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Title: A PHASE 3, MULTICENTER, RANDOMIZED, OPEN-LABEL STUDY TO EVALUATE THE LONG-TERM SAFETY AND TOLERABILITY OF ORAL ATOGEPANT FOR THE PREVENTION OF MIGRAINE IN PARTICIPANTS WITH EPISODIC MIGRAINE

Statistical Analysis Plan Date: June 23, 2020

1 Title Page

STATISTICAL ANALYSIS PLAN

A PHASE 3, MULTICENTER, RANDOMIZED, OPEN-LABEL STUDY TO EVALUATE THE LONG-TERM SAFETY AND TOLERABILITY OF ORAL ATOGEPANT FOR THE PREVENTION OF MIGRAINE IN PARTICIPANTS WITH EPISODIC MIGRAINE

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Study Statistician:	[redacted]
Sponsor Name and Legal Registered Address**:**	Allergan Pharmaceuticals International Limited Marlow International The Parkway, Marlow SL7 1YL United Kingdom

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Table 3-1 Abbreviations and Definitions of Terms

Abbreviation/Term	Definition
AE	adverse event
AIM-D	Activity Impairment in Migraine - Diary
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
C-SSRS	Columbia–Suicide Severity Rating Scale
eCRF	electronic case report form
ePRO	electronic patient report outcome
ECG	electrocardiogram, electrocardiographic
EM	episodic migraine
ET	early termination
INR	international normalized ratio
ITT	intent-to-treat
MedDRA	Medication Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMRM	mixed-effects model for repeated measures
PCS	potentially clinically significant
PID	participant identification
PT	preferred term
Q1	first quartile (25th percentile of the data)
Q3	third quartile (75th percentile of the data)
QD	once daily
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using the Bazett formula ($QTcB = QT/(RR)^{1/2}$)
QTcF	QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/(RR)^{1/3}$)
SAE	serious adverse event
SAP	statistical analysis plan
SI	Le Système International d'Unités (International System of Units)
SOC	standard of care
TBL	total bilirubin
TEAE	treatment-emergent adverse event
WHO	World Health Organization

4 Introduction

This statistical analysis plan (SAP) details comprehensive, technical specifications of the statistical analyses of the [redacted] safety data outlined and/or specified in the protocol amendment #2 (dated 24 April 2020) of Study 3101-302-002. Specifications of tables, figures, and data listings are contained in a separate document.

This study is a multicenter, randomized, open-label, 52-week, long-term safety study conducted in the United States and will enroll approximately 700 participants from approximately 115 sites. Participants will be randomized in a ratio of 5:2 to the following treatment groups: atogepant 60 mg QD or oral standard of care (SOC) migraine prevention medication.

All participants randomized to oral SOC migraine prevention medication will be treated with a medication recognized as safe and effective for the prevention of migraine. The selection of this initial migraine preventive medication is based on investigator judgment in consultation with the participant. For participants who do not tolerate this initial preventive medication or for whom the medication is not sufficiently effective (per investigator judgment), the investigator may choose to:

1. Prescribe an alternative medication from the medicines recognized as safe and effective for the prevention of migraine (Protocol Section 5.6.3), *OR*
2. Prescribe an alternative migraine preventive medication not listed in the medicines recognized as safe and effective for the prevention of migraine [redacted]), *OR*
3. Not prescribe an alternative migraine preventive medication.

Two groups of participants will be eligible to participate in this study.

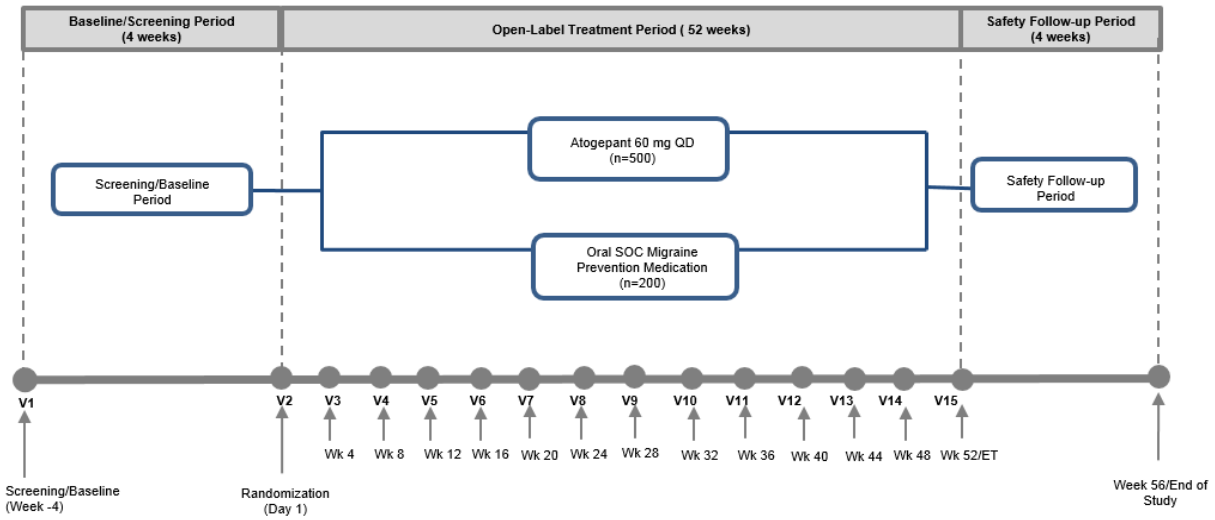
- De Novo Participants - participants with no previous exposure to atogepant and who meet the inclusion criteria and do not meet the exclusion criteria (referred to as De Novo Participants).
- Study CGP-MD-01 Completers - participants who completed Study CGP-MD-01 (Visit 8) without significant protocol deviations (eg, noncompliance to protocol-required procedures) and who meet the inclusion criteria and do not meet the exclusion criteria (referred to as CGP-MD-01 Completers).
    - For participants who completed Study CGP-MD-01, there will be a time gap from the time of completion of Study CGP-MD-01 to the start of this study.

For this reason, participants from Study CGP-MD-01 will need to re-establish study eligibility. In addition, these participants will have their baseline migraine days re-established during the screening period, but this will not be used as an inclusion/exclusion criteria for randomization.

A minimum of 200 participants randomized to atogepant must be classified as De Novo Participants.

The study will consist of a 4-week screening and baseline period, a 52-week treatment period, and a safety follow-up period of 4 weeks. For participants randomized to the atogepant arm, a safety follow-up visit will occur 4 weeks after the last dose of atogepant. For participants randomized to the oral SOC migraine prevention medication arm a safety follow-up visit will occur 4 weeks after the last visit in the treatment period. There will be 16 scheduled clinic visits. De Novo Participants and Study CGP-MD-01 Completers will complete all 16 study visits, including the 28-day screening period.

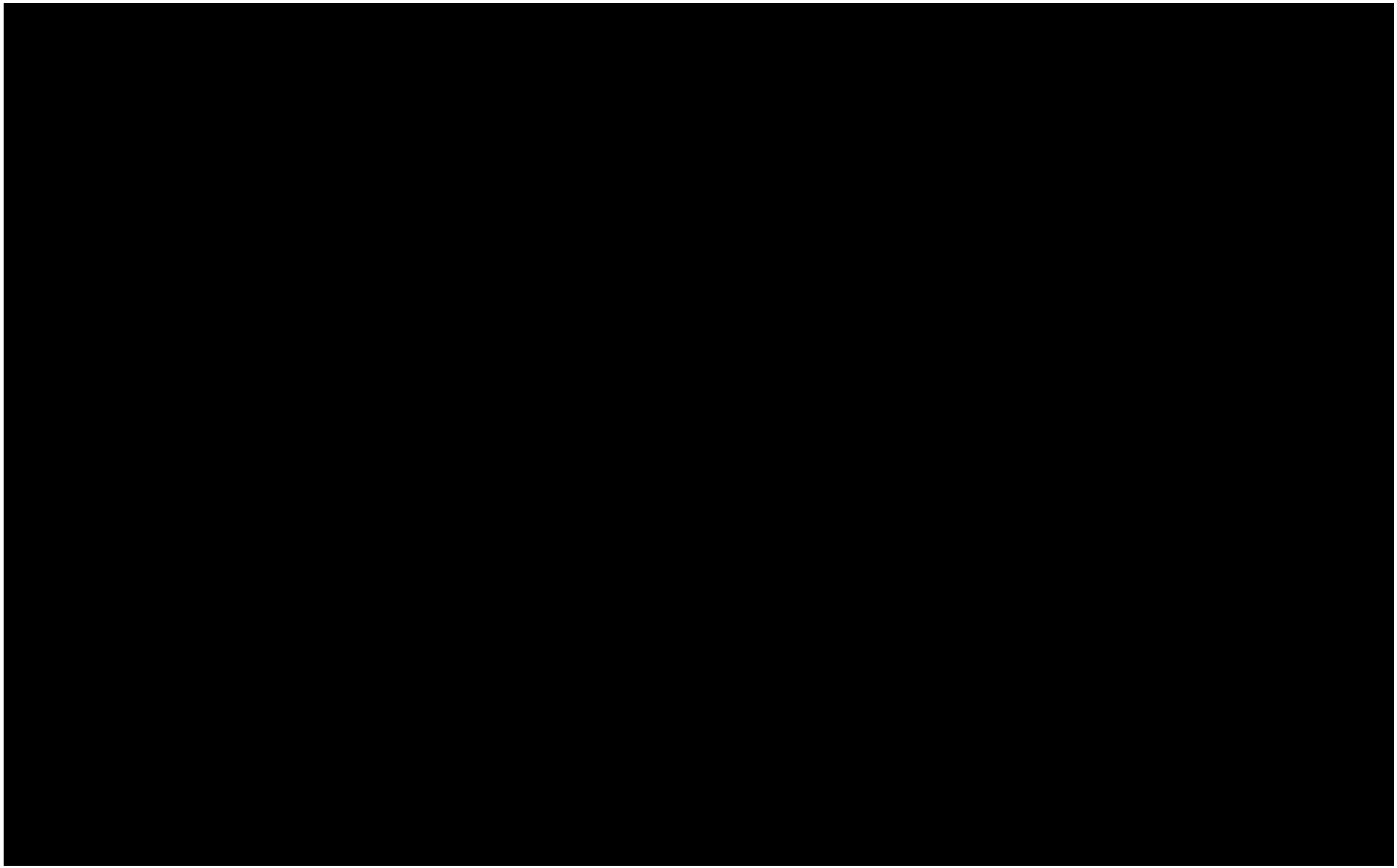
Figure 4-1 Study Design

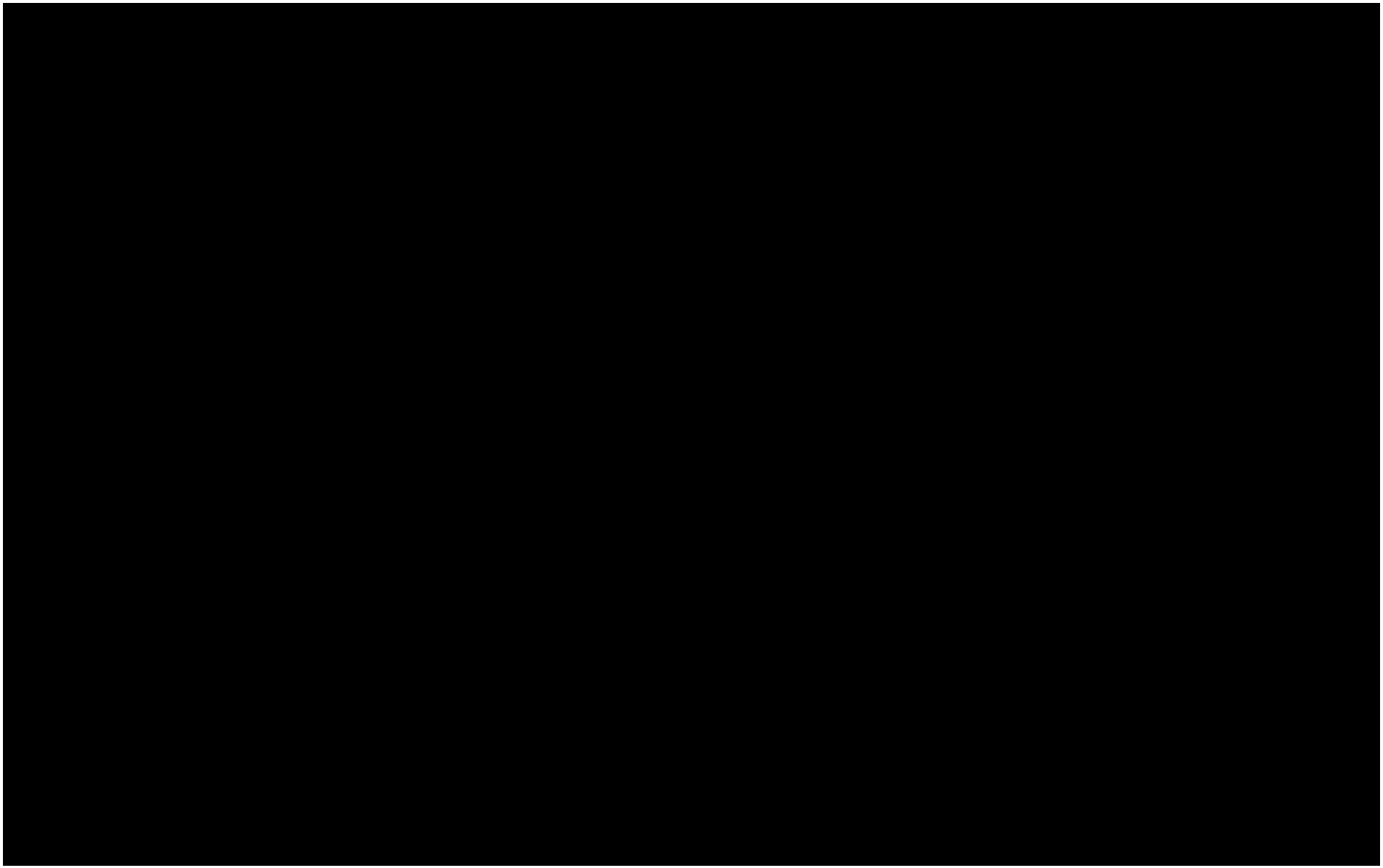


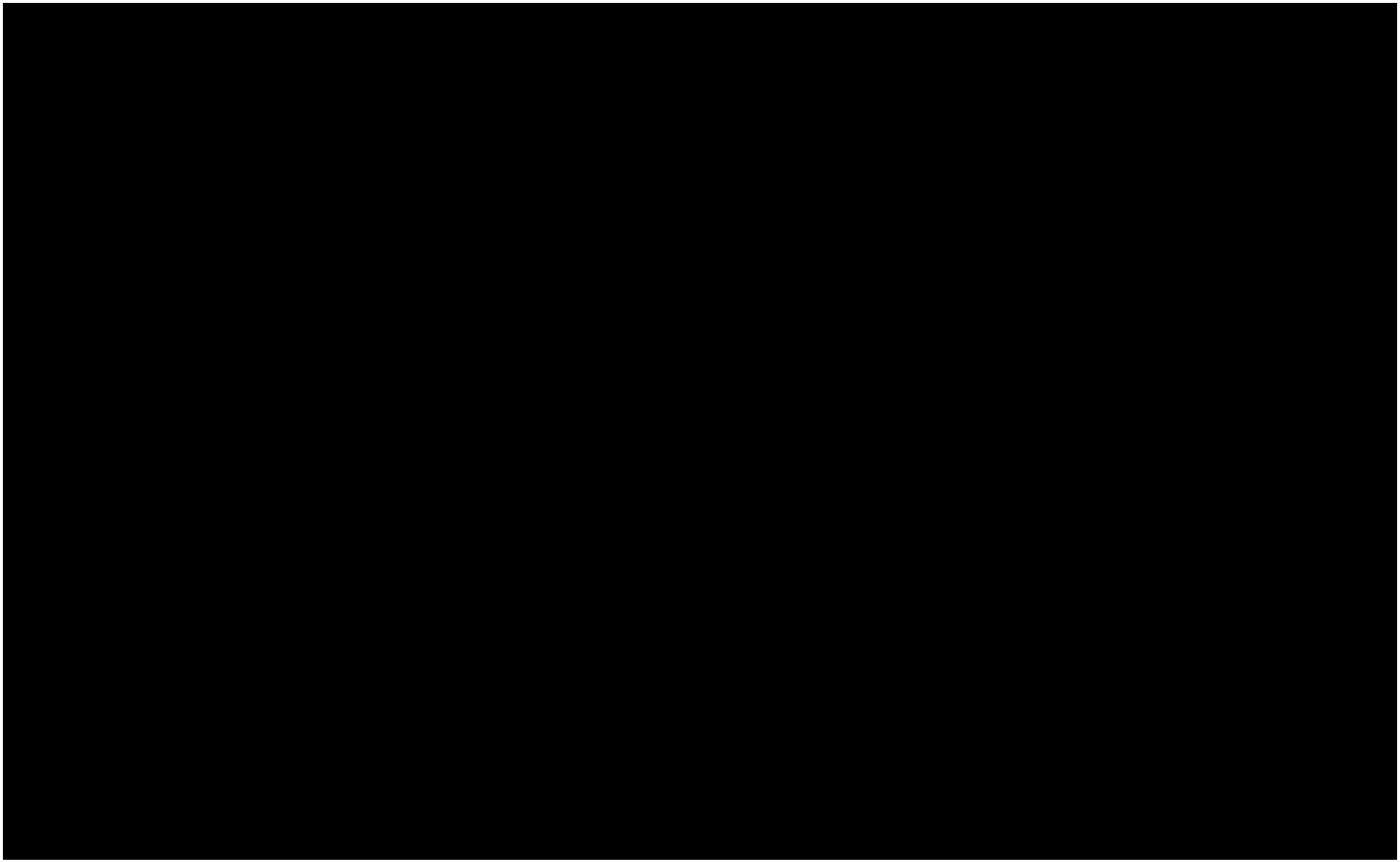
ET = early termination; QD = daily; V = visit.

