STATISTICAL ANALYSIS PLAN

Protocol Number:	1620302
Title:	A Phase 3, Randomized, Double-Blind, Placebo Controlled, Multi-Center Trial to Evaluate the Efficacy and Safety of DaxibotulinumtoxinA for Injection to Treat Moderate to Severe Glabellar Lines (SAKURA-2)
Study Phase:	3
Sponsor:	Revance Therapeutics, Inc. 7555 Gateway Blvd. Newark, CA 94560
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
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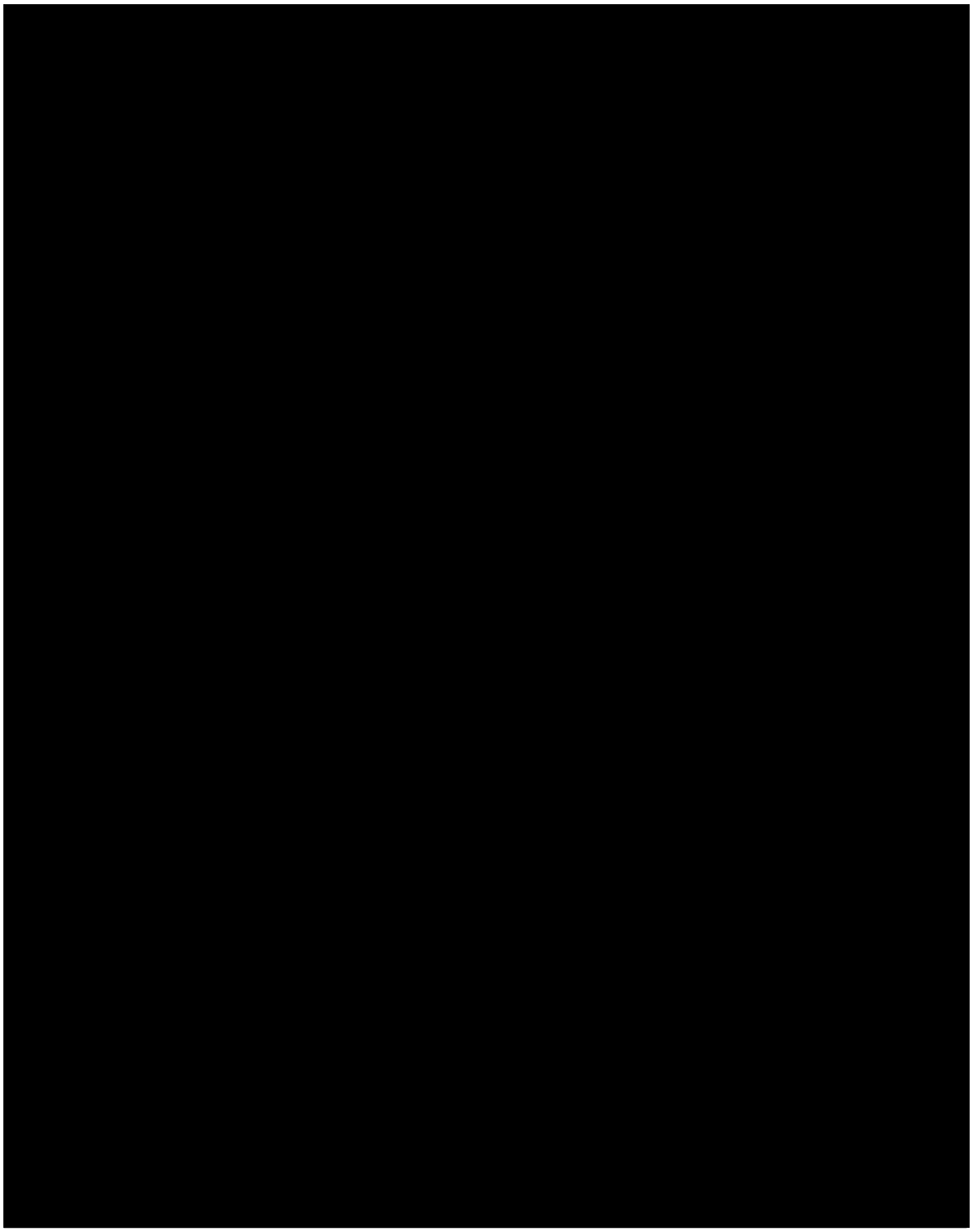

