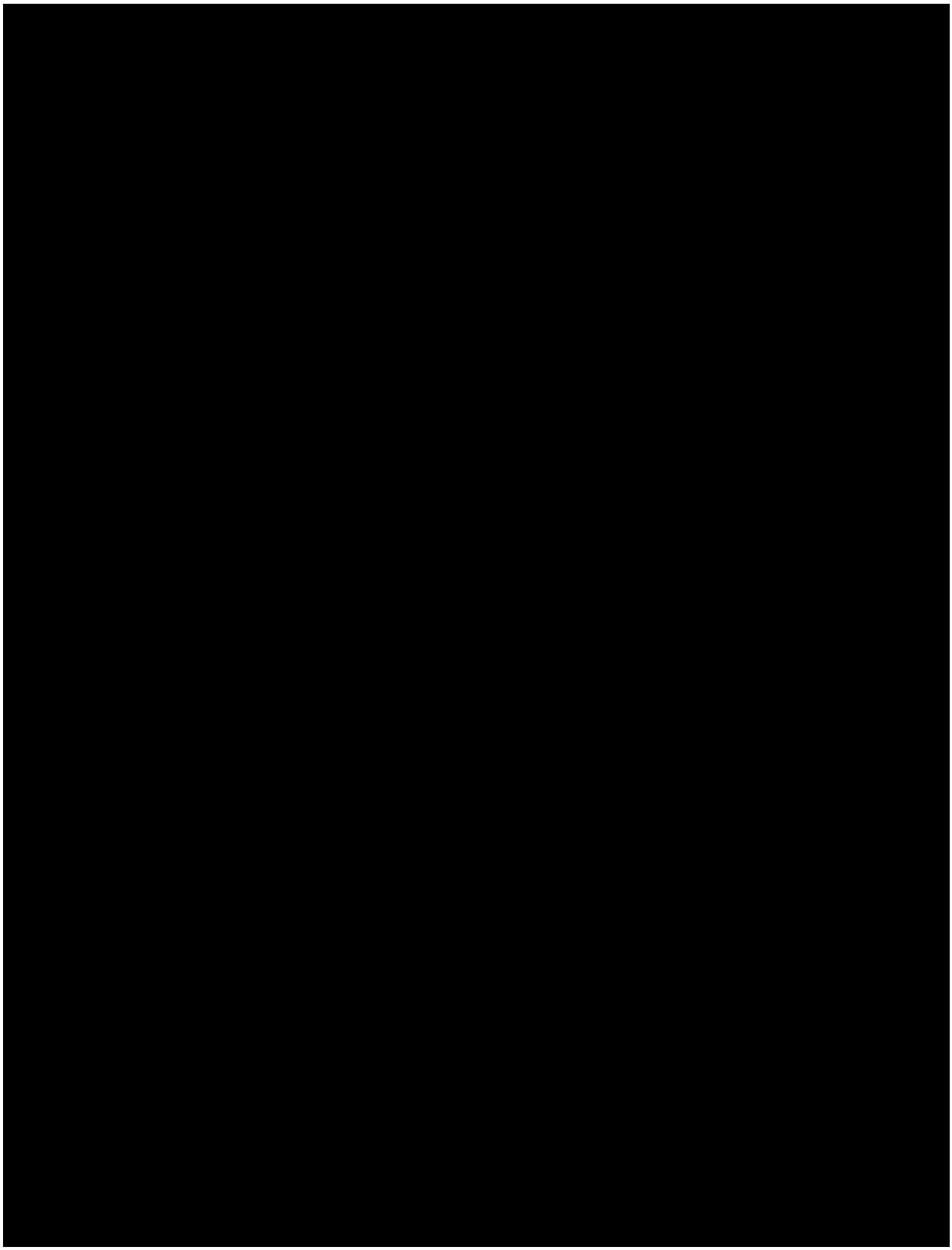