Table 4-1 Schedule of Activities (SoA) for in-Person Visits Conducted Prior to or During the COVID-19 Pandemic

[redacted]







5 Study Objectives

The study objective is to evaluate the safety and tolerability of daily treatment with atogepant 60 mg QD when administered over 52 weeks for the prevention of migraine in participants with EM.

6 Analysis Populations

The analysis populations will consist of participants as defined below.

The Intent-to-Treat (ITT) Population includes of all randomized participants.

The Safety Population includes all participants who received at least 1 dose of study intervention (atogepant or SOC medication). All safety analyses will be performed using the Safety Population, which is defined for the atogepant arm, as well as the SOC arm, and based on the treatment actually received, regardless of assigned treatment according to the planned randomization. Participants will be summarized according to the study treatment received for majority of treatment period.

[redacted]

7 Participant Disposition

The number of participants in the ITT and Safety Populations will be summarized by treatment group; the number of participants in the mITT Population will be summarized for the atogepant arm; the number of participants screened will be summarized overall. The number of participants in the ITT Population will also be summarized by treatment group for each enrollment category (De Novo Participants and CGP-MD-01 Completers). For CGP-MD-01 Completers, the number of participants in the placebo arm and pooled atogepant arm will be further summarized. In addition, the number of participants in the Safety Population will be summarized by treatment group [redacted]

Screen-failure participants (ie, participants screened but not randomized) and the associated reasons for failure to randomize will be tabulated overall for the all screened participants. The number and percentage of participants who enter the open-label treatment period, complete the open-label treatment period and of participants who prematurely discontinue during the same period will be presented for each treatment group and pooled across treatment groups for all randomized participants. The reasons for premature discontinuation from the open-label treatment period as recorded on the termination pages of the electronic case report forms will be summarized (number and percentage) by treatment group. The percentage is relevant to the total number of randomized participants. Similar disposition information will be presented for the safety follow-up period. All randomized participants who prematurely discontinue during the open-label treatment period or the safety follow-up period will be listed by discontinuation reason.

8 Demographic and Other Baseline Characteristics

Demographic parameters (age; age groups [< 20, 20-29, 30-39, 40-49, 50-59, 60-69, and ≥ 70; < 40 years, ≥ 40 years to < 65 years, ≥ 65 years; < 75 years, ≥ 75 years]; race; race group [white, all other races]; ethnicity; sex), baseline characteristics (weight; height; and body mass index, calculated as weight [kg]/(height [m])^2) will be summarized descriptively by treatment group for the Safety Population. Similar summary table will also be provided in the atogepant arm for mITT Population. Continuous variables will be summarized by number of participants and mean, SD, median, first quartile (Q1), third quartile (Q3), minimum, and maximum values. Categorical variables will be summarized by number and percentage of participants.

Abnormalities in participants' medical and surgical history will be coded using the Medical Dictionary for Regulatory Activities, version 20.1 or newer. The number and percentage of participants with abnormalities in medical and surgical history in each system organ class and preferred term will be summarized by treatment group for the Safety Population.

[redacted]

Prior medication is defined as any medication taken before the first dose of open-label study treatment. Concomitant medication is defined as any medication taken on or after the date of the first dose of the open-label study treatment.

Prior medication use will be summarized by the number and percentage of participants in each treatment group receiving each medication within each therapeutic class for the Safety Population. Concomitant medication use will be summarized by the number and percentage of participants in each treatment group receiving each medication within each therapeutic class for the open-label treatment period and safety follow-up period for the Safety Population. If a participant took a specific medication multiple times or took multiple medications within a specific therapeutic class, that participant would be counted only once for the coded drug name or therapeutic class. Any prior and concomitant medications will be included in listings. The World Health Organization (WHO) Drug Dictionary Enhanced, March 2017 or newer, will be used to classify prior and concomitant medications by therapeutic class and drug name.

Protocol deviations will be defined in Protocol Deviation Requirement Specification, including importance classification. The number and percentage of participants with significant protocol deviations will be summarized by treatment group for randomized participants.

[redacted]

9 Extent of Exposure and Treatment Compliance

9.1 Extent of Exposure

Exposure to open-label study treatment for the Safety Population during the treatment period will be summarized for treatment duration, calculated as the number of days from the date of the first dose of open-label study treatment taken to the date of the last dose taken, inclusive. For participants randomized to the SOC arm, the treatment duration is regardless of switching to different SOC medications during the treatment period. For those participants who were still taking SOC study medication during the safety follow-up period, the last dose date will be determined up to Visit 16. The number and percentage of participants with each treatment duration of ≥ 1 day, ≥ 28 days, ≥ 56 days, ≥ 84 days, ≥ 90 days, ≥ 112 days, ≥ 140 days, ≥ 168 days, ≥ 180 days, ≥ 196 days, ≥ 224 days, ≥ 252 days, ≥ 270 days, ≥ 280 days, and ≥ 360 days will be summarized by treatment group. Descriptive statistics (number of participants, mean, SD, median, Q1, Q3, minimum, and maximum) will also be summarized by treatment group.

Participant-years, defined as exposure to the study treatment in years, will be summarized by treatment group for the Safety Population.

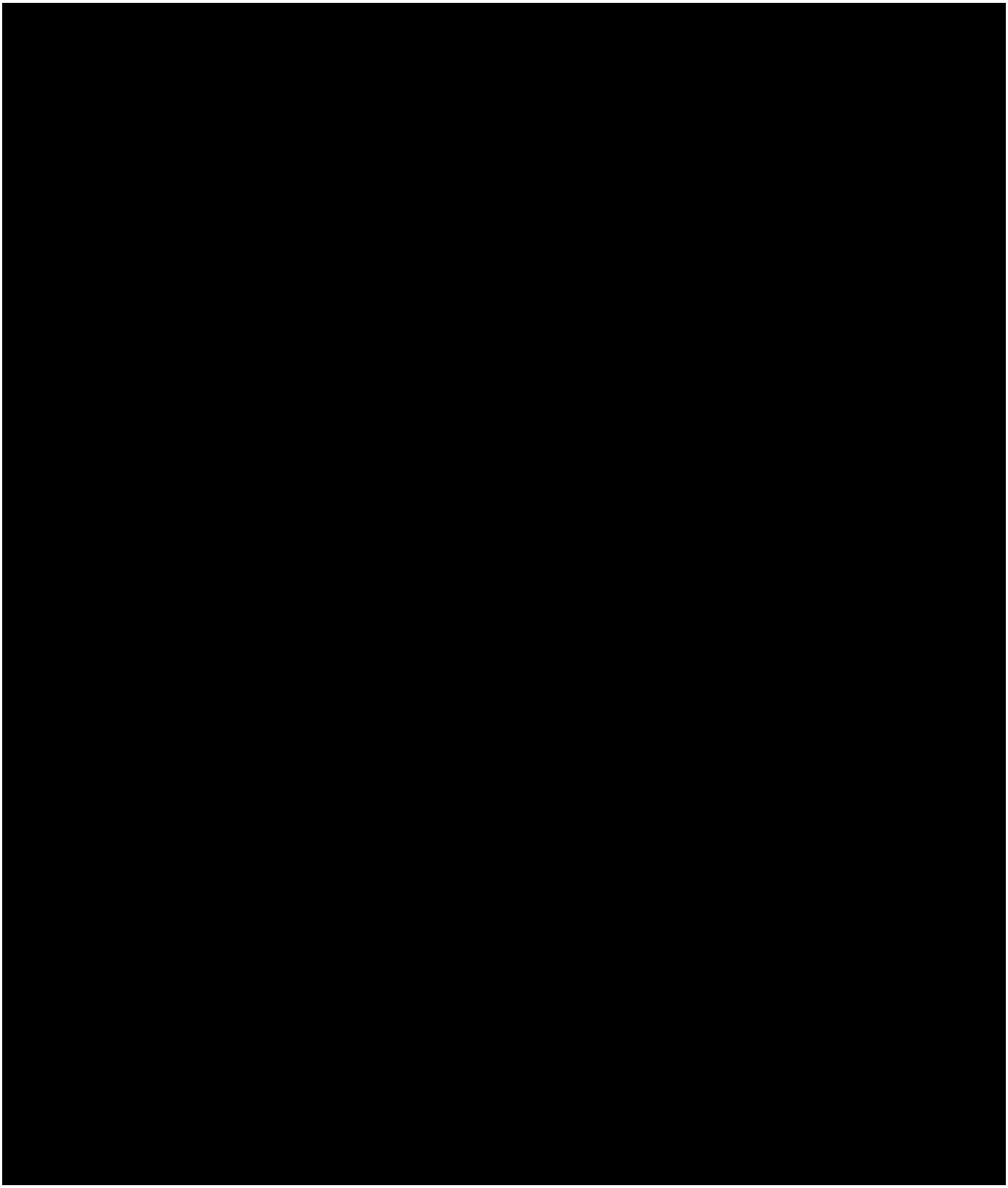
The number and percentage of participants who take 1, 2, 3, 4, or ≥ 5 SOC medications during the study will be tabulated only for the SOC arm using the Safety Population. Descriptive statistics will also be provided for the number of SOC medications taken during the study.

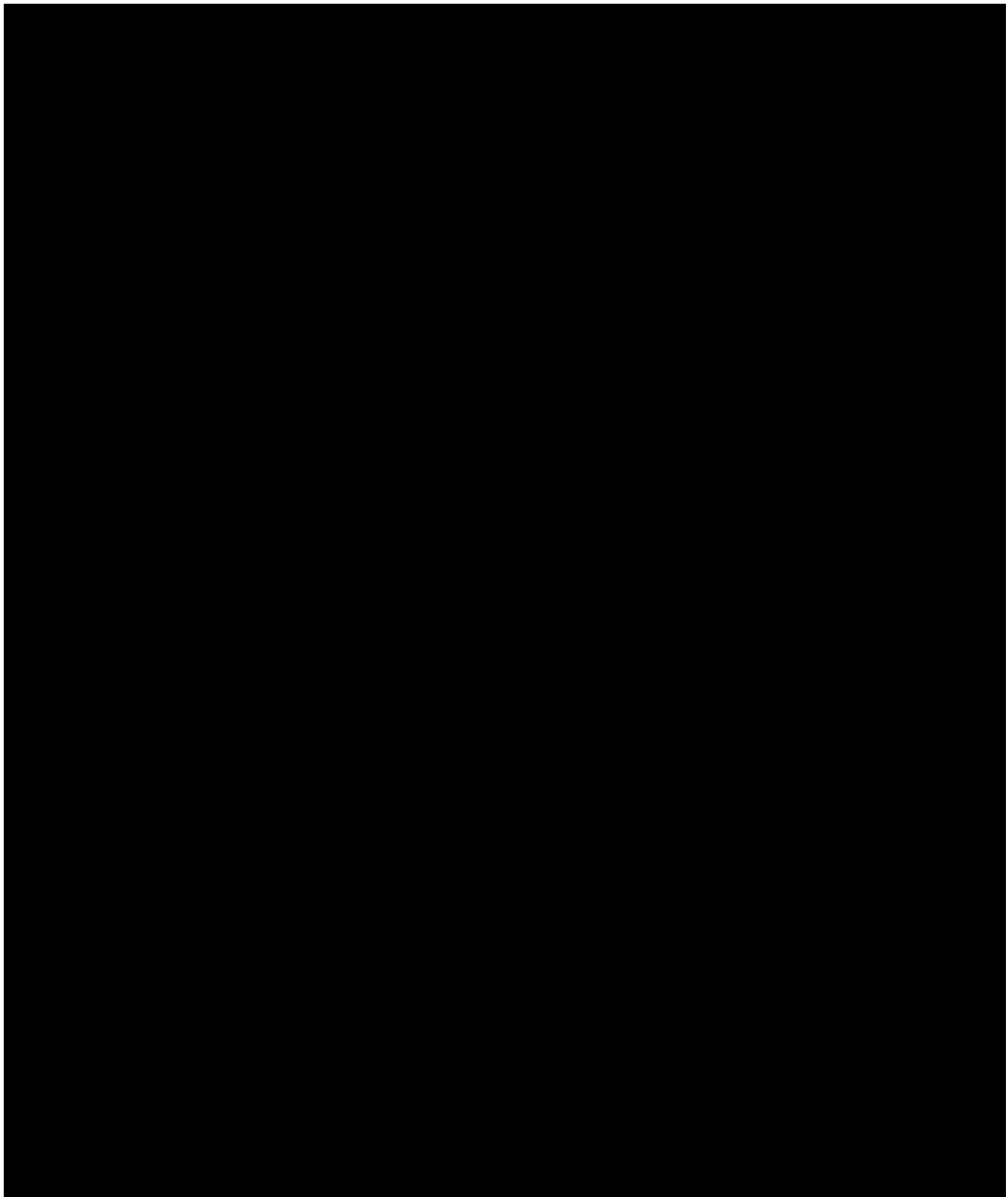
The number and percentage of participants who take the initial assigned SOC medication will be tabulated by mechanism of action and medication only for the SOC arm using the Safety Population. Similar tabulation will be provided for participants who stop the initial assigned SOC medication and further tabulated by the corresponding reason for stopping the medication. In addition, the number and percentage of participants who take the initial SOC medication, continue the medication until end of open-label treatment, stop the medication, and the reason for stopping it will be presented for the SOC arm using the Safety Population. Similar tabulation will be provided for each alternative SOC medication.

9.2 Measurement of Treatment Compliance

Dosing compliance for a specified period is defined as the total number of open-label study medications actually taken by a participant during that period divided by the number of open-label study medications that were expected to be taken during the same period multiplied by 100. The total number of capsules actually taken during a specific period will be calculated

from the study medication record. Descriptive statistics for open-label study medication dosing compliance together with the compliance categories (< 80%, 80% - 120%, > 120%) will be summarized only for the atogepant arm at each period between 2 consecutive visits, as well as during the whole open-label treatment period of the study for the Safety Population.