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LIST OF TABLES

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
CRF(s)	Case Report Form(s)
FASE	Facial Age Self Evaluation
[redacted]	[redacted]
GAIS	Global Aesthetic Improvement Scale
IGA-FWS	Investigator Global Assessment-Facial Wrinkle Severity
IPR	Independent Panel Review
ITT	Intent-to-treat
MedDRA®	Medical Dictionary for Regulatory Activities
mL	Milliliter
MRC	Medical Research Council
N	Number of Patients
PFWS	Patient Facial Wrinkle Severity
PP	Per-Protocol
Revance	Revance Therapeutics, Inc.
SAE	Serious Adverse Event
SAS®	Statistical Software from SAS Institute Inc.
SD	Standard Deviation
UPT	Urine Pregnancy Test
WOCBP	Women of Childbearing Potential
WHO	World Health Organization

1. INTRODUCTION

The safety and effectiveness of botulinum toxin type A to act on the neuromuscular junction and relieve muscle spasm and its clinical effects such as strabismus, pain, and facial wrinkles has been well established for over 20 years (Scott, 1981; Carruthers, 1992; Spencer, 2002).

This statistical analysis plan (SAP) describes the objectives of the study and the efficacy and safety assessments that are collected. The primary, secondary, and exploratory efficacy endpoints and the safety endpoints are defined, and the statistical methods used to analyze them are presented. Table shells for the planned end-of-text tables, figures, and listings are included following the text of the SAP.

2. STUDY OBJECTIVES

The study objective is to evaluate the efficacy and safety of a single treatment of DaxibotulinumtoxinA for Injection for the treatment of moderate to severe glabellar lines compared to placebo.

2.1. Overall Study Design and Plan

This is a phase 3, double blind, placebo-controlled, multi-center trial to evaluate the efficacy and safety of a single intramuscular (IM) treatment of DaxibotulinumtoxinA for Injection for the temporary improvement in the appearance of glabellar lines in adults compared to a placebo.

The duration is up to 38 weeks on trial, including a screening period of up to two weeks followed by a single treatment and a follow-up period of up to 36 weeks post-treatment. All patients will be followed for at least 24 weeks post-treatment. Starting at Week 24 post-treatment, patients will be followed until their wrinkle severity in the glabellar lines at maximum frown returns to baseline in both the Investigator Global Assessment-Facial Wrinkle Severity (IGA-FWS) and Patient Facial Wrinkle Severity (PFWS) assessments.

[redacted]

2.3. Determination of Sample Size

Estimates of treatment efficacy taken from trial RT002-CL002 show that a sample size of 200 and 100 for DaxibotulinumtoxinA 40 U for injection and placebo, respectively, [redacted] between treatment groups for the response rate of key secondary endpoints on later visits.

2.4. Treatments Administered

Approximately 300 adult patients with moderate to severe glabellar lines will be enrolled.

[redacted]

3. Efficacy and Safety Assessments

The primary efficacy assessments will include investigator assessment of glabellar line severity and glabellar line improvement, and patient assessment of glabellar line severity and improvement.

3.1. Frown Wrinkle Severity – Patient and Investigator Global Assessment

Frown wrinkle severity is assessed by both the patient (Patient Frown Wrinkle Severity [PFWS]) and the investigator (Investigator Global Assessment Frown Wrinkle Severity [IGA-FWS]) using the same 4-point rating scale, as shown in Table 3.1.1-1.

The severity is assessed at maximum frown and at rest after maximum frown by both the patient and the investigator. The scores range from 0 = none to 3 = severe.