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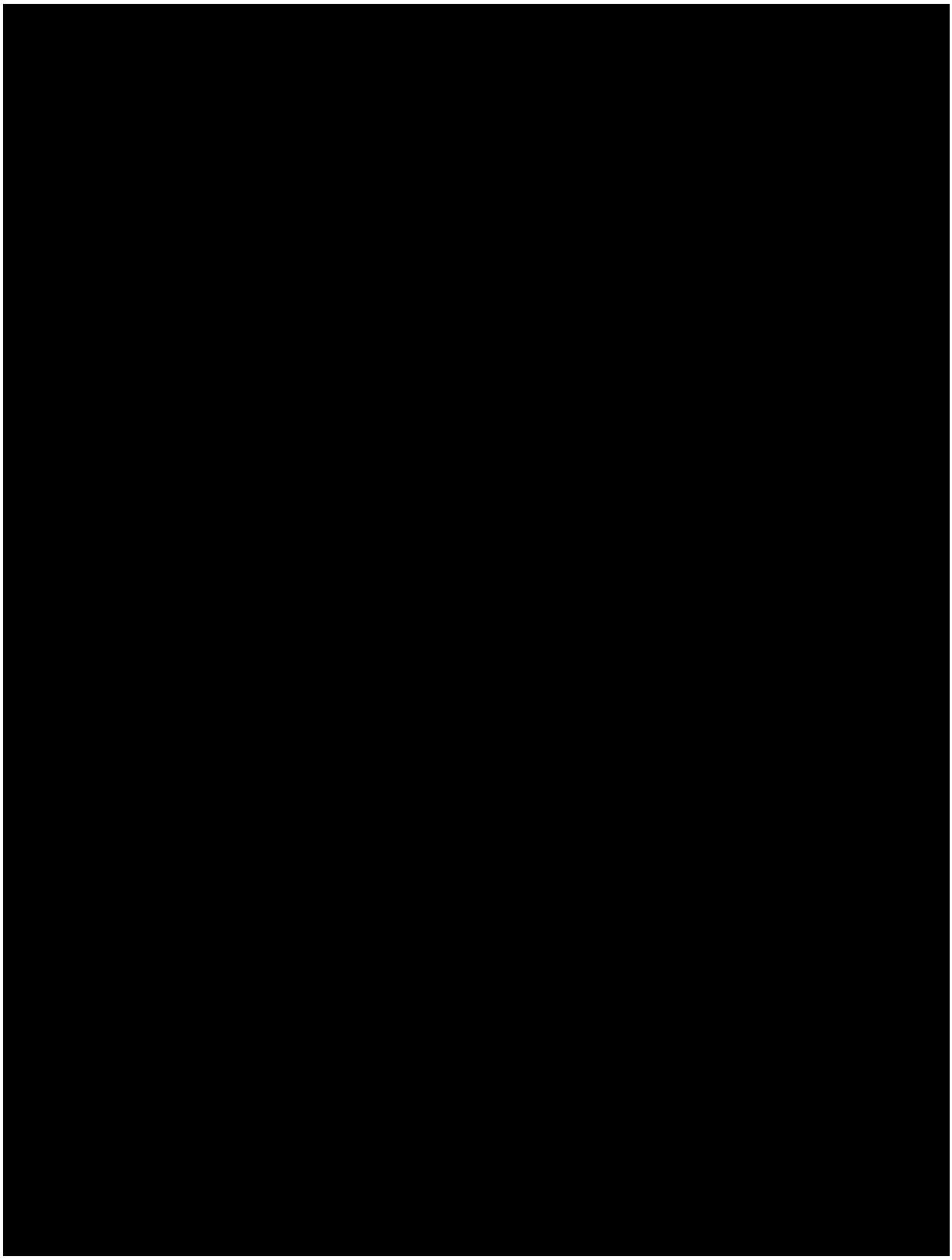