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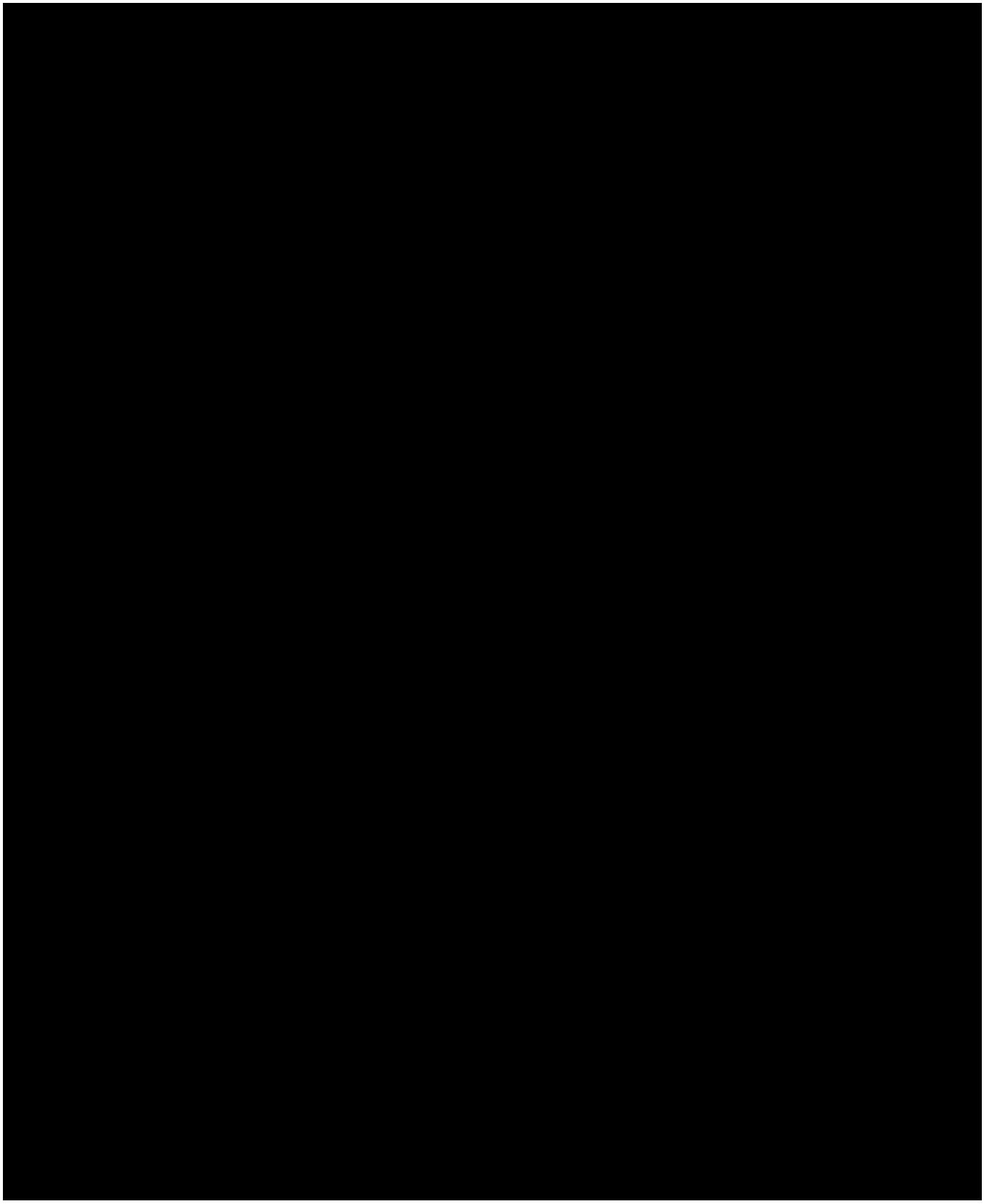
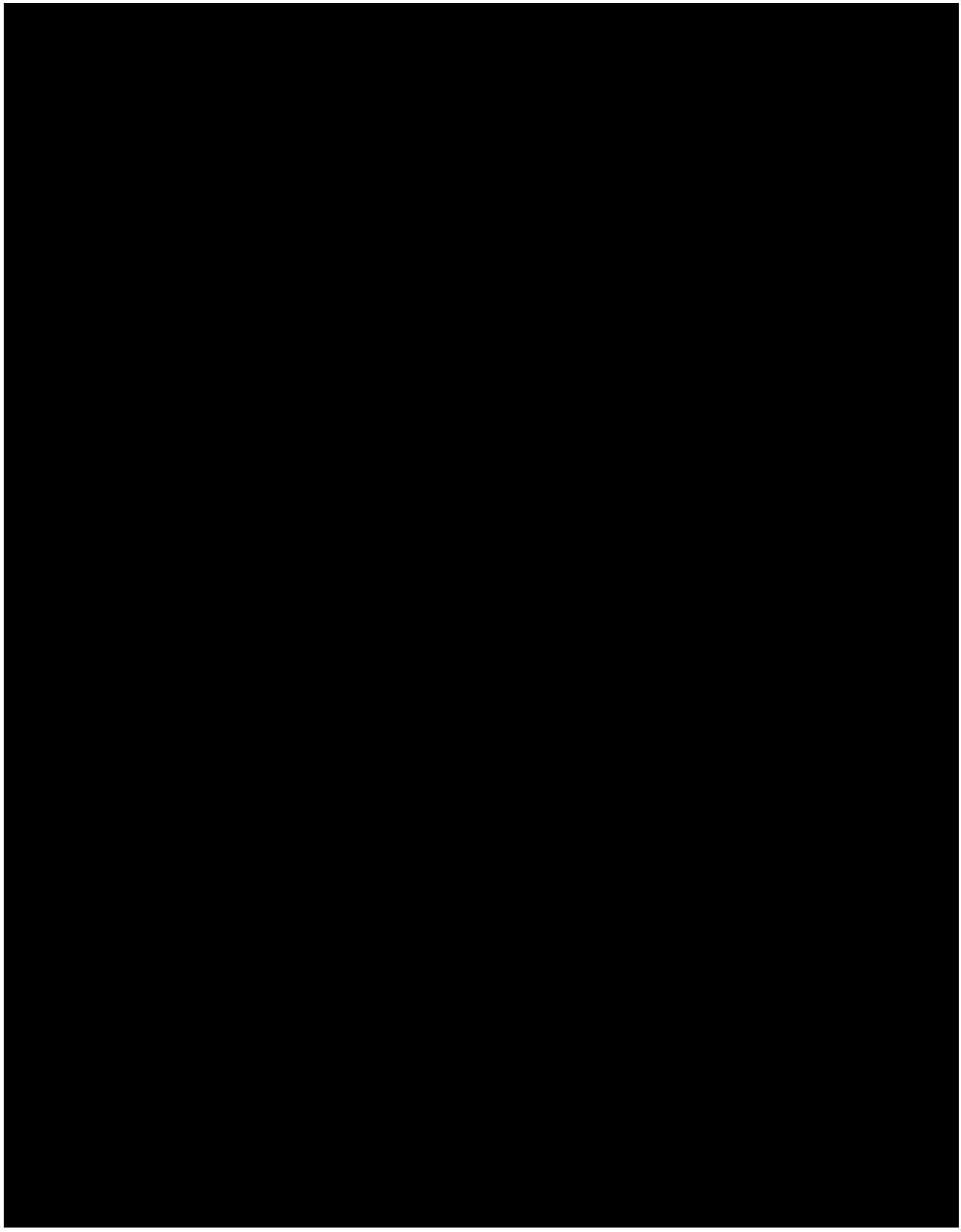




11 Safety Analyses

The safety analysis will be performed using the Safety Population. The safety parameters will include adverse events (AEs), clinical laboratory, vital sign, electrocardiographic (ECG), and C-SSRS. For clinical laboratory, vital sign, and ECG, the last nonmissing safety assessment before the first dose of treatment will be used as the baseline for all analyses of that safety parameter. Continuous variables will be summarized by number of participants and mean, SD, median, Q1, Q3, minimum, and maximum values. Categorical variables will be summarized by number and percentage of participants.

11.1 Adverse Events

Adverse events will be coded by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), version 21.0 or newer.

An AE will be considered as a treatment-emergent adverse event (TEAE) if the AE began or worsened (increased in severity or became serious) on or after the date of the first dose of open-label study treatment. For participants randomized to the atogepant arm, an AE that occurs more than 30 days after the last dose of open-label study treatment or Visit 16 whichever comes later will not be counted as a TEAE. For participants randomized to the SOC arm, an AE that occurs after Visit 16 will not be counted as a TEAE. Per case report form instructions, a new AE record will be created for any AE that worsens; therefore, for participants randomized to the atogepant arm, TEAEs can be identified as those AEs with recorded onset date on or after the date of the first dose of open-label study treatment within 30 days after the last dose of open-label study treatment or Visit 16 whichever comes later. For participants randomized to the SOC arm with available Visit 16 information, TEAEs can be identified as those AEs with recorded onset date on or after the date of the first dose of open-label study treatment and up to Visit 16; for participants randomized to the SOC arm but missing Visit 16 information, TEAEs are identified as those AEs with recorded onset date on or after the date of the first dose of open-label study treatment. An AE will be considered as a treatment-emergent SAE (TESAE) if it is a TEAE that also meets SAE criteria. TEAEs that started after the date of last dose of study treatment will be considered as newly emergent.

Overall summary of AEs will be provided on a per-participant basis for categories of TEAEs, treatment-related TEAEs, deaths, TESAEs, and TEAEs leading to study discontinuation.

The number and percentage of participants reporting TEAEs in each treatment group will be tabulated by system organ class and preferred term, and further categorized by severity to the study treatment.

The number and percentage of participants reporting treatment-related TEAEs in each treatment group will be tabulated by system organ class and preferred term.

The number and percentage of participants reporting newly emergent TEAEs in the atogepant arm will be tabulated by system organ class and preferred term.

The number and percentage of patients in the Safety Population who have TEAEs leading to premature discontinuation of the study treatment will be summarized by system organ class, preferred term and treatment group.

The incidence of common (≥ 2% of participants in any treatment group) TEAEs will be summarized by system organ class, preferred term, and treatment group.

The number and percentage of participants who have TESAE in each treatment group will be tabulated by system organ class and preferred term.

In addition, separate tabular displays will be presented for patients who died, participants with SAEs, and participants with TEAEs leading to premature discontinuation.

11.2 Clinical Laboratory Assessments

Descriptive statistics for clinical laboratory values (in both SI and conventional units) at baseline, postbaseline, and changes from baseline values at each postbaseline timepoint will be presented by treatment group for the following laboratory parameters:

Hematology:	Hemoglobin, hematocrit, red blood cell count, red blood cell indices (mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration), white blood cell count, including differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), platelet count
Chemistry:	Sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, creatine kinase, total protein, albumin, calcium, phosphorus, uric acid, total cholesterol
Urinalysis:	Specific gravity, pH

In addition, descriptive statistics for values and changes from the baseline values in conventional units at each assessment time point will be presented for selected clinical laboratory parameters listed in Appendix I. A description of reporting the lab values in conventional units in patient narratives (along with the standard reporting in SI units) is presented at the end of Appendix I.

Clinical laboratory test values will be considered potentially clinically significant (PCS) if they meet either the lower-limit or higher-limit PCS criteria listed in Table 11-1. The normal range for eGFR was not specified by the lab. Therefore, eGFR<60 mL/min/1.73m^2 is defined in Table 11-1 to classify renal function as the category of "Moderate eGFR Decrease or Worse" based on FDA guidance on PK studies in patients with impaired renal function. The number and percentage of participants who have PCS postbaseline clinical laboratory values will be tabulated by treatment group. The percentages will be calculated relative to the number of participants with available non-PCS baseline values and at least 1 postbaseline assessment. The numerator will be the total number of participants with available non-PCS baseline values and at least 1 PCS postbaseline value during the study. A supportive tabular display of participants with PCS postbaseline values will be provided, including the PID number, baseline and all postbaseline (including non-PCS) values.

In addition, a tabular display showing all AEs that occurred in participants who had PCS postbaseline clinical laboratory values will be provided.

Potential Hy's Law criteria within a 24-hour window is defined by a postbaseline elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3 x ULN, along with total bilirubin (TBL) ≥ 2 x ULN and a non-elevated alkaline phosphatase (ALP) < 2 x ULN, all based

on blood draws collected within a 24-hour period. Potential Hy's Law criteria without time window is defined by maximum of post baseline elevation of ALT or AST ≥ 3 x ULN, along with maximum of post baseline elevation of TBL ≥ 2 x ULN. Patients who meet the potential Hy's Law criteria from the first dose of study drug to the end of study will be summarized. Supportive tabular displays will also be provided.

Table 11-1 Criteria for Potentially Clinically Significant Laboratory Values

[redacted]

The number and percentage of participants meeting each of the following criteria for postbaseline hepatic laboratory abnormalities listed in Table 11-2 will be summarized by treatment group. The percentages will be calculated relative to the number of participants with at least 1 available postbaseline assessment. The numerator will be the total number of participants having at least 1 postbaseline value that meets the specific category during the study. A supportive listing will also be provided.

Table 11-2 Criteria for Hepatic Laboratory Abnormalities

[redacted]

Table 11-2 Criteria for Hepatic Laboratory Abnormalities

[redacted]

The number and percentage of participants with an adjudicated case (i.e., ALT ≥ 3 x ULN and/or AST ≥ 3 x ULN) will be summarized by treatment group and by relationship of ALT or AST elevation to study medication. The percentages will be calculated relative to the number of participants with an adjudicated case. The numerator will be the number of participants with an adjudicated case in the specific category of relationship. If a participant has more than 1 adjudicated case, he or she will be counted in the most relevant category of relationship.

Participants with an adjudicated case (i.e. ALT ≥ 3 x ULN or AST ≥ 3 x ULN) will be listed with their ALT and AST assessments, adjudication dates, relationship of ALT or AST elevation to study medication, and confounding factor(s). Additional listings will be provided for participants who meet ALT ≥ 3 x ULN or AST ≥ 3 x ULN and/or potential Hy's law and have one of the following categories: at least 1 abnormal liver biochemistry risk factor, at least 1 liver disease sign and symptom, at least 1 liver diagnostic test performed, consultation with a specialist for liver evaluation, liver lab tests performed, and drug screen performed, respectively.

A listing of urine pregnancy test results will be provided for female participants of child-bearing potential with at least one positive result.

11.3 Vital Signs

Descriptive statistics for vital signs (systolic and diastolic blood pressures [sitting and standing], pulse rate [sitting and standing], respiratory rate, temperature, weight, orthostatic systolic blood pressure, orthostatic diastolic blood pressure, and orthostatic pulse rate) values at baseline, postbaseline, and changes from baseline values at each postbaseline timepoint will be presented by treatment group. Orthostatic vital sign values (orthostatic systolic and diastolic blood pressures, and orthostatic pulse rate) are defined as the corresponding standing measurement minus sitting measurement of systolic and diastolic blood pressures and pulse rate respectively.

Vital sign values will be considered PCS if they meet both the observed value criterion and the change from baseline value criterion, if both criteria are available, or meet either the observed value criterion or the change from baseline value criterion that will be detailed in Table 11-3. The number and percentage of participants who have PCS postbaseline vital sign values will be tabulated by treatment group. The percentages will be calculated relative to the number of participants who have available baseline or non-PCS baseline (for parameters with only the observed value criterion) values and at least 1 postbaseline assessment. The numerator will be the total number of participants with at least 1 PCS postbaseline value during the study. A supportive listing of participants with PCS postbaseline values will be provided. In addition, a tabular display showing all AEs that occurred in participants who had PCS postbaseline vital sign values will be provided.

Table 11-3 Criteria for Potentially Clinically Significant Vital Signs

11.4 Electrocardiograms

Descriptive statistics for ECG parameters (ie, heart rate, PR interval, QRS interval, RR interval, QT interval, and QTc interval) at baseline, postbaseline, and changes from baseline values at each postbaseline timepoint will be presented by treatment group.

ECG parameter values are considered PCS if ECG values meet either the actual value or change from baseline PCS high criteria listed in Table 11-4. The number and percentage of participants with PCS postbaseline values will be tabulated by treatment group. The percentages will be calculated relative to the number of participants with an available non-PCS baseline value and at least 1 postbaseline assessment. The numerator will be the total number of participants with an available non-PCS baseline value and at least 1 PCS postbaseline ECG value during the study. A supportive listing of participants with PCS postbaseline values will be provided. A listing of all AEs for participants with PCS ECG values will also be provided.

Table 11-4 Criteria for Potentially Clinically Significant Electrocardiograms

[redacted]

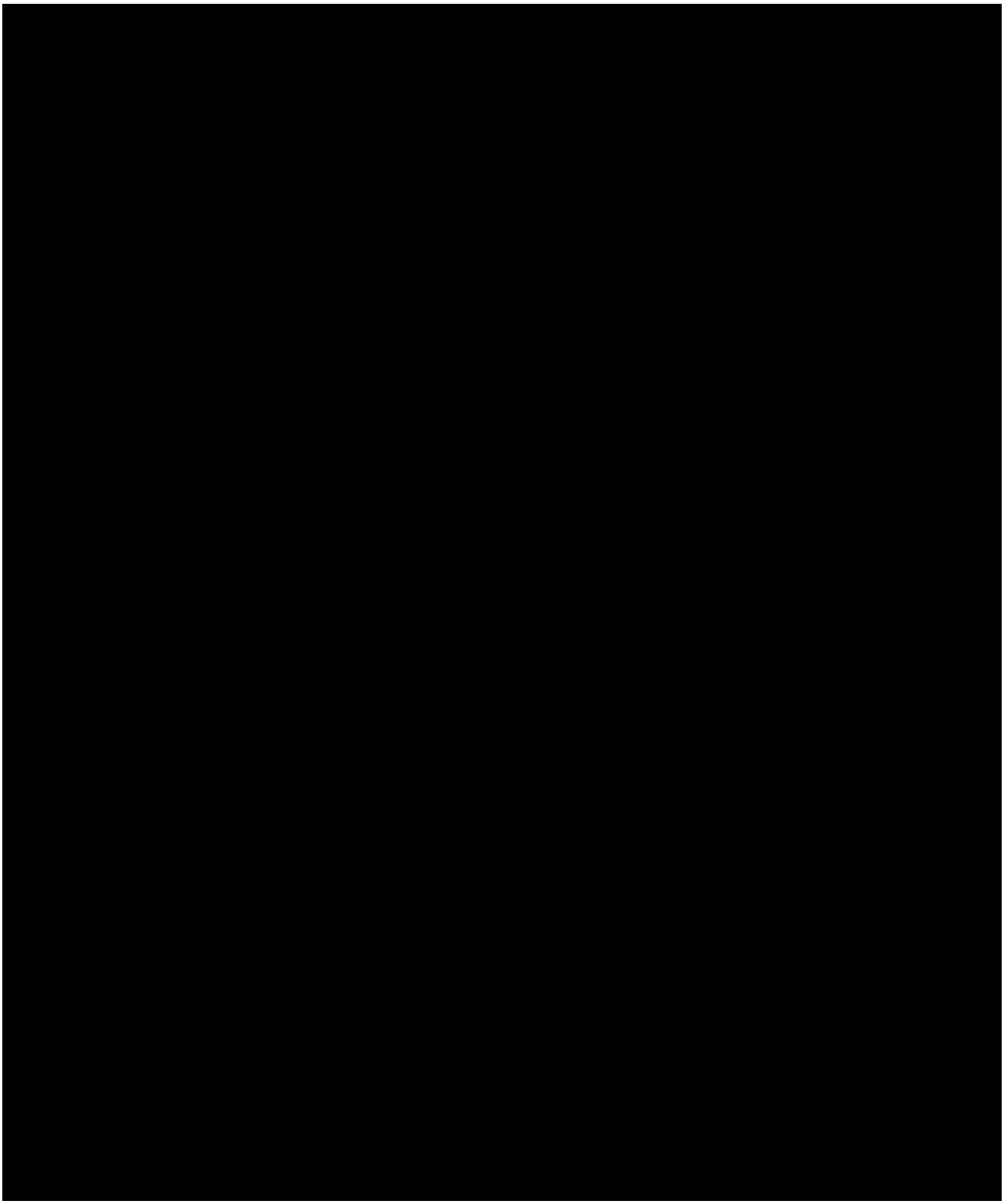
To evaluate ECG postbaseline values of clinical interest, the number and percentage of participants with post-treatment QTcF > 450 msec, > 480 msec, and > 500 msec will be tabulated by treatment group.