Table 3.1.1-1 Frown Wrinkle Severity

Rating Score	Frown Wrinkle Severity	Description
0	None	No wrinkles
1	Mild	Very shallow wrinkles
2	Moderate	Moderate wrinkles
3	Severe	Deep wrinkles

3.1.1. Primary Efficacy Endpoint

The **primary efficacy endpoint** is derived from the maximum frown scores obtained at Week 4, and is defined as achieving a score of 0 or 1 (none or mild) and an improvement of at least two points from baseline on both the IGA-FWS and PFWS scales concurrently. The response will be abbreviated as “2-point composite response” henceforth.

[redacted]

[redacted]

[redacted]

3.2. Additional Assessments

3.2.1. Patient Diary

Patients will capture their assessment of the appearance of the lines at maximum frown, in a diary for the initial 2-week post treatment period, using the 4 point severity scale given in Table 3.1.1-1. [redacted]

3.2.2. Patient Global Satisfaction with Treatment Questionnaire

Patients will be asked how satisfied or dissatisfied they are with the treatment results using a 7 point scale at Week 4. This treatment questionnaire will be based on how the treated area of the face looks (see Table 3.2.2-2). [redacted]

Table 3.2.2-2 Global Satisfaction with Treatment Questionnaire Scale

Rating Score	Wrinkle Improvement
0	Very Dissatisfied
1	Dissatisfied
2	Somewhat Dissatisfied
3	Neither Satisfied Nor Dissatisfied
4	Somewhat Satisfied
5	Satisfied
6	Very Satisfied

3.2.3. Global Aesthetic Improvement Scale

The Investigator and patient will assess the visual appearance (at maximum frown and at rest after maximum frown) of the glabellar line improvement from the baseline condition using the following 7 point severity Global Aesthetic Improvement Scale (GAIS, Table 3.2.3-3).

Table 3.2.3-3 Global Aesthetic Improvement Scale

Rating Score	Wrinkle Improvement
-3	Very Much Worse
-2	Much Worse
-1	Worse
0	No Change
1	Improved
2	Much Improved
3	Very Much Improved

[redacted]

3.2.5. Facial Age Self Evaluation

Patients will rate their perceived age on a Facial Age Self Evaluation (FASE) questionnaire and rate their perception of how old they think they look following the treatment (older than actual age, younger than actual age, actual age). These responses will be used as exploratory endpoints.

[redacted]

3.3. Safety Assessments

3.3.1. Adverse Events

All adverse events (AEs) will be recorded and classified on the basis of MedDRA terminology. AE severity will be graded as mild, moderate, or severe as defined in Section 6.1.2 of the protocol. AEs with an onset on or after the date and time of study treatment will be Treatment-emergent.

The safety endpoints derived from the AEs are:

- Frequency, severity and relationship to study drug of treatment-emergent adverse events during the first four weeks post treatment and the overall study duration
- Frequency, severity and relationship to study drug of treatment-emergent serious adverse events during the first four weeks post treatment and the overall study duration

[redacted]

3.3.3. Clinical Laboratory Data

As outlined in Table 3.3.3-4, non-fasting samples for hematology, chemistry, coagulation (prothrombin time) and urinalysis will be collected at Screening, Week 4, and at the Final Evaluation Visit. [redacted]

Table 3.3.3-4 Clinical Laboratory Tests

Serum Chemistry	Hematology	Urinalysis	Additional Tests
Glucose	Hemoglobin	Overall Assessment and Clinical Significance	Prothrombin time (PT)
Total bilirubin	Hematocrit		Urine Pregnancy (WOCBP only)
Alkaline phosphatase	Red Blood Cell Count		[redacted]
Blood urea nitrogen	Platelet Count		
Alanine aminotransferase	Leukocyte Count (total)		
Aspartate aminotransferase	Leukocyte Count (differential)		

WOCBP = Women of child-bearing potential

[redacted]

3.3.5. Vital Signs

Vital signs (i.e., body temperature, respiration rate, sitting radial pulse rate, and sitting systolic and diastolic blood pressures) will be obtained at the Screening and Treatment Visit (pre- and post-treatment), Week 2, Final Evaluation or Early Discontinuation Visits and at any visit where signs or symptoms of botulinum toxicity are reported.