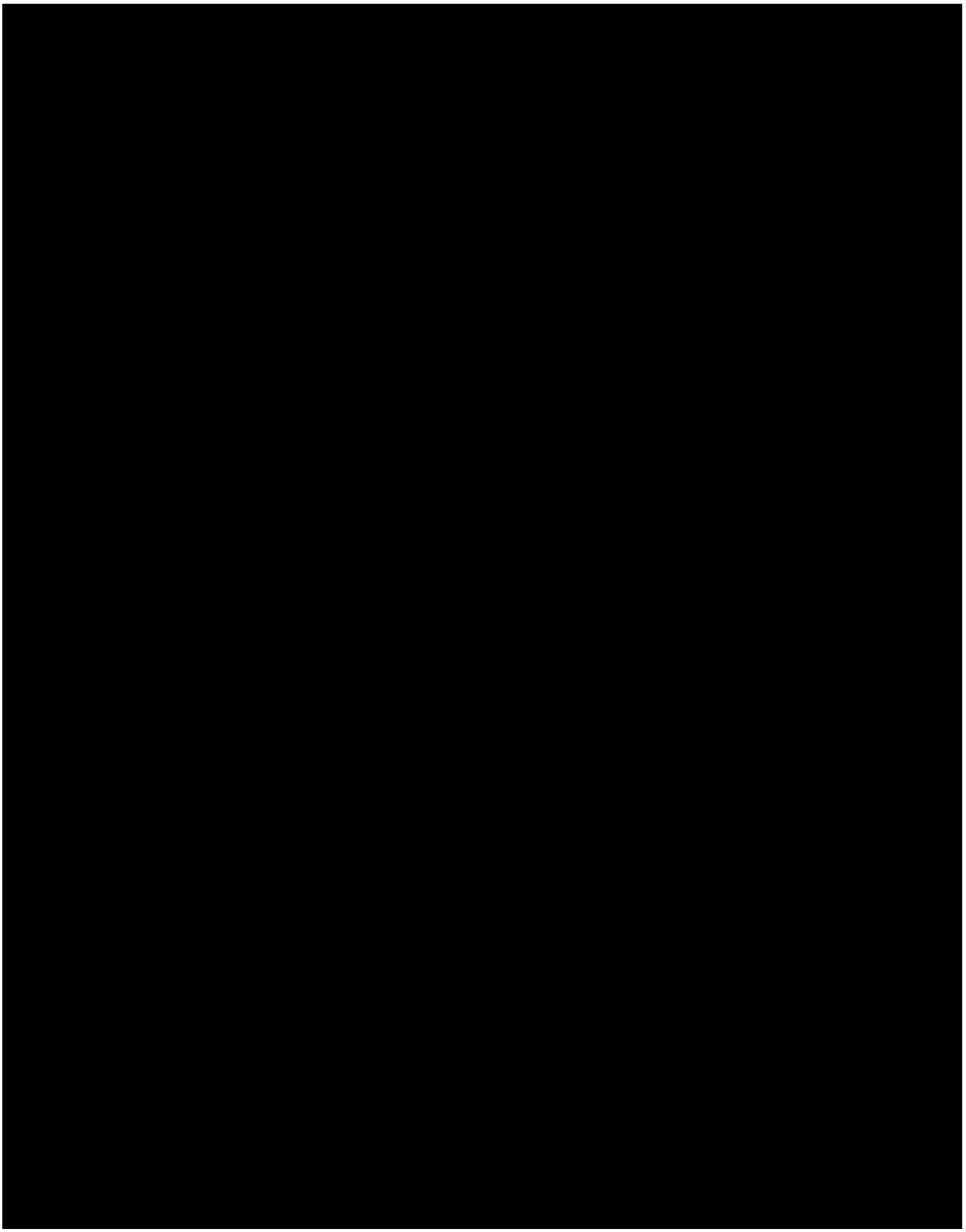

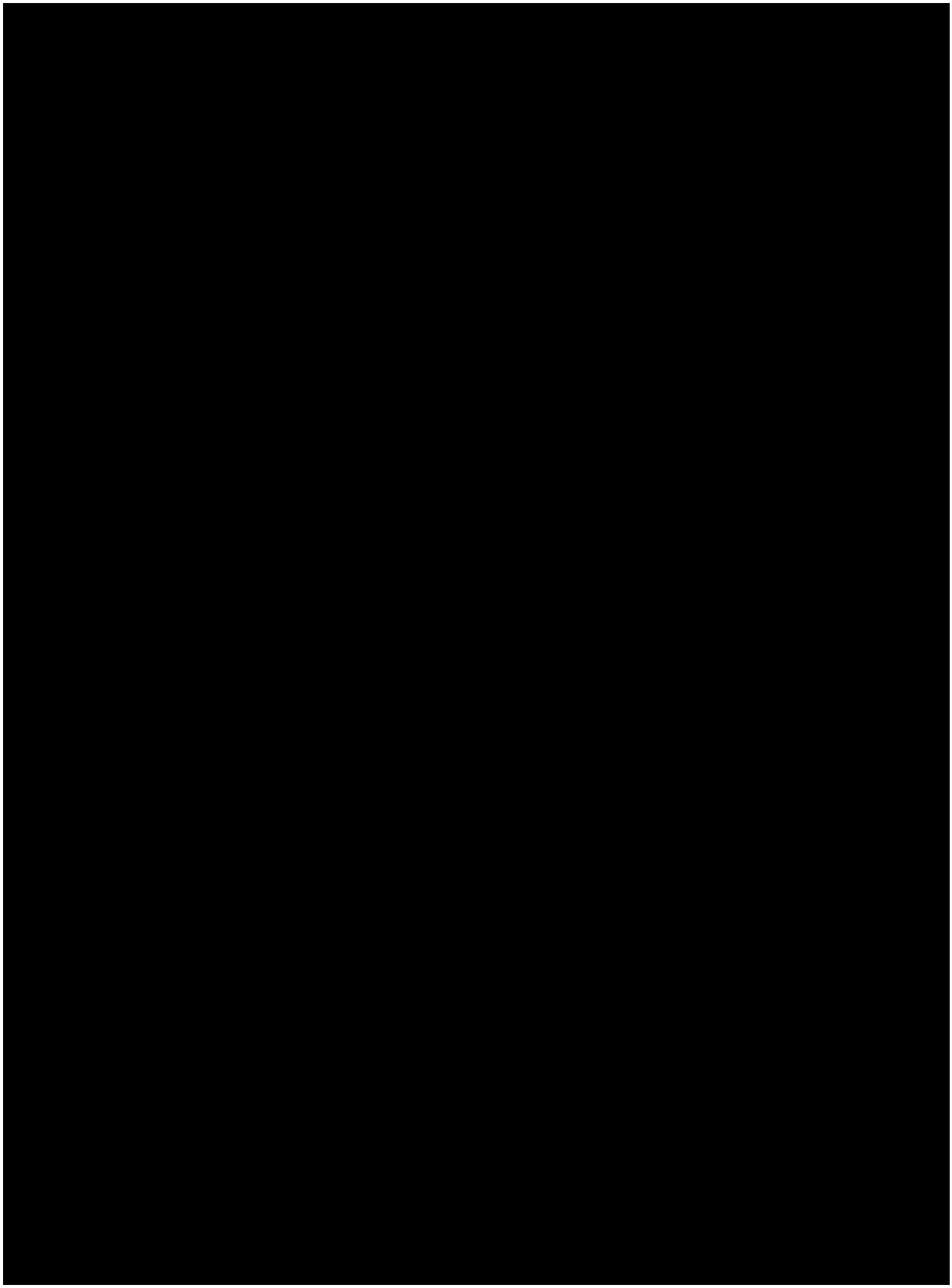

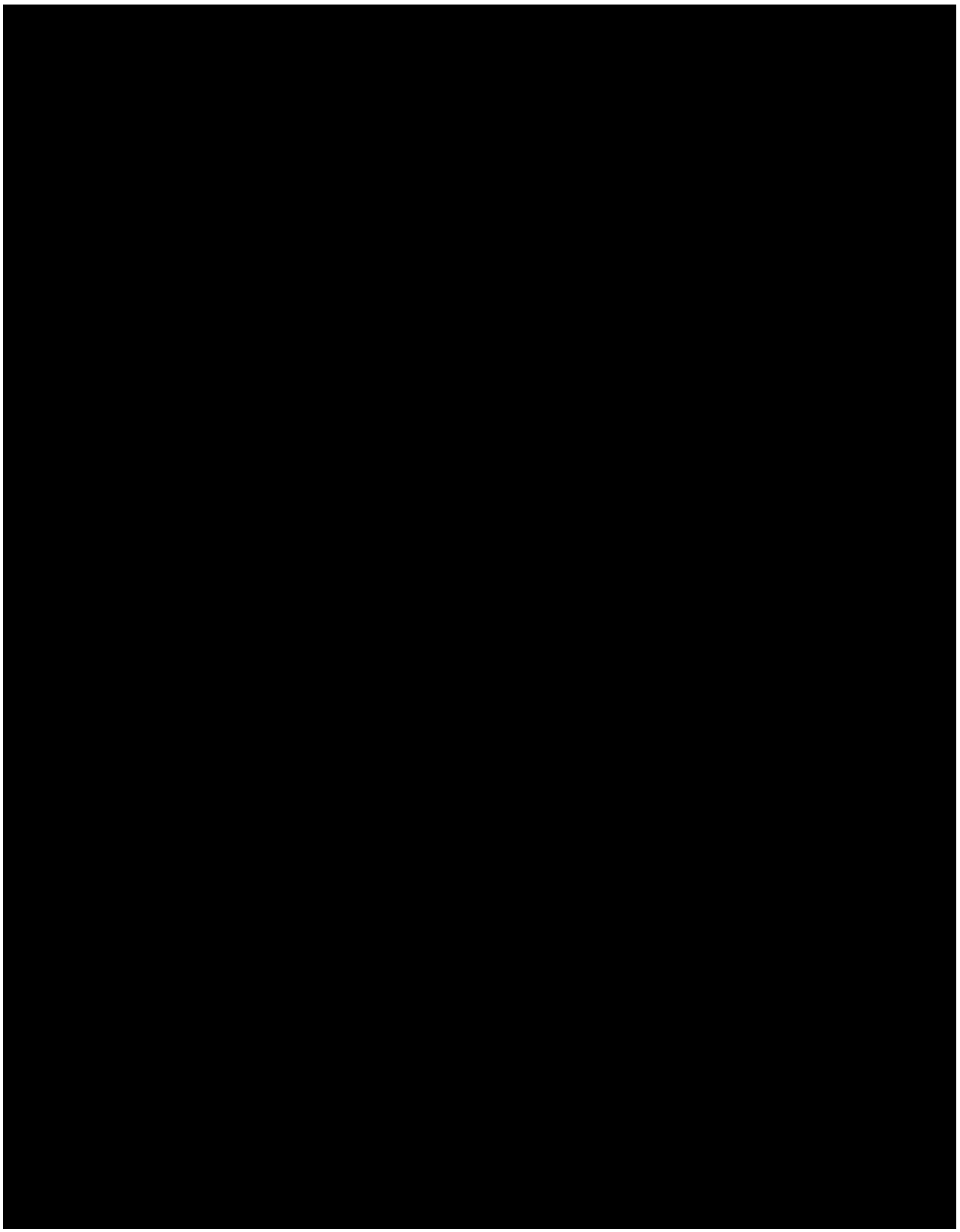

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5.6 Rule of exclusion criteria of analysis sets

Table 5-18 Subject Classification

Analysis Set	PD ID that cause subjects to be excluded	Non-PD criteria that cause subjects to be excluded
RAN	INCL01* M-INCL05-randomized in error	Not randomized
FAS	INCL01*	Not in RAN; Mis-randomized subjects
SAF	INCL01*	No study drug taken

*Written informed consent must be obtained before any assessment is performed.

5.7 Descriptions of some efficacy endpoints

5.7.1 Investigator's Global Assessment grading (IGA)

Table 5-19 IGA

IGA score	*Cutaneous Lichen Planus*	*Mucosal Lichen Planus*	*Lichen Planopilaris*
0 - Clear	No disease. Possible flat, hyperpigmented lesions.	No disease.	No active disease. Hypopigmented, cicatricial patches. Pull test negative.