The number and percentage of participants with an increase > 30 msec but ≤ 60 msec, and with an increase > 60 msec in QTcF will be tabulated. Participants will be counted only once for the most severe category. A supportive listing of participants with postbaseline QTcF increases > 30 msec will be provided, including the PID number, study center, and all QTc values (including changes from baseline). A listing of all AEs for participants with postbaseline QTcF increases > 30 msec will also be provided.

A shift table from baseline to the end of open-label treatment period in the investigator's overall interpretation of the ECG will be presented by treatment group for the following categories: normal; abnormal, not clinically significant; abnormal, clinically significant. A tabular display of participants with postbaseline clinically significant ECG abnormalities according to the investigator's overall interpretation will be provided.

11.5 Columbia-Suicide Severity Rating Scale

For C-SSRS, the number and percentage of participants with suicidal ideation or suicidal behavior as recorded on the C-SSRS will be summarized by treatment group for the Safety Population. The distribution of responses for most severe suicidal ideation and most severe suicidal behavior in the participant's lifetime history, in the past 6 months, in the open-label treatment period, and in the safety follow-up period will also be presented by treatment group. Supportive listings will be provided and will include the PID number, study center number, treatment group, lifetime history, and postbaseline values. Intensity of suicidal ideation and suicidal behavior type will also be included in these listings.



[redacted]

14 Interim Analysis

None.

15 Determination of Sample Size

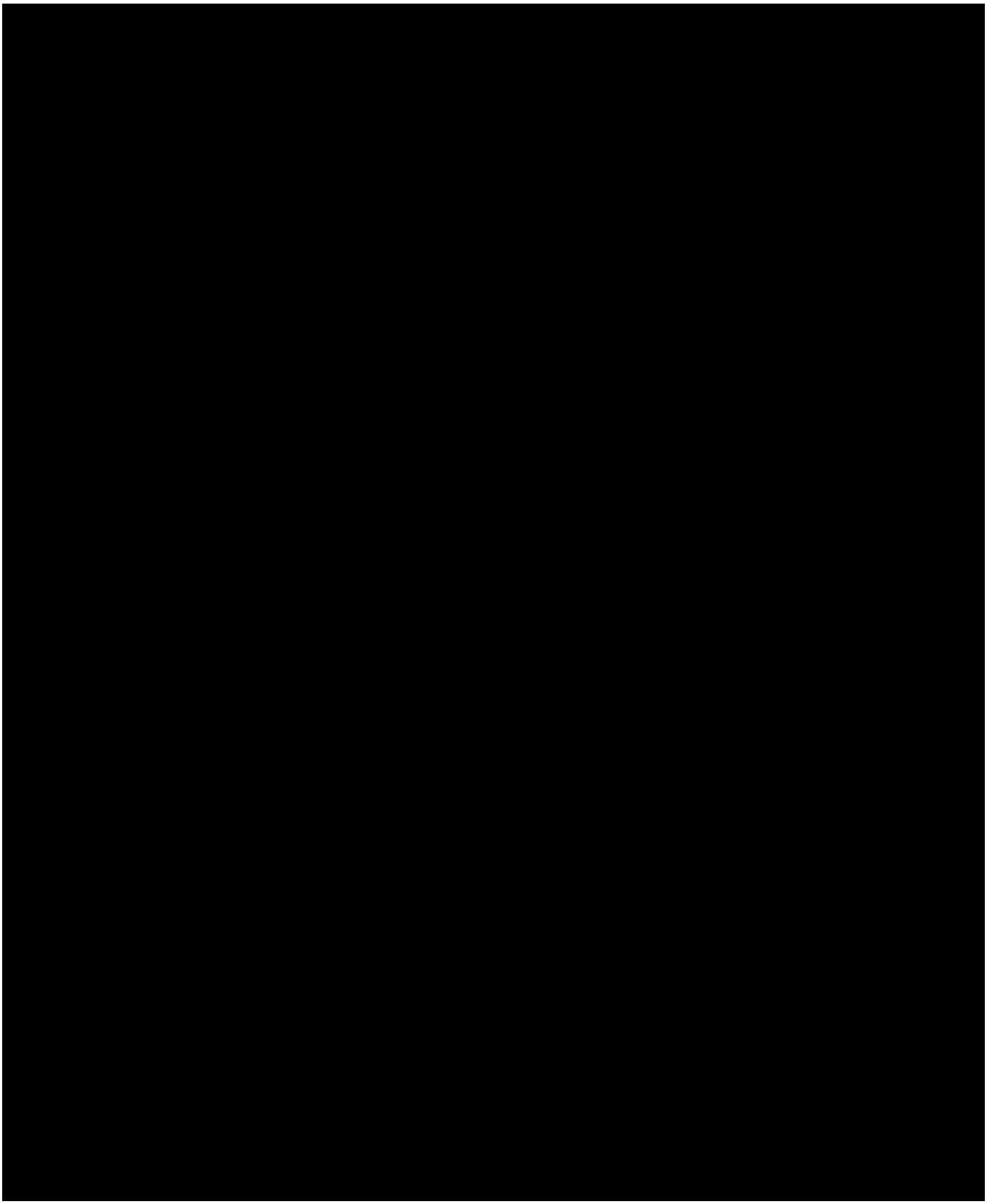
This study plans to randomize a total of 700 participants. Participants will be randomized 5:2 to receive atogepant 60 mg QD or oral SOC migraine prevention medication. Based on data from previous studies (Aurora et al, 2011; Rapoport et al, 2006), it is estimated that approximately 60% of those participants will complete 6 months of treatment, and of those 65% will complete 12 months of treatment.

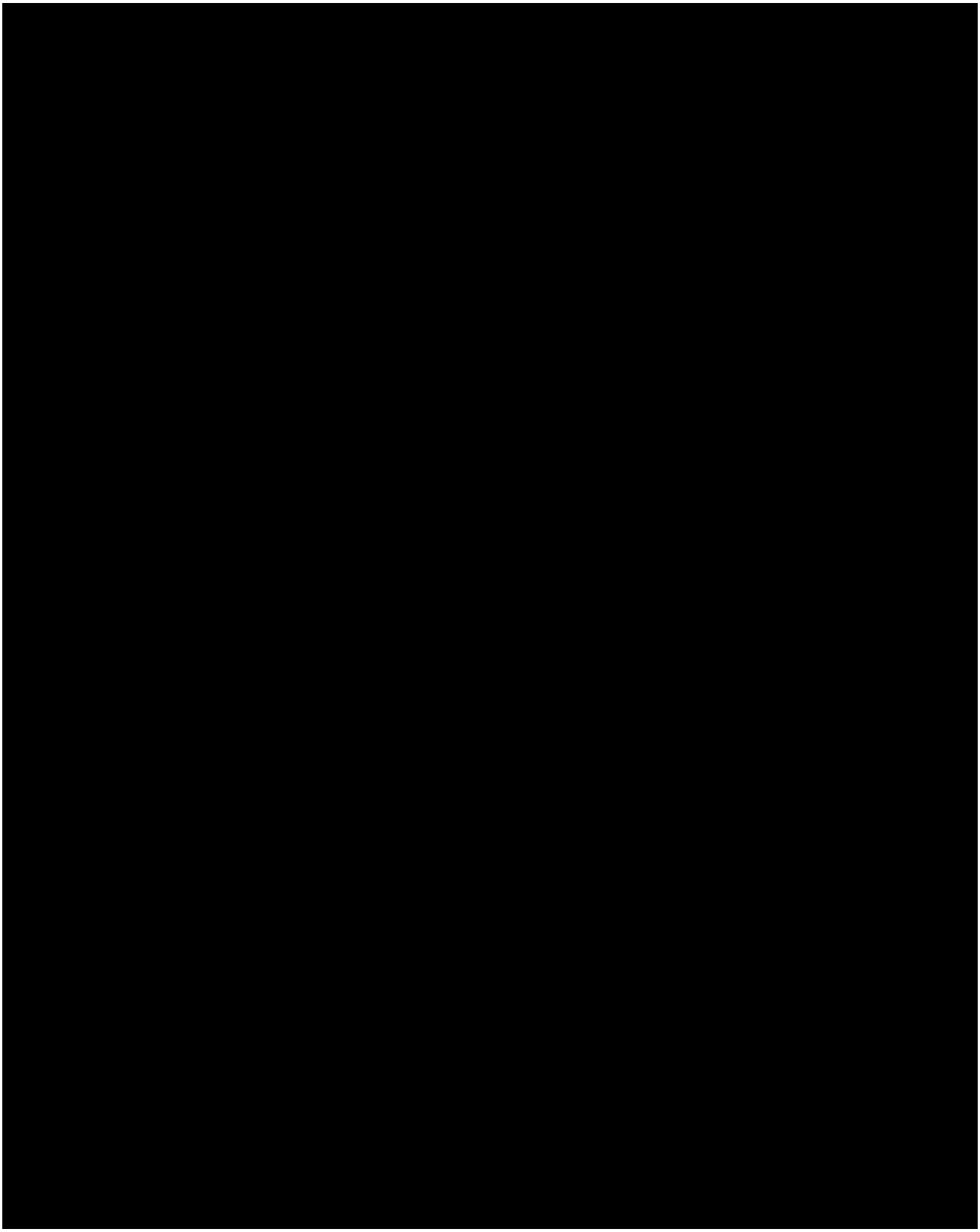
16 Statistical Software

[redacted]

17 Data Handling Convention

[redacted]





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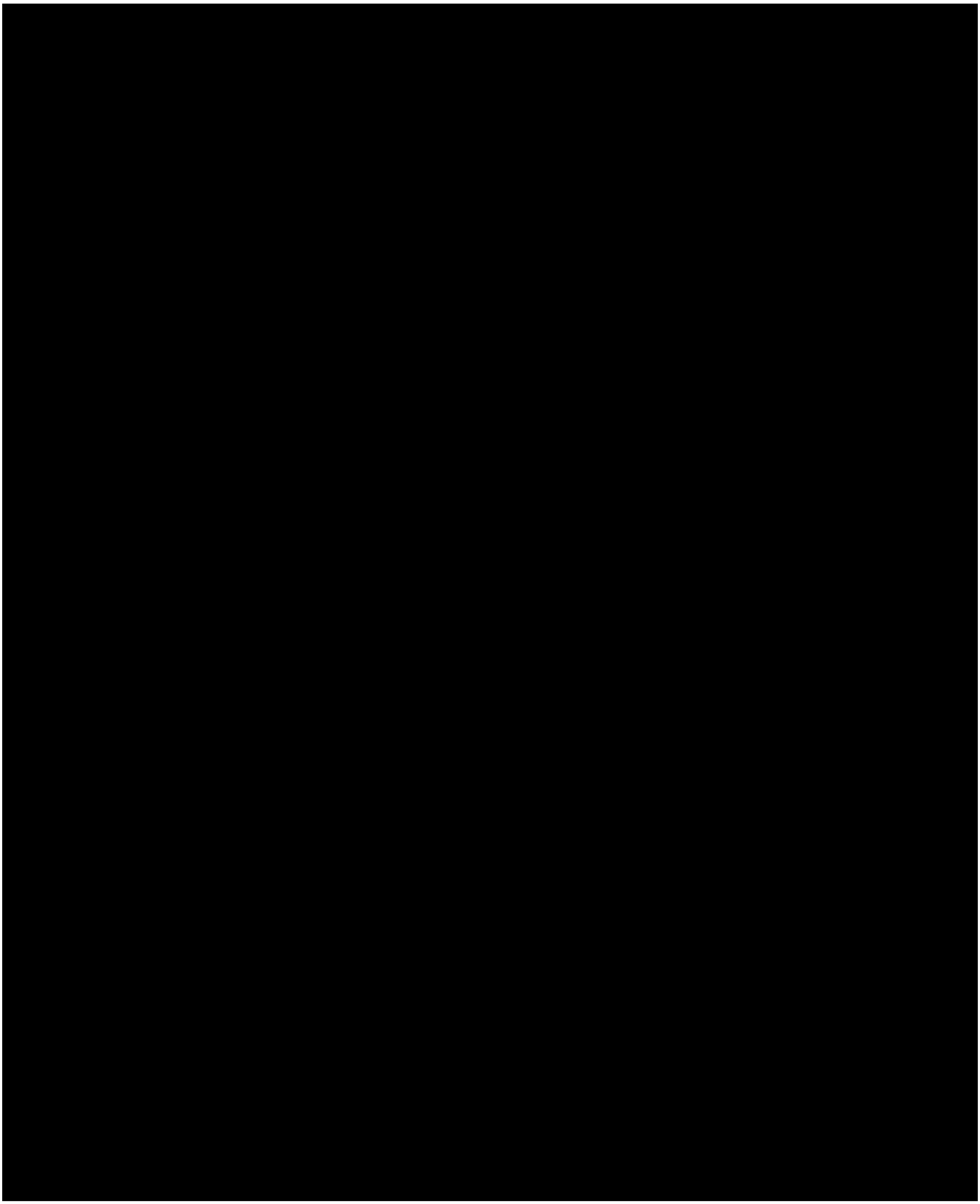


[redacted]

17.4 Missing Date of the Last Dose of Study treatment

When the date of the last dose of the open-label study treatment is missing, all efforts should be made to obtain the date from the Investigator. If it is still missing after all efforts have been made, the last available study medication date will be used in the calculation of treatment duration for participants randomized to the atogepant arm. For participants randomized to the SOC arm, if their SOC treatment is ongoing at the end of study, the last visit date during the study (including safety follow-up period) will be used to impute the last dose of their SOC treatment for the calculation of treatment duration.

17.5 Missing Severity Assessment for Adverse Events

If severity is missing for an AE that started before the date of the first dose of open-label study treatment, an intensity of mild will be assigned. If severity is missing for an AE that started on or after the date of the first dose of open-label study treatment, an intensity of severe will be assigned. The imputed values for severity assessment will be used for the incidence summary; the values will be shown as missing in the data listings.

17.6 Missing Causal Relationship to Study treatment for Adverse Events

If the causal relationship to the open-label study treatment is missing for an AE that started on or after the date of the first dose of open-label study treatment, a causality of yes will be assigned. The imputed values for causal relationship to open-label treatment will be used for the incidence summary; the values will be shown as missing in the data listings.

17.7 Missing Date Information for Adverse Events

The following imputation rules only apply to cases in which the start date for AEs is incomplete (ie, partly missing).

[redacted]

[redacted]

17.8 Missing Date Information for Prior or Concomitant Medications

For prior or concomitant medications, including rescue medications, incomplete (ie, partly missing) start dates and/or stop dates will be imputed. When the start date and the stop date are both incomplete for a participant, the start date will be imputed first.

17.8.1 Incomplete Start Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication start date. If the stop date is complete (or imputed) and the imputed start date is after the stop date, the start date will be imputed using the stop date.