3.3.6. Physical Examination

A physical examination, in addition to vital signs, [redacted], general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, heart, lungs,

abdomen, lymph nodes, and extremities will be conducted at Screening, Week 2 and Final Evaluation or Early Discontinuation Visits. Significant physical examination findings that are present prior to investigational product administration are to be included on the Medical History page.

Significant physical examination findings which meet the definition of an adverse event will be recorded on the adverse event page post-treatment.

3.3.7. 12-Lead ECG

At Screening and Week 4, a single standard supine 12-Lead ECG will be obtained.

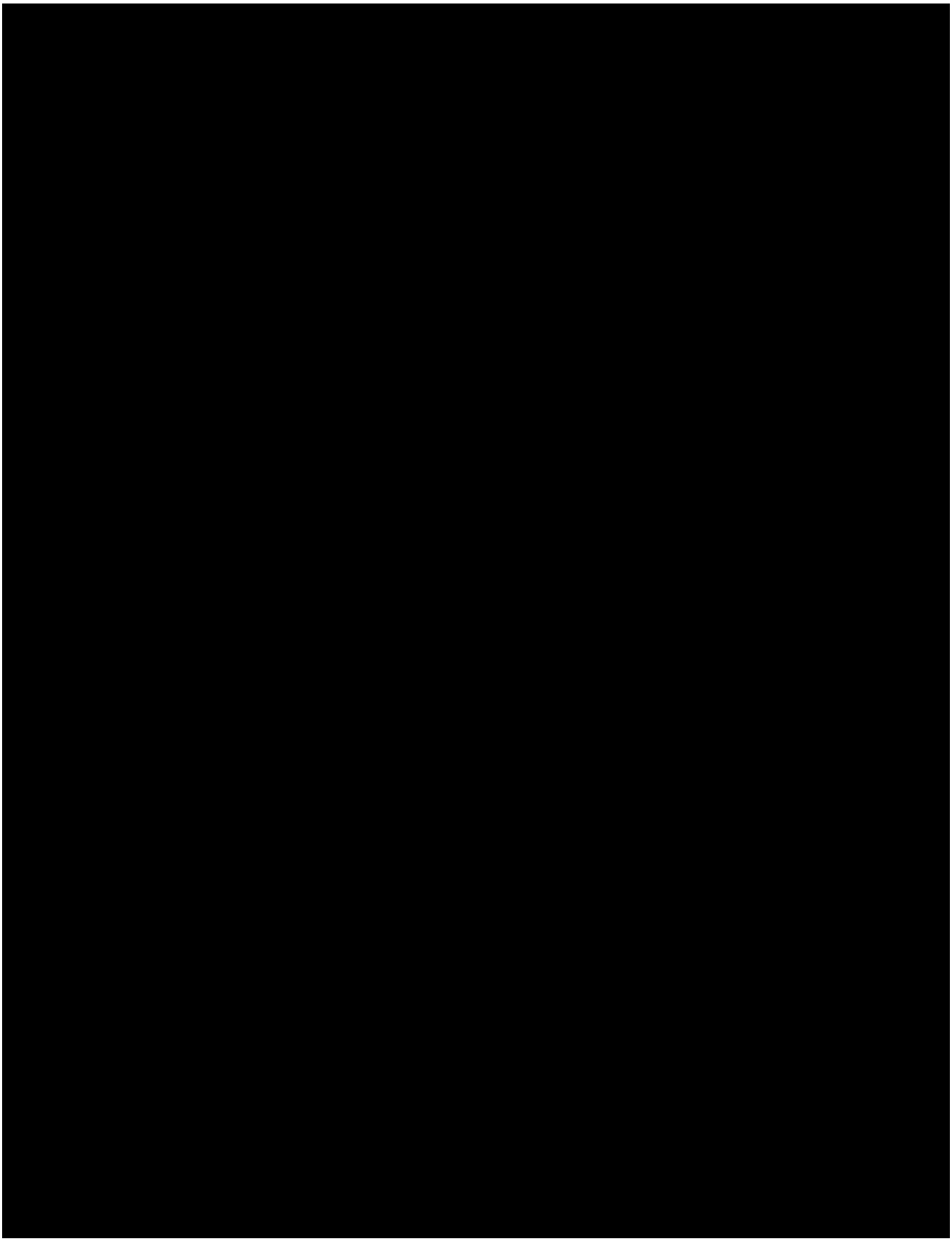
3.3.8. Injection Site Evaluation

Injection sites will be evaluated at the Screening Visit, Treatment Visit pre- and post-treatment, Follow-up Visits, and Final Evaluation Visit or Early Discontinuation Visit, if applicable. The assessment will be done as a global evaluation of the 5 injection sites (Table 3.3.8-5).