1 - Minimal	Barely palpable (<0.5 mm), scattered papules, mild erythema. Typically associated with minimal pruritus.	Reticular, white, patch-type striations involving any oral or genital mucosal site(s) ("Wickham Striae"). Absence of ulcers. Typically associated with no symptoms.	Predominantly inactive disease (hypopigmented cicatricial patches). Absence of disease spreading. Pull test negative. Minimal scalp erythema and/or perifollicular erythema without scale. Typically associated with minimal pruritus.
2 - Mild	Moderately elevated papules (<1 mm) and/or small plaques (<2 cm^2). Involvement of limited areas, erythema. Typically associated with mild pruritus.	Plaque-type, mucosal lichen planus involving any oral or genital mucosal site(s). Absence of ulcers or presence of one focal ulceration (<0.5 cm^2). Typically associated with mild pain or sensitivity.	Rare perifollicular erythema, rare perifollicular hyperkeratosis and interfollicular scale. Stable or slowly spreading disease. Pull test negative. Typically associated with mild pruritus.
3 - Moderate	Thick, elevated (<2 mm), hypertrophic, violaceous papules or presence of non-hypertrophic, plaque-like disease (>2 cm^2), either generalized or involving specific areas or specific locations (e.g. face, neck). Red/violaceous erythema, possible scales. Typically associated with moderate pruritus.	Desquamative gingivitis or vulvitis. Presence of unilateral or bilateral ulcerations involving any oral or genital mucosal site(s). Overall area affected by ulceration should be <2 cm^2. Typically associated with moderate pain and sensitivity.	Hairless patches with perifollicular and interfollicular erythema, follicular hyperkeratosis and interfollicular scaling. Active spreading disease. Pull test positive for telogen hairs. Typically associated with moderate pruritus, pain and/or burning.
4 - Severe	Generalized, papular or plaque-type, elevated lesions (>2 mm) OR localized hypertrophic lesions (>2 cm^2). Marked red/violaceous erythema. Possible scales, blisters and ulcers. Typically associated with severe pruritus.	Presence of bilateral or extensive unilateral ulcers involving any oral or genital mucosal site(s). Overall area affected by ulceration should be >2 cm^2. Possible esophageal involvement (established by endoscopy). Typically associated with severe pain and sensitivity.	Hairless patches with perifollicular and interfollicular, intense erythema, extensive perifollicular and interfollicular scaling. Crusting, pustules. Active spreading disease. Pull test positive for telogen or anagen hairs. Typically associated with severe pruritus, pain and/or burning.

The grading should be mainly driven by the lesion characteristics. Symptoms, such as pain

or pruritus, may or may not be associated.

5.7.2 Patient Assessment of Itch (NRS)

Itch is assessed with the following questions:

- "Overall, how severe was your lichen planus-related itching during the past 24 hours?"
- "How severe was your lichen planus-related itching **at the worst moment** during the past 24 hours?"
- "Overall, how bothered were you by your lichen planus-related itching during the past 24 hours?"

Answers are given on a numeric rating scale (NRS). The Patient Assessment of Itch will be assessed on all subjects.

5.7.3 Patient Assessment of Pain (NRS)

Pain is assessed with the following questions:

- "Overall, how severe was your lichen planus-related pain during the past 24 hours?"
- "How severe was your lichen planus-related pain **at the worst moment** during the past 24 hours?"
- "Overall, how bothered were you by your lichen planus-related pain during the past 24 hours?"

Answers are given on a numeric rating scale (NRS). The Patient Assessment of Pain will be assessed on all subjects.

5.7.4 Physician´s assessment of surface area of disease (PSAD)

Assessment scores range from 0-5, with lower scores corresponding to lower percentages of surface area with disease.