[redacted]

17.8.2 Incomplete Stop Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication stop date. If the date of the last dose of study treatment is missing, replace it with the last visit date in the imputations described below. If the imputed stop date is before the start date (imputed or nonimputed start date), the imputed stop date will be equal to the start date.

[redacted]

17.9 Character Values of Clinical Laboratory Parameters

If the reported value of a clinical laboratory parameter cannot be used in a statistical summary table because, for example, a character string is reported for a parameter of the numeric type, a coded value must be appropriately determined for use in the statistical analyses. The actual values, however, as reported in the database will be presented in the data listings.

[redacted]

18 Covid-19 Related Analyses

To eliminate immediate potential hazards to participants and study staff due to the COVID-19 pandemic while ensuring participant safety and maintaining data integrity, a protocol clarification letter and subsequently a corresponding protocol amendment were sent to sites to allow remote visits.

This section specifies analyses for evaluating the impact of COVID-19.

[redacted]

18.2 Safety and Other Evaluations

This section specifies analyses related to the COVID-19 pandemic from the following aspects:

- Disposition
- Study visit (missing entire visit due to COVID-19 or missing assessments due to COVID-19)
- Protocol deviation
- Study drug disruption due to COVID-19
- TEAEs related to COVID-19

The Safety Population will be used for the planned analyses described above.

The number of participants impacted by COVID-19 during the study will be summarized by treatment group and overall. In addition, the number of participants impacted by COVID-19 and their corresponding disposition status in the open-label treatment period and the follow-up period will be summarized respectively.

The number of participants who missed at least one entire visit due to COVID-19 will be summarized by treatment group and overall. Furthermore, the number of participants who missed at least one assessment due to COVID-19 will be summarized by assessment category (laboratory, C-SSRS, urine pregnancy test, vital signs, ECG, and ePRO) and overall. Similar summaries will be provided by visit.

The number of participants with significant protocol deviation due to COVID-19 will be provided. The number of participants with study drug disruption due to COVID-19 will be provided as well. The number of participants with TEAEs related to corona virus infection or coronavirus test positive will be provided.

Supporting listings for the described analyses above will be provided.

19 Changes to Analyses Specified in Protocol

None.

20 References

Aurora SK, Winner P, Freeman MC, Spierings EL, Heiring JO, DeGryse RE, et al. OnabotulinumtoxinA for treatment of chronic migraine: pooled analyses of the 56-week PREEMPT clinical program. Headache. 2011 Oct;51(9):1358-1373.

Kenward MG, Roger JH. Small sample inference for fixed effects from restricted maximum likelihood. Biometrics 1997; 53:983-97.

Rapoport A, Mauskop A, Diener HC, Schwalen S, Pfeil J. Long-term migraine prevention with topiramate: open-label extension of pivotal trials. Headache. 2006 Jul-Aug;46(7):1151-1160.

21 Appendices

APPENDIX I. REPORTING SELECTED LABORATORY PARAMETERS IN CONVENTIONAL UNIT

All clinical laboratory parameters will be reported in the International System (SI) units as standard practice. In addition, descriptive statistics for values and changes from baseline in conventional units at all assessed visits will be reported for selected laboratory parameters as listed in Table 21-1 below.

Table 21-1 List of Selected Parameters to be Reported in Conventional Units

Number	*Laboratory Parameter*	*Conventional Unit*	*Decimal Places*
1	Alanine Aminotransferase (SGPT)	U/L	0
2	Albumin	g/dL	1
3	Alkaline Phosphatase	U/L	0
4	Aspartate Aminotransferase (SGOT)	U/L	0
5	Bilirubin, Direct (Conjugated)	mg/dL	1
6	Bilirubin, Indirect (Unconjugated)	mg/dL	1
7	Bilirubin, Total	mg/dL	1
8	Blood Urea Nitrogen	mg/dL	0
9	Calcium	mg/dL	1
10	Cholesterol, HDL	mg/dL	0
11	Cholesterol, LDL	mg/dL	0
12	Cholesterol, LDL direct and calculated (combined) *(This lab parameter could be the same as #11)*	mg/dL	0
13	Cholesterol, Total	mg/dL	0
14	Creatine Kinase	U/L	0
15	Creatinine	mg/dL	1
16	Glucose	mg/dL	0
17	Insulin	uIU/mL	1
18	Triglycerides	mg/dL	0
19	Uric Acid	mg/dL	1
20	Hemoglobin	g/dL	1

Patient narratives will also include the values in conventional units for the selected lab parameters (Table 21-1). That will be accomplished by presenting the values in conventional units within the parentheses next to the values in SI units. As shown in Table 21-2 below for 'Bilirubin, Total' parameter, for which 'umol/L' is the SI unit and 'mg/dL' is the conventional unit.

Table 21-2 Presenting Laboratory Data Using SI and Conventional Units in Narratives

LABORATORY DATA						
Lab Test	**Test Name**	**Normal Range**		**VISIT01**	**VISIT05**	**VISIT07**
		Low	**High**	**2012-07-03**	**2012-08-07**	**2012-09-04**
CHEMISTRY	Bilirubin, Total (umol/L(mg/dL))	0 (0)	18.81 (1.1)	6.84 (0.4)	5.13 (0.3)	5.13 (0.3)

APPENDIX II. SUMMARY OF CHANGES FOR AMENDMENT 1

Amendment #1 specifies the following changes to the Statistical Analysis Plan for Study 3101-302-002 dated 18 Mar 2019.

1. For safety analyses, participants will be summarized according to the study treatment period received for majority of treatment period.
2. Remove ISS related subgroup analyses in the summary tables for disposition, exposure, and TEAEs.
3. Update the age groups for demographic parameters.

[redacted]

6. Concomitant medication use will be summarized for open-label treatment period and safety follow-up period.
7. Update treatment duration in align with ISS.

[redacted]

16. Update the TEAE definition for SOC to consider the situation of missing Visit 16.
17. Clarify Newly emergent AEs is for TEAEs occurred after the date of last dose of study treatment.
18. Add a list of selected parameters in conventional units in Appendix I.
19. Remove criteria and analysis for vital sign values of clinical interest.
20. Delete the shift table for clinical lab parameters.
21. Update lab data PCS criteria.
22. Add the listing for urine pregnancy test results.

23. Update ECG PCS criteria and add analyses for ECG values of clinical interest.
24. Update the analysis window for eDiary data at baseline period.

[redacted]

30. Add a section to COVID-19 related analysis

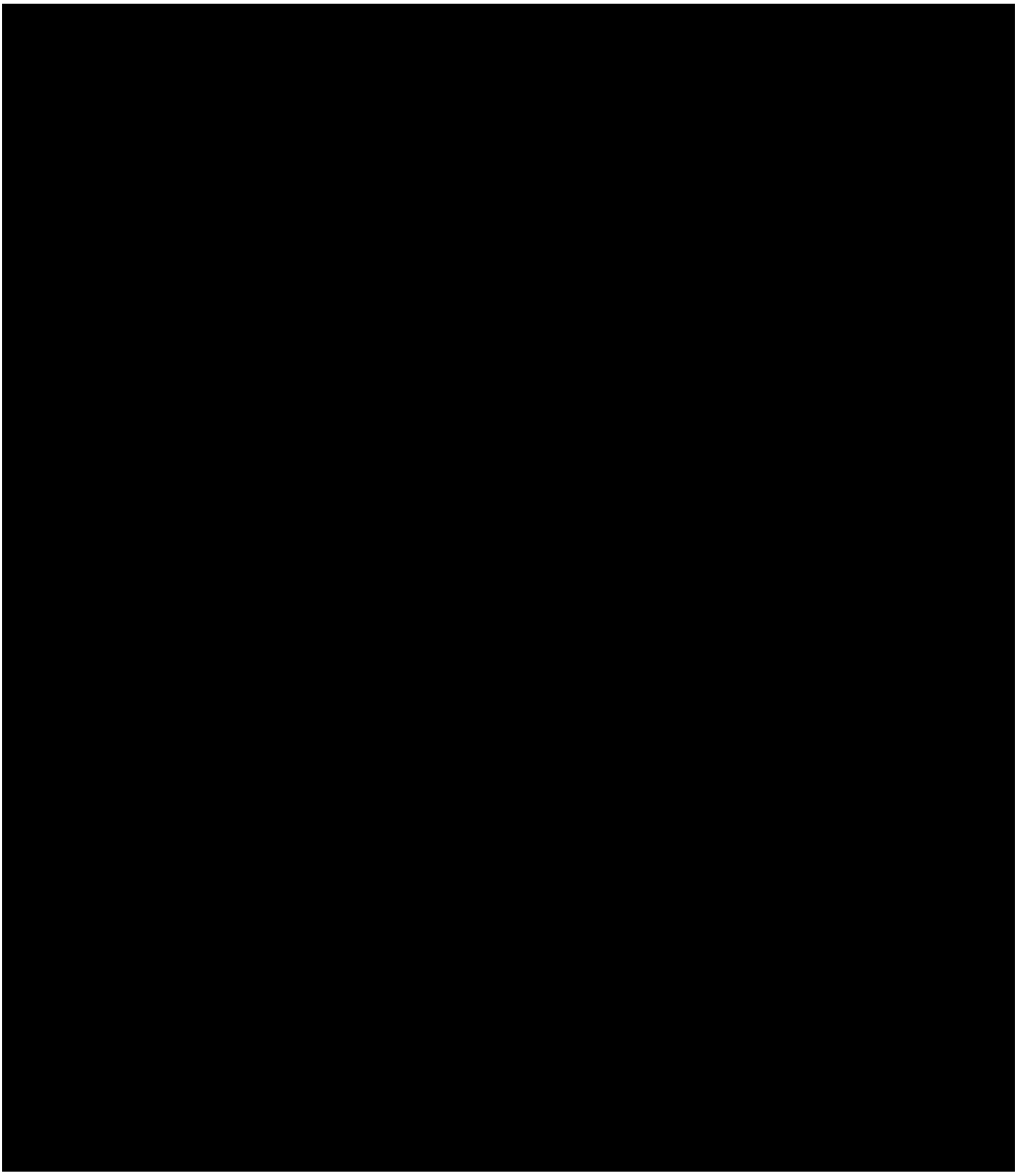
The details related to content changes are provided below. Minor editorial and document formatting revisions have not been summarized.

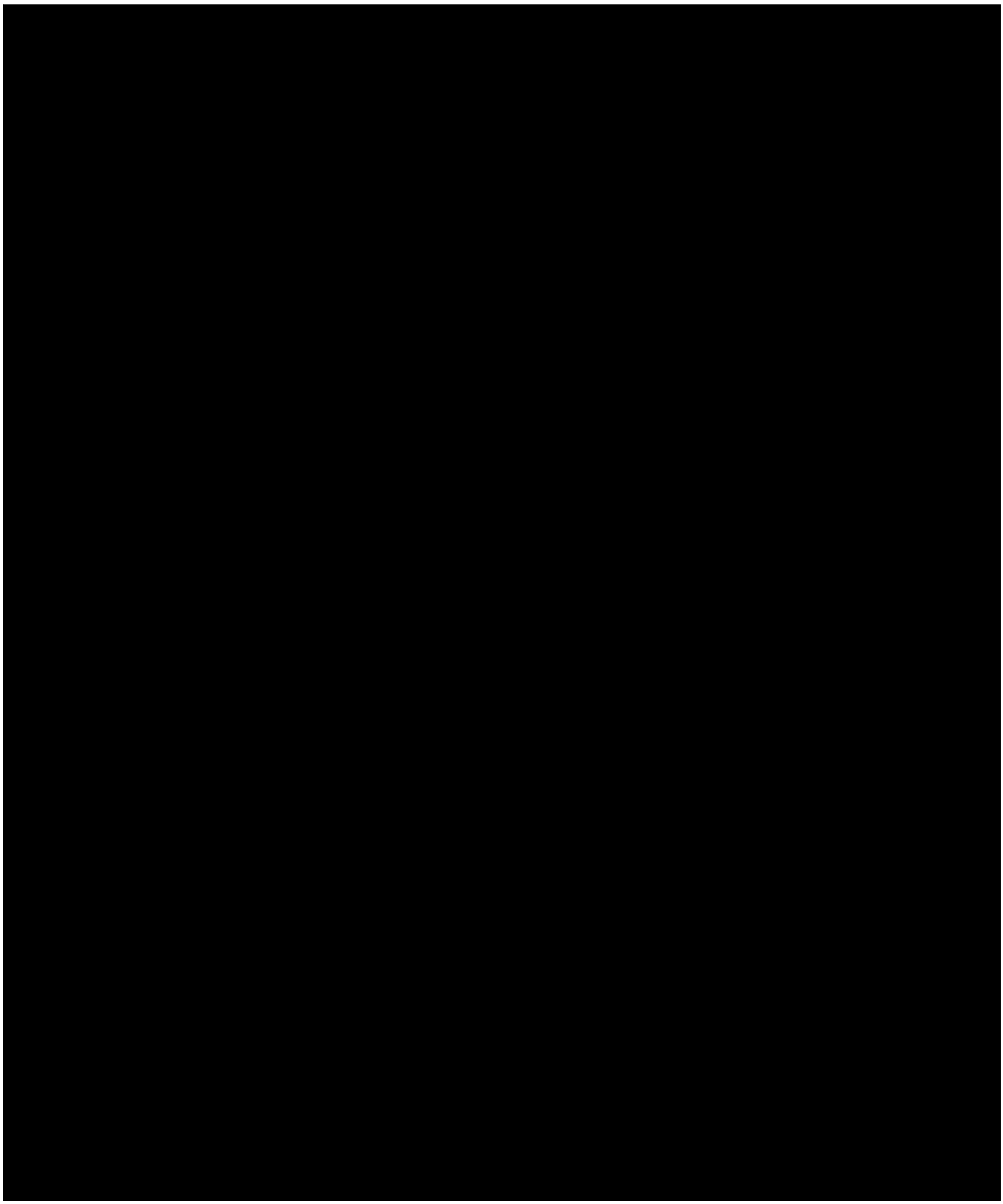
Section 4 Introduction

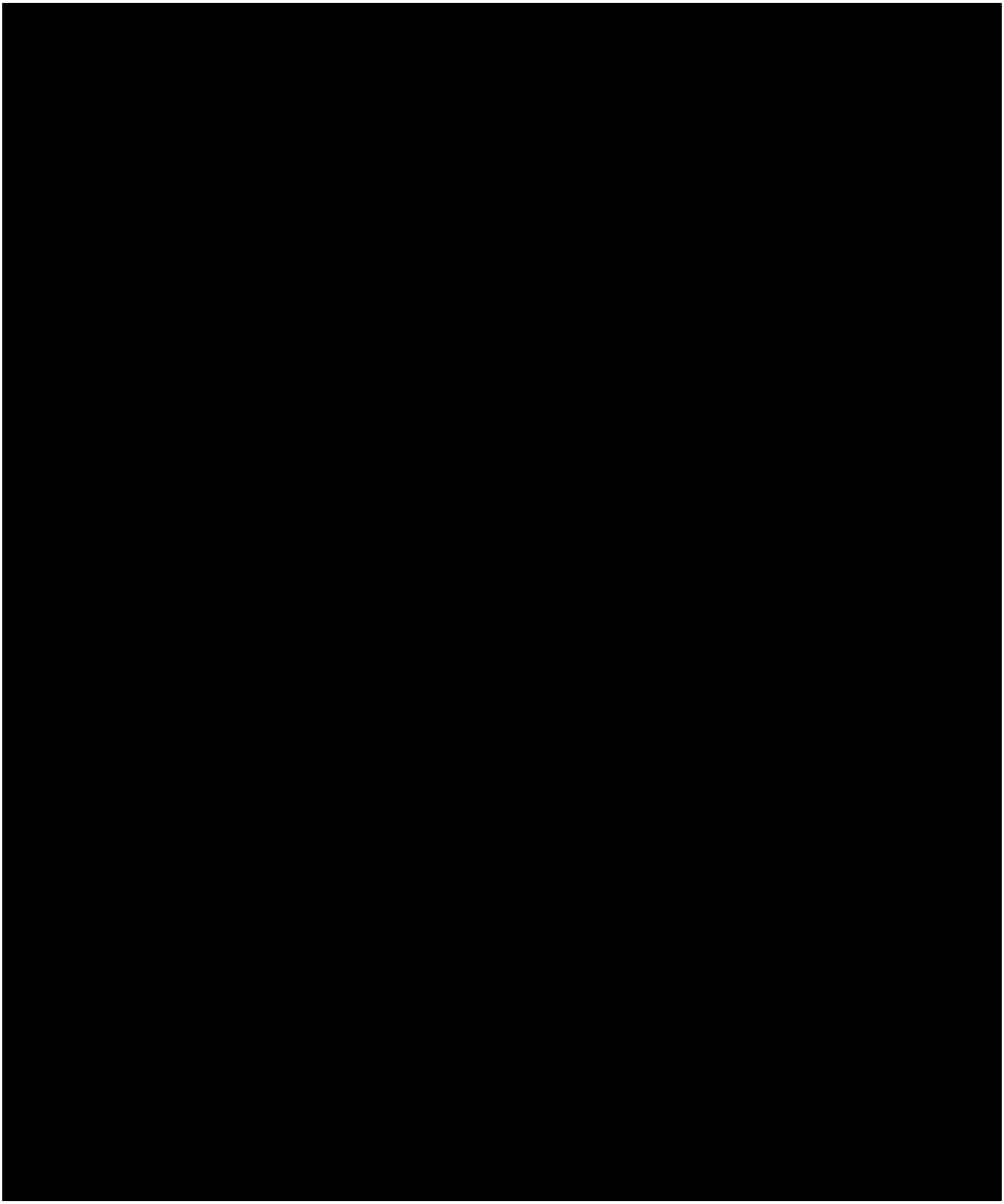
The title of Table 4-1 is revised as Schedule of Activities (SoA) for in-Person Visits Conducted Prior to or During the COVID-19 Pandemic

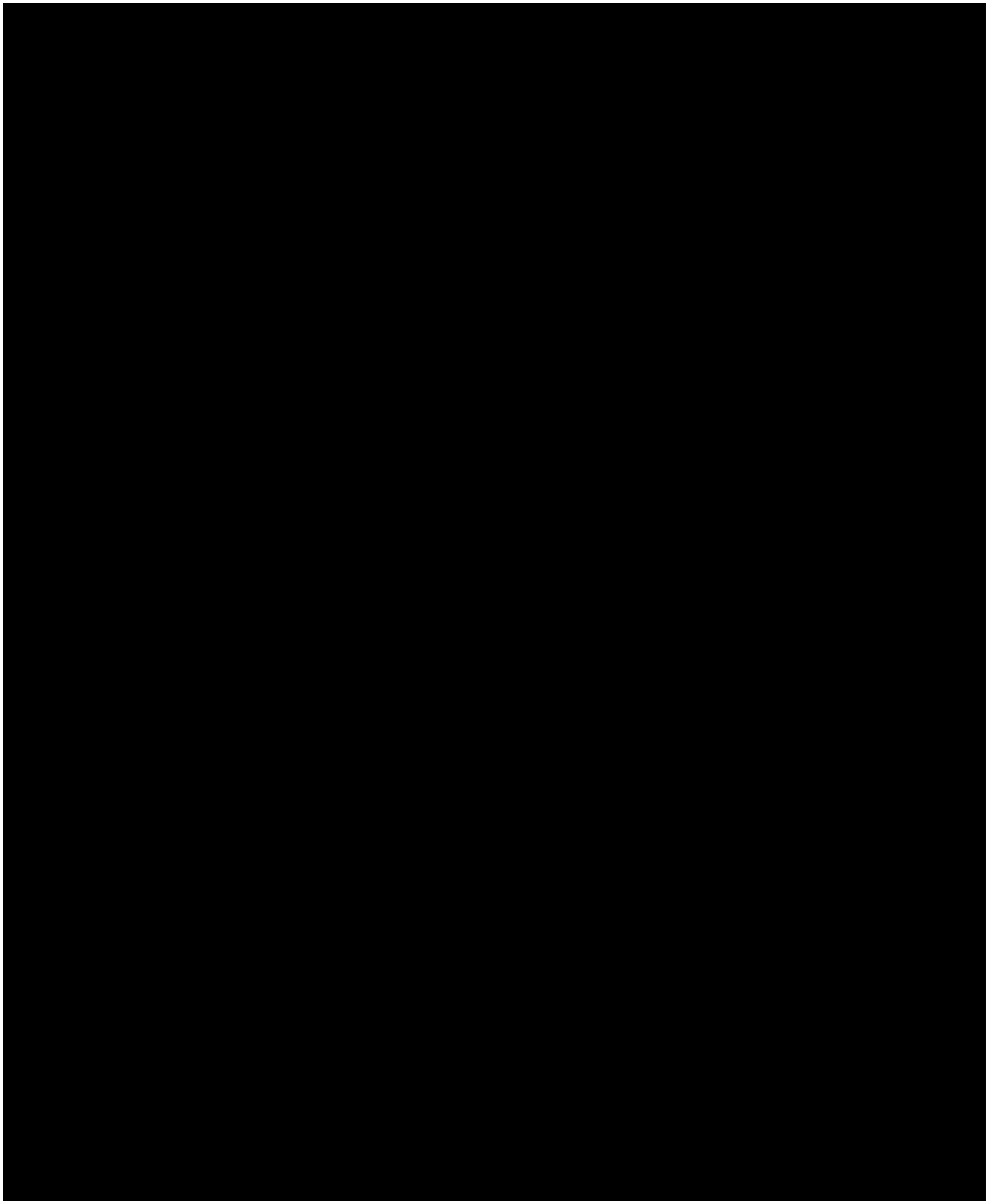
[redacted]

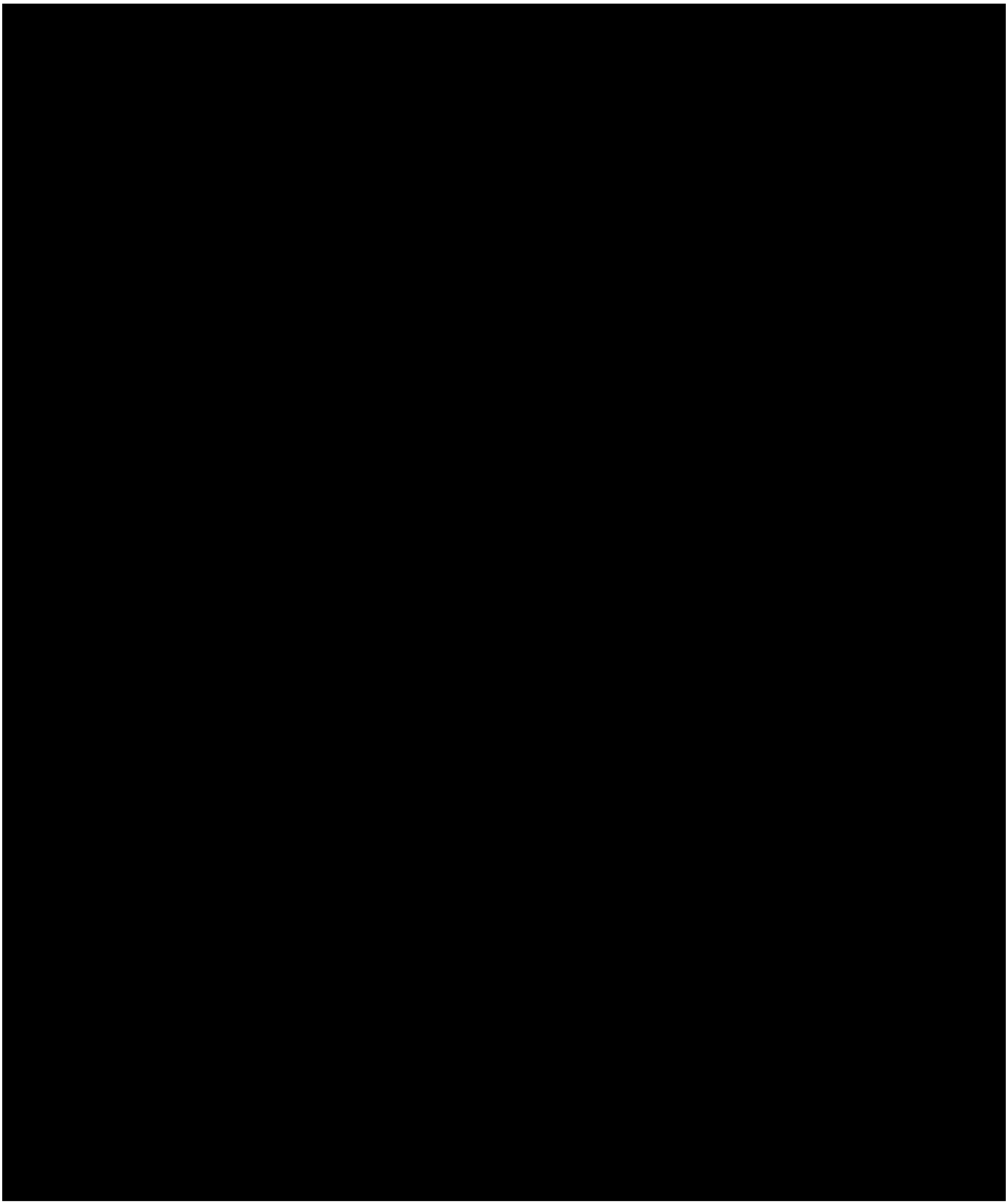
[redacted]











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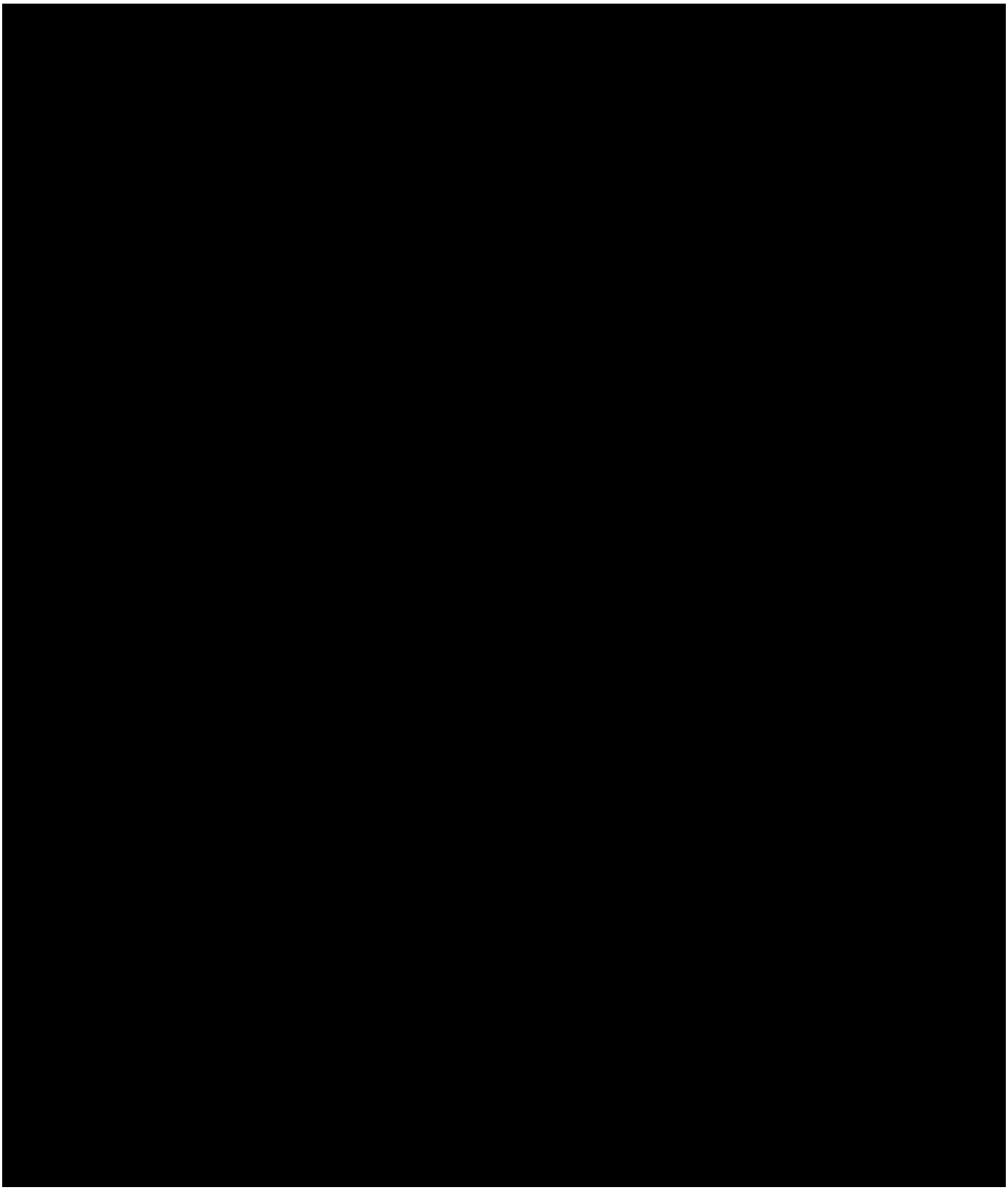

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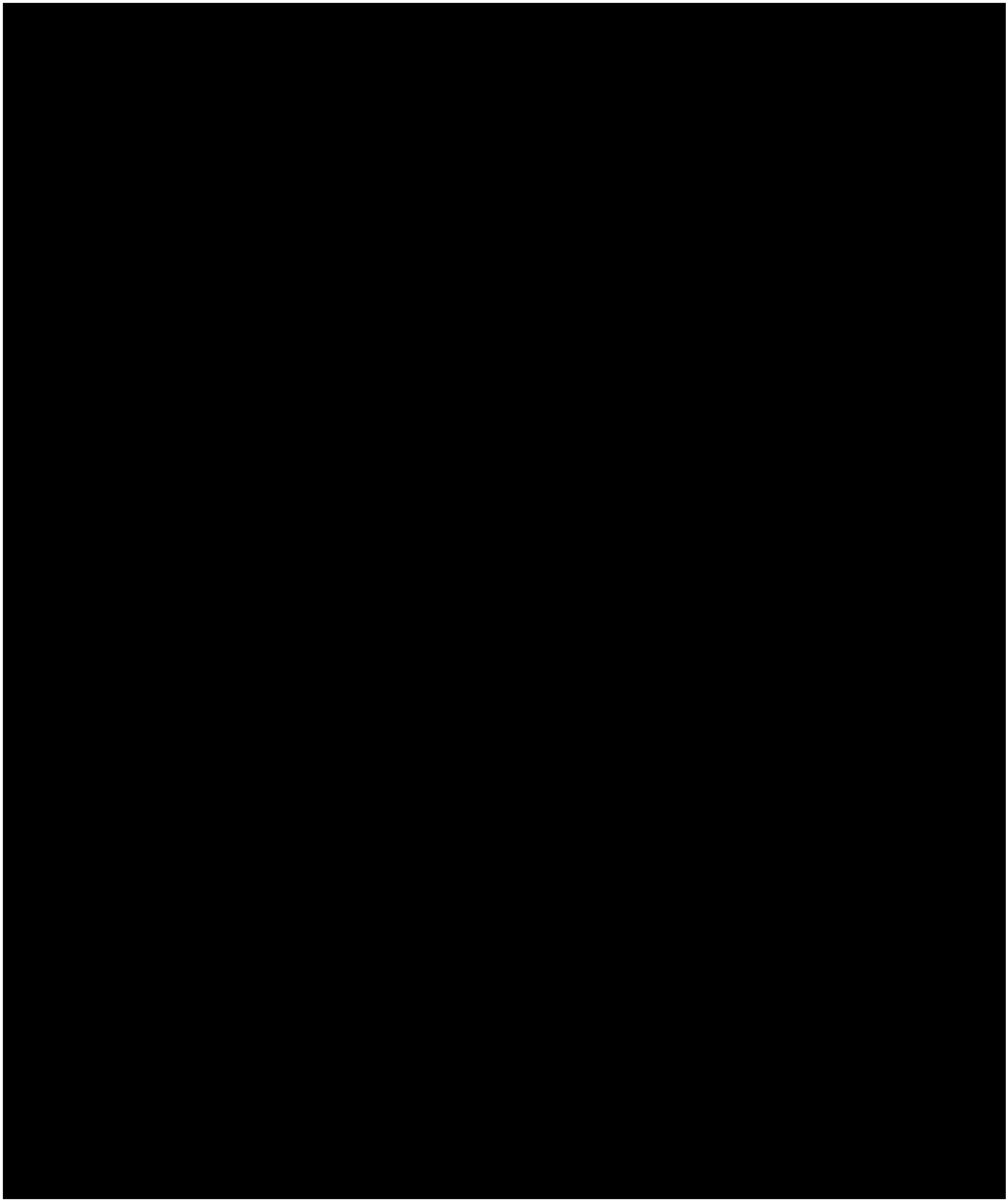