0: clear

1: <2% of the total body surface area. Small, localized papules

2: 2-9% of the total body surface area. Lesions affecting limited areas (e.g. wrists or ankles)

3: 10-29% of the total body surface area. Lesions affecting extensive areas (e.g. upper limbs or back)

4: 30-50% of the total body surface area. Lesions affecting extensive areas or in multiple locations (e.g. trunk and lower/upper limbs)

5: >50% of the total body surface area. Generalized involvement

As reference, the percentages utilized for the Body Surface Area (BSA) assessment should be considered (head=10%, trunk=30%, upper limbs=20%, lower limbs=40%).

Post-inflammatory hyperpigmentation should NOT be considered as surface area affected by the disease.

The PSAD assessment is required for all subjects enrolled in the CLP cohort. In addition, the PSAD assessment is required for subjects enrolled in the MLP cohort in case they have a **concomitant** cutaneous involvement.

5.7.5 Reticulations, erythema and ulcerations (REU) score

The REU score is applied for all patients in the MLP cohort who have an **oral** presentation of the disease. In addition, the REU scoring is also done for patients in the CLP cohort in case they have a concomitant **oral** involvement.

The assessment is done as follows:

The oral cavity is divided into the following 10 sites:

- upper/lower labial mucosa
- right buccal mucosa
- left buccal mucosa
- dorsal tongue
- ventral tongue
- floor of mouth
- hard palate mucosa
- soft palate/tonsillar pillars
- maxillary gingiva
- mandibular gingiva

The severity of the lesions is scored for each site individually according to the presence of reticular/hyperkeratotic, erosive/erythematous and ulcerative lesions:

- **Reticulation:** reticular/hyperkeratotic lesions: 0 - 1
  - 0: no white striations
  - 1: presence of white striations or keratotic papules
- **Erythema:** erosive/erythematous lesions by area of involvement: 0 - 3
  - 0: no lesion
  - 1: lesions < 1 cm^2
  - 2: lesions 1 - 3 cm^2
  - 3: lesions > 3 cm^2
- **Ulceration:** ulcerative lesions by area of involvement: 0-3
  - 0: no lesion
  - 1: lesions < 1 cm^2
  - 2: lesions 1 - 3 cm^2
  - 3: lesions > 3 cm^2

For each of the 3 clinical dimensions, a score is then derived by summation of the scores from

all 10 oral cavity sites: Reticular score = ∑R, erythema score = ∑E, and ulcerative score = ∑U. These 3 scores then add up to a **total weighted score: ∑R + ∑(E x 1.5) + ∑(U x 2.0).**

5.7.6 Lichen planopilaris Activity Index (LPPAI)

The LPPAI assesses symptoms (pruritus, pain, burning), signs (erythema, perifollicular erythema and scale), a measure of activity (pull test) and extension of disease. These subjective and objective measures are assigned numeric values to establish a disease activity score. Whenever possible, the LPPAI assessment should be performed by the same evaluator throughout the study. It is applied for subjects in the LPP cohort only.

Table 5-20 LPPAI

Symptoms	**Score**
Pruritus	0 - 3
Pain	0 - 3
Burning	0 - 3
Signs	
Scalp erythema	0 - 3
Perifollicular erythema	0 - 3
Perifollicular scale	0 - 3
Pull test	0 / 1 & anagen / total
Spreading	0 - 2

Score for signs and symptoms: 0=absent, 1=mild, 2=moderate, 3=severe

Score for anagen pull test: To conduct the anagen pull test grasp a small group of 10 - 20 hairs between the thumb, second and third finger at the scalp end of the hair shafts and pull away from the scalp with a slow, firm perpendicular force to slide the fingers to the ends of the hair. The result is recorded both as a binary value (**0** for **no** anagen hairs, **1** for the **presence** of anagen hairs) and as anagen hairs/total hairs pulled.

Score for spreading: 0 = no spreading, 1 = indeterminate, 2 = spreading. When the hair loss is difficult to judge, the issue of spreading is recorded as indeterminate.

The weights given to the symptoms (30%), signs (30%), anagen pull test (25%) and presence of spreading (15%) then lead to the final equation:

LPPAI (0-10) = (pruritus + pain + burning + scalp erythema + perifollicular erythema + perifollicular scale)/3 + 2.5x(pull test) + 1.5x(spreading/2)

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