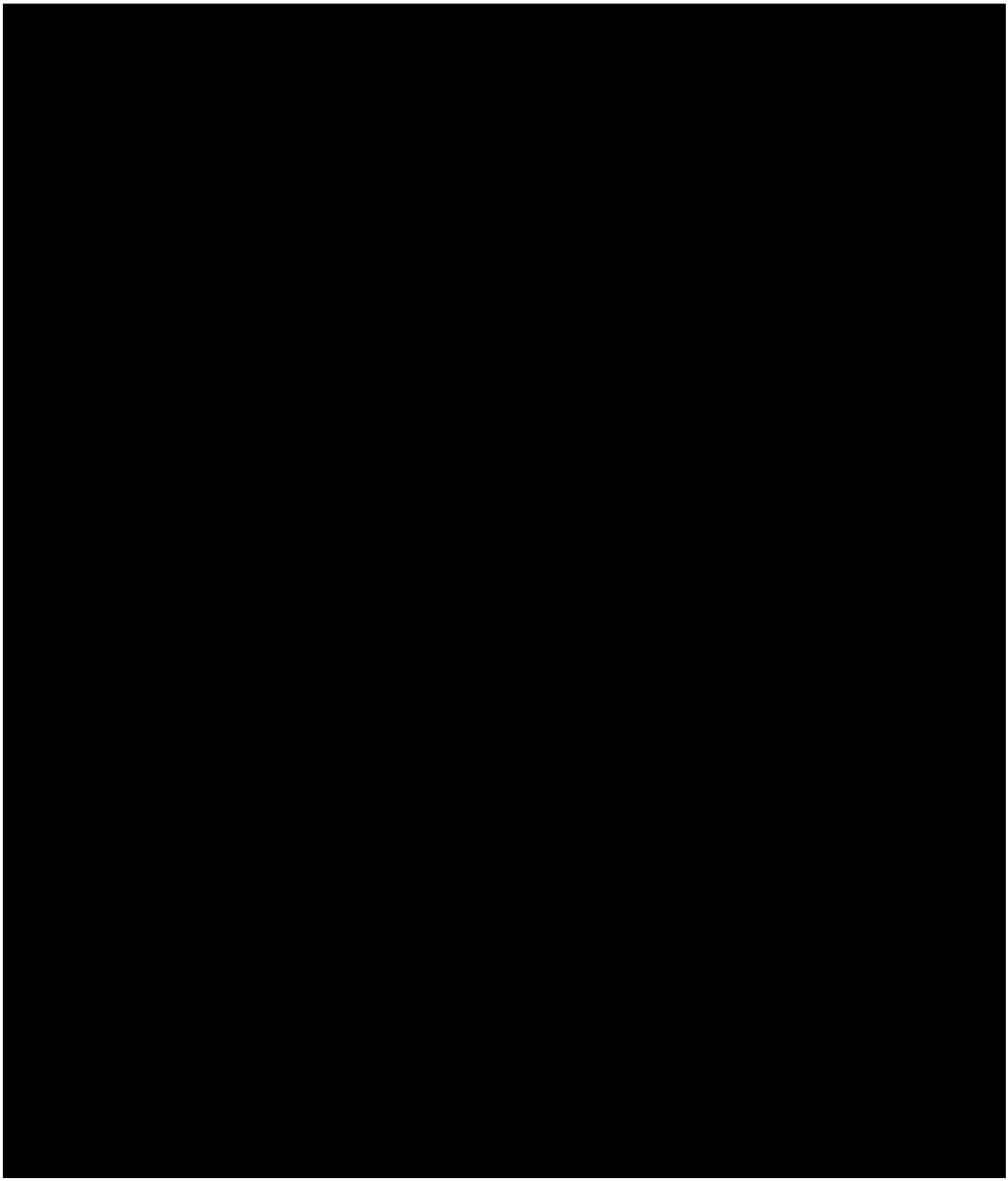

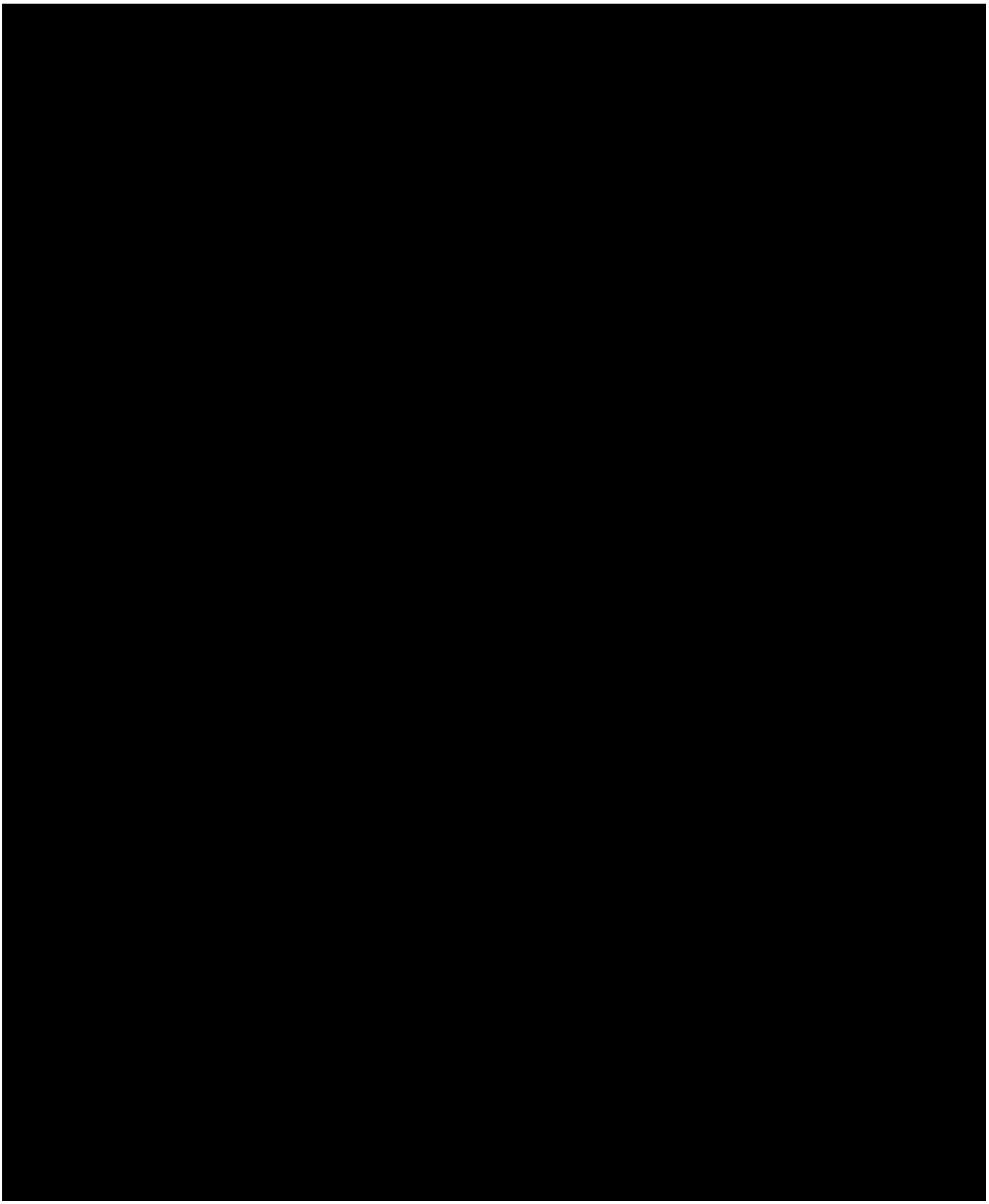

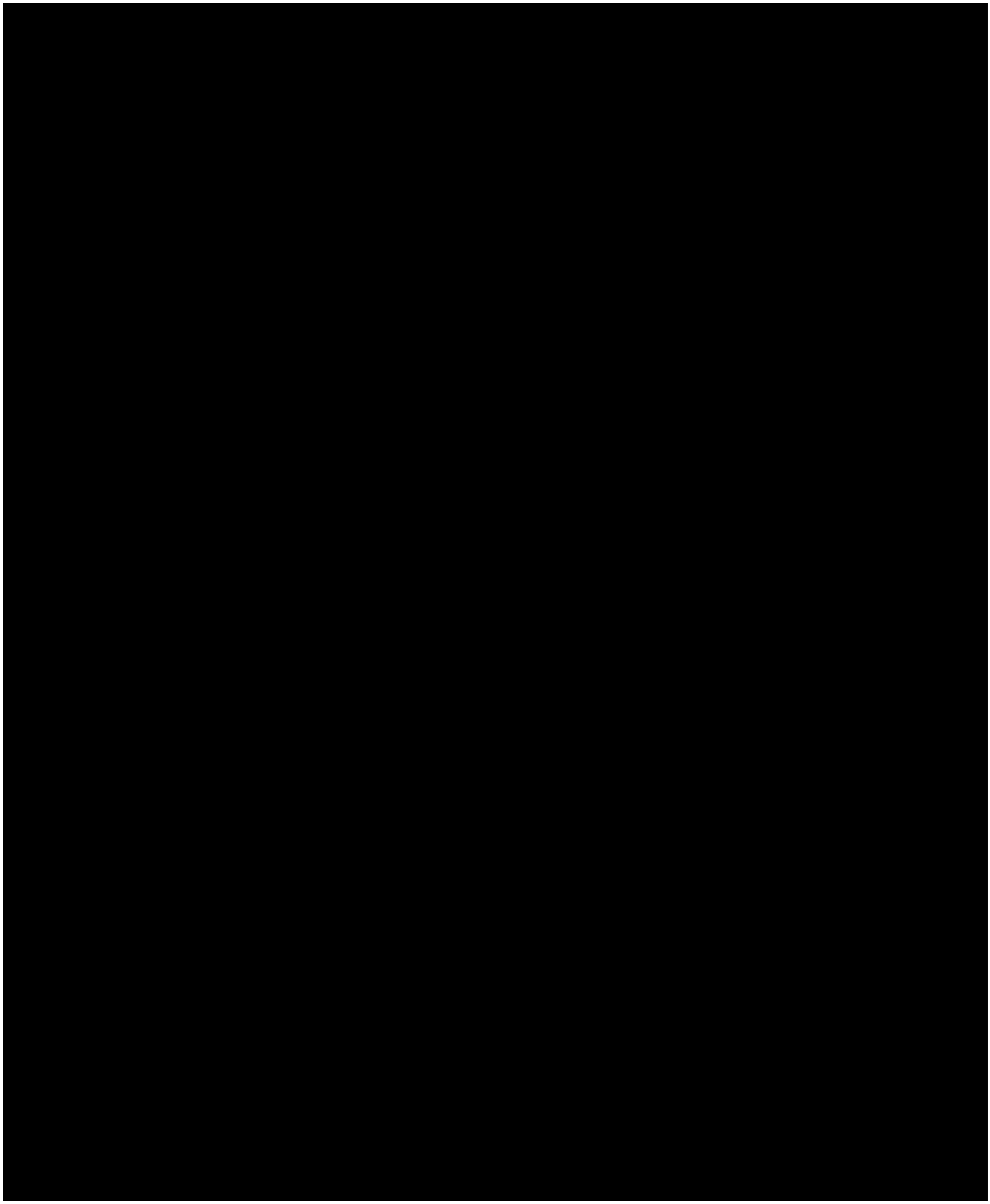

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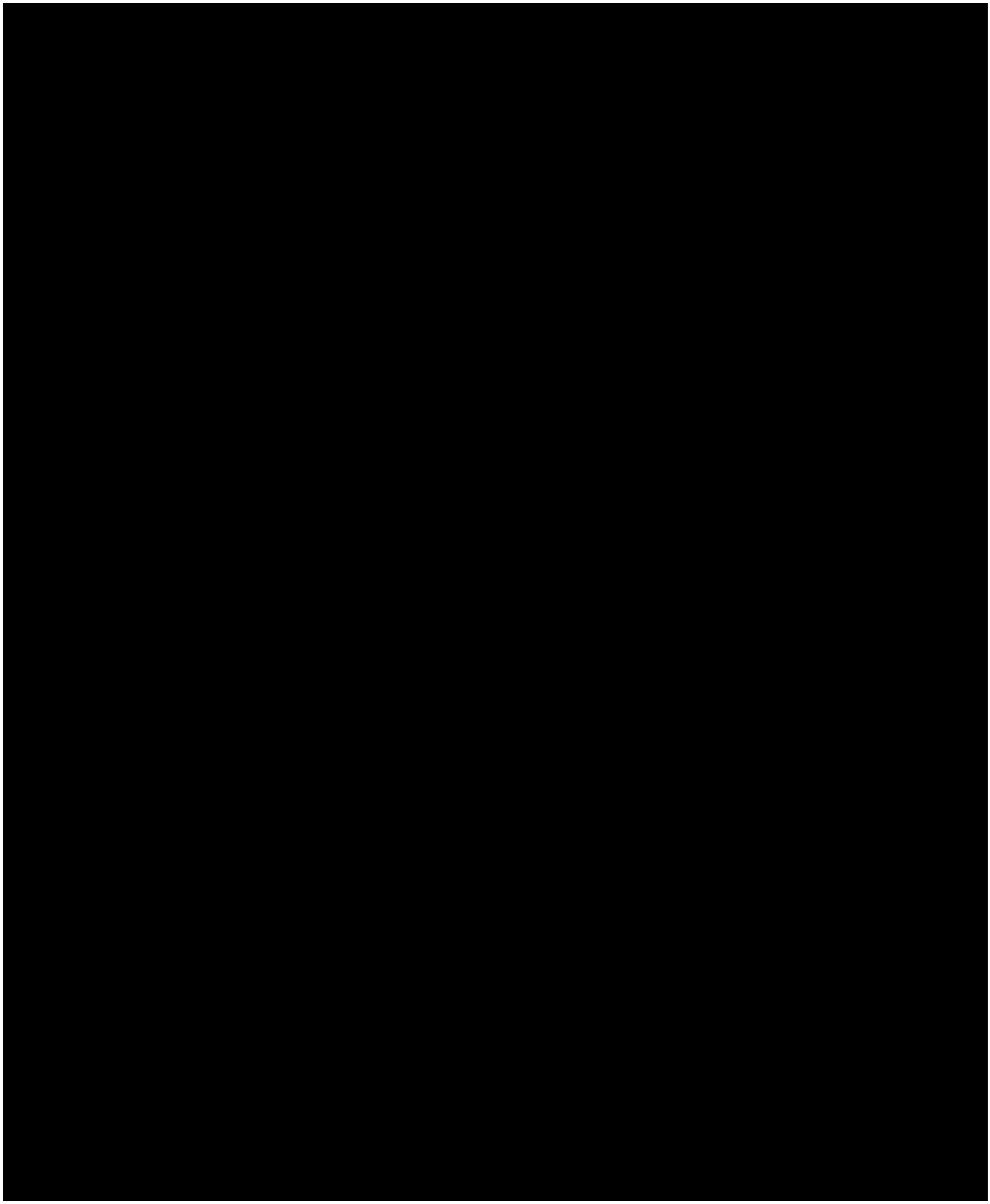

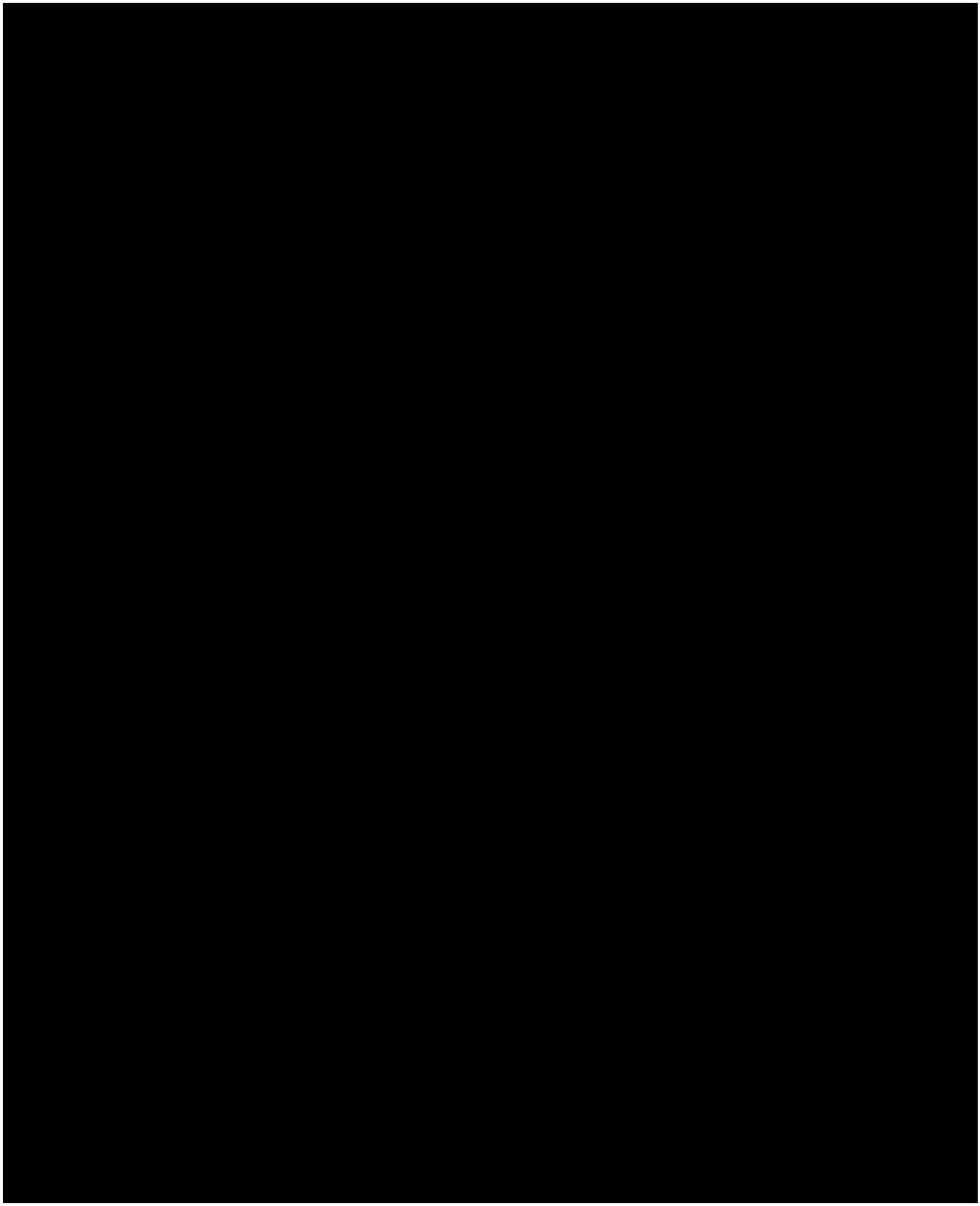

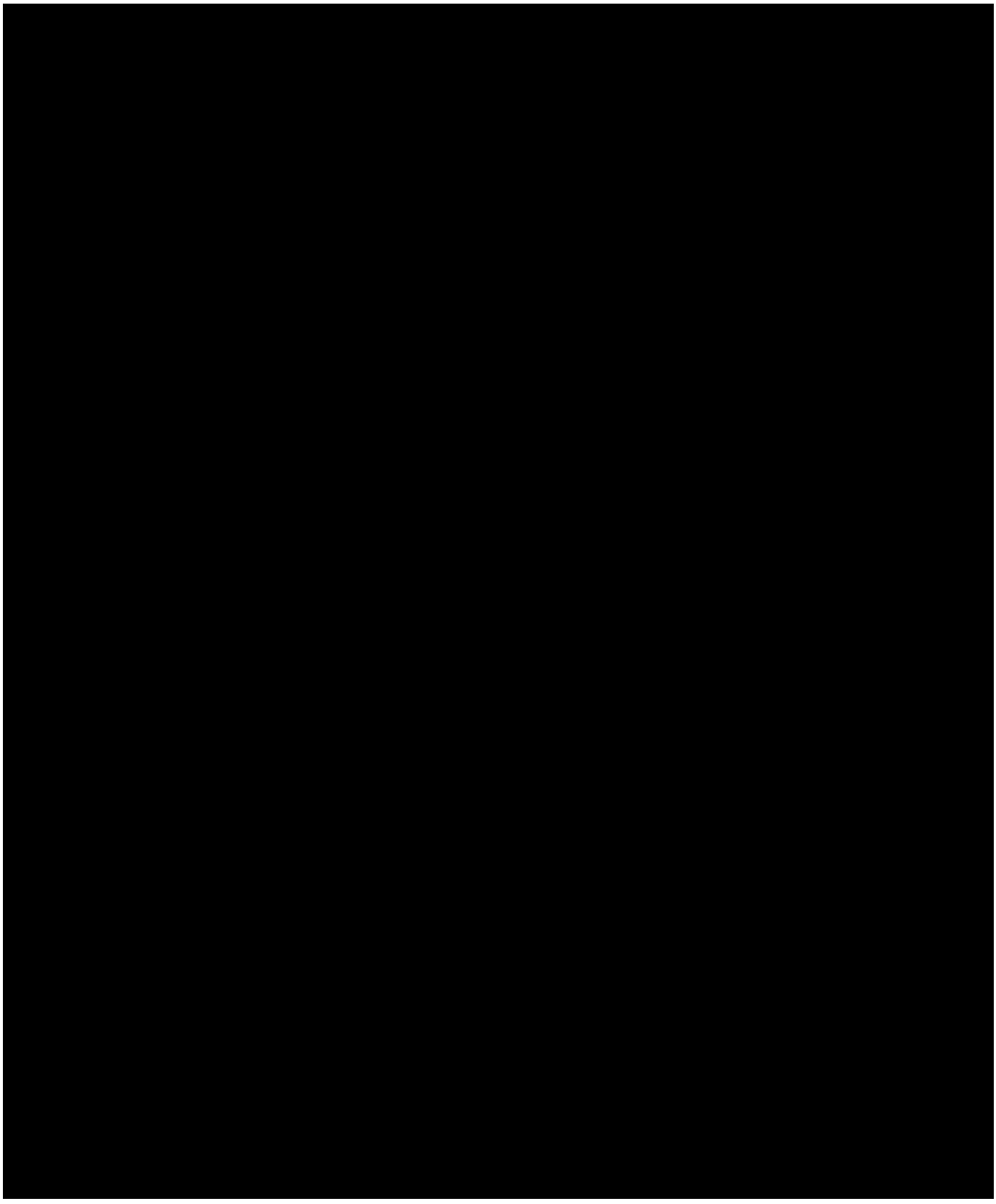

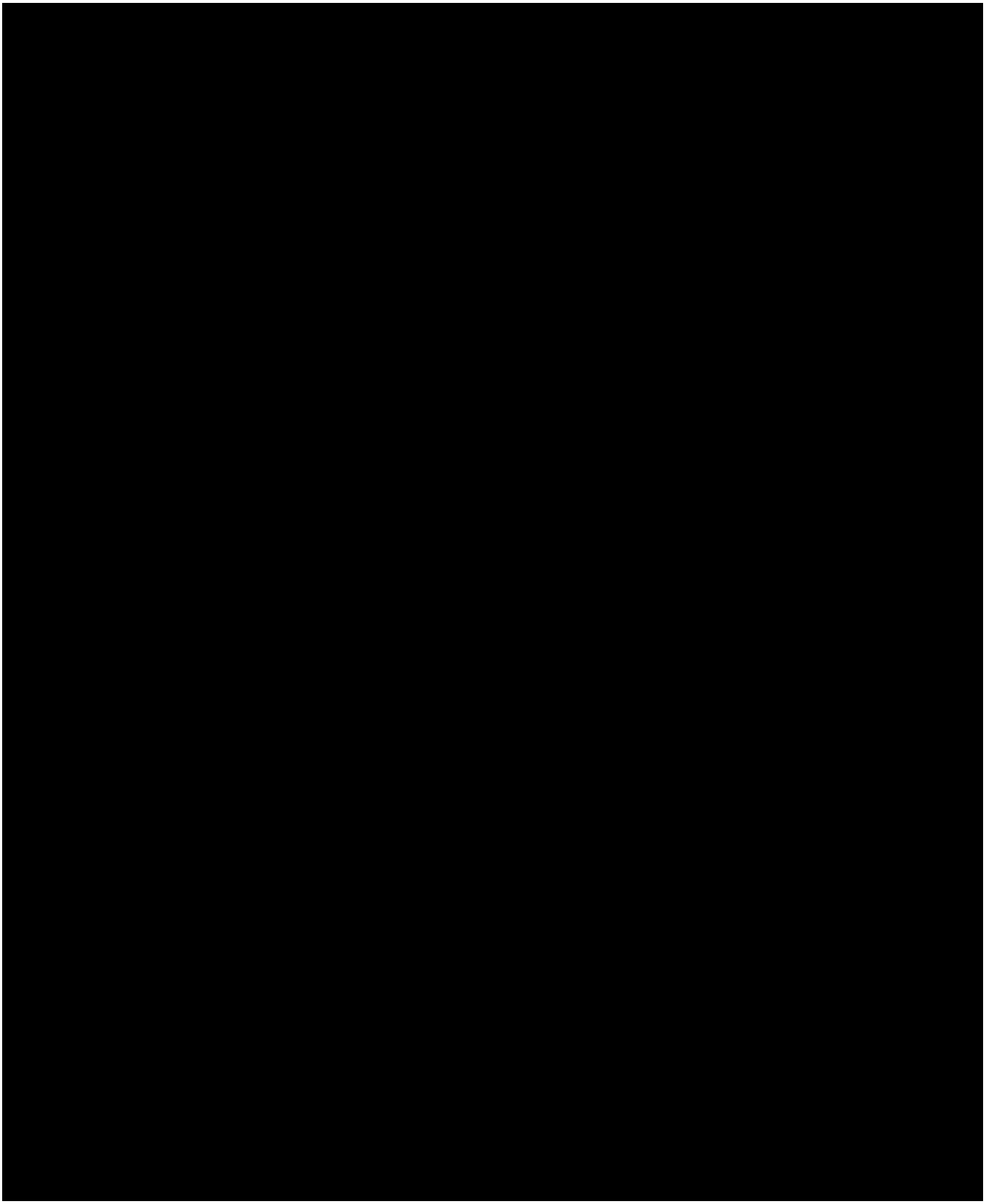

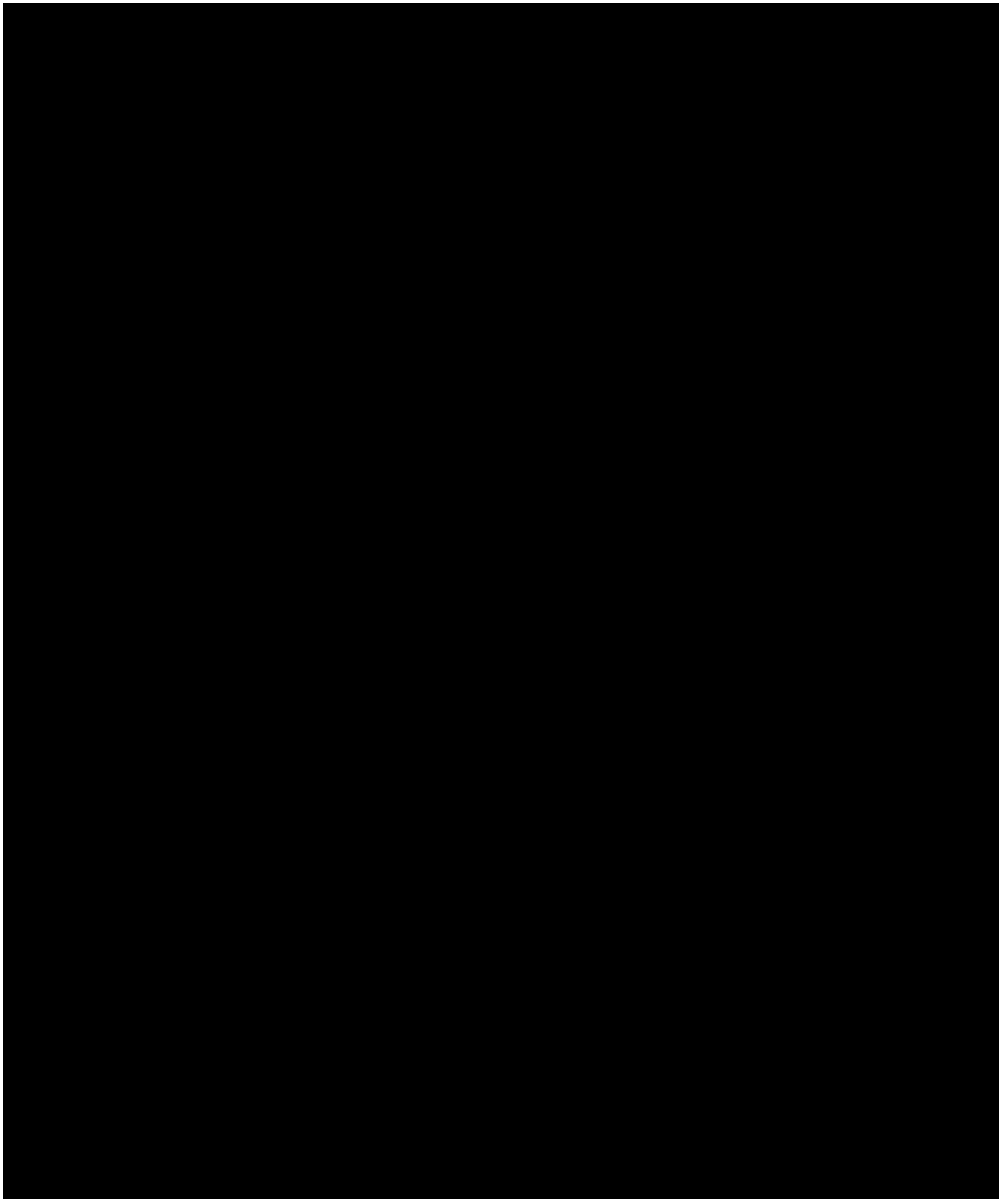

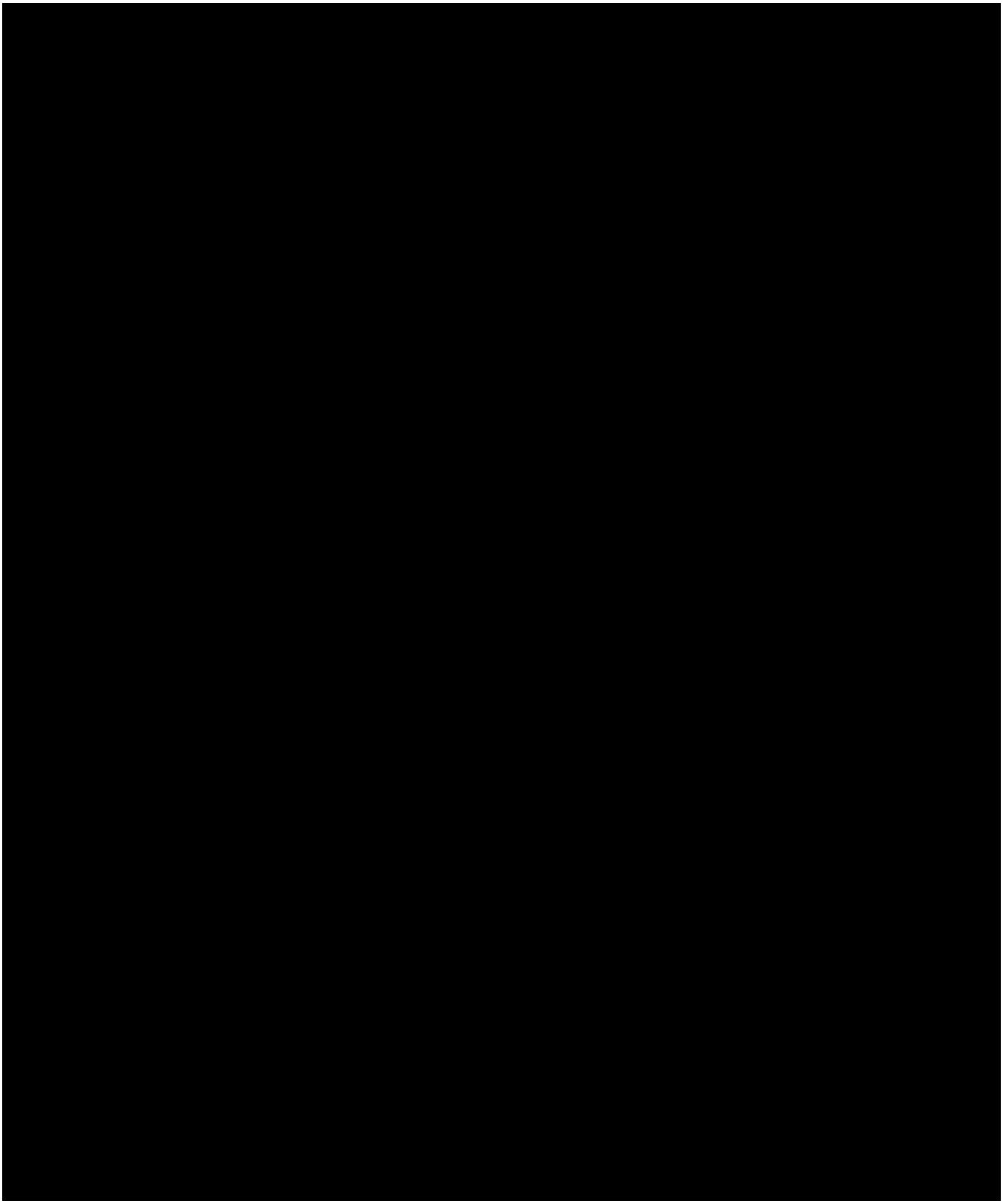

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Electronic Signatures

User	Date	Justification
[redacted]	23-Jun-2020 15:27:18 (GMT)	Subject Matter Expert Approval
[redacted]	23-Jun-2020 18:58:16 (GMT)	Document Originator Approval
[redacted]	23-Jun-2020 14:11:37 (GMT)	Manager Approval
[redacted]	23-Jun-2020 20:37:32 (GMT)	Manager Approval