Table 3.3.8-5 Injection Site Evaluation

	Present?	
Assessment Descriptor	**Yes**	**No**
Erythema		
Edema		
Burning or Stinging (sensation as described by patient)		
Itching (sensation as described by patient)		
Bruising		

[redacted]



4. Statistical Methods

All statistical programming will be performed using statistical analysis system (SAS) version 9.3 or higher.

[redacted]

4.1. Analysis Populations

4.1.1. Intent-to-Treat Population

All patients who are randomized and receive treatment will be included in the Intent-to-Treat (ITT) population. The summaries will be by treatment as randomized.

4.1.2. Per Protocol Population

The Per-Protocol (PP) population will include patients from the ITT population who complete the first 4-weeks of the study without a major protocol violation. [redacted]

[redacted]

4.1.3. Safety Population

All patients who are randomized, receive treatment, and have provided at least one post-treatment safety assessment will be included in the Safety population. The summaries will be by treatment actually received.

4.2. Patient Disposition

The number and percentage of patients who have signed informed consent, been randomized, received treatment, and completed key visits will be tabulated by treatment group overall and by trial center (or pooled center, as appropriate) and included in a listing. Reasons for not completing the study will also be tabulated by treatment group and overall and by trial center using numbers and percentages; this data will also be included in a listing. For those patients who are considered to have failed screening, the reason(s) for failure will be provided in a listing.

The number and percentage of patients included and excluded from the analysis populations (ITT, PP and safety) will be tabulated overall and for each treatment group. Reason(s) for exclusion from each population will be summarized and listed.

[redacted]

Major protocol deviations will be listed and summarized by treatment group.

4.3. Demographic and Baseline Characteristics

Descriptive statistics will be used to summarize demographic and baseline characteristics by treatment group and overall. Continuous variables will be summarized using the number of non-missing observations, mean, standard deviation, median, minimum and maximum. Categorical data will be summarized using the number and percentage of patients in each category. Demographic data include age, sex, race and ethnicity. Age in years will categorized as 18 to 45, >45 to 55, and >55 to 75 for summarizing by treatment group and overall. Baseline characteristics include Prior Botulinum Toxin Type A, Time Since Last Prior Botulinum Toxin Type A Injection, and Fitzpatrick Skin Type, as well as the baseline assessment of the efficacy questionnaires, PFWS, IGA-FWS, FLIS, [redacted] Summaries will be produced for the ITT

and PP populations by randomized treatment; and, for the Safety population by actual treatment received.

4.4. Medical History

Medical history will be classified on the basis of MedDRA terminology, using the latest terminology at the time of database finalization. Medical history will be summarized by treatment group, system organ class, and preferred term, and will be listed.

4.5. Prior and Concomitant Medications

Prior therapies/medications recorded at Screening but no longer being taken, and concomitant therapies/medications recorded at Screening and still being taken or being taken at each trial visit, will be coded using the World Health Organization (WHO) drug dictionary and summarized by treatment group and overall, Anatomical Therapeutic Chemical (ATC) second level term, and preferred name for the Safety population. Prior and concomitant medications will be summarized separately.

4.6. Efficacy Analyses

Descriptive statistics will be provided for all efficacy variables at all timepoints by treatment group.

[redacted]

[redacted]

4.6.1. Primary Efficacy Analysis

The proportion of patients who have a 2-point composite response at Week 4 will be compared between daxibotulinumtoxinA and placebo [redacted]. As a sensitivity analysis, the primary analysis will be repeated [redacted]

P-values [redacted] will be provided. The point estimates for the difference will be calculated [redacted]
The 2-sided, 95% CIs will be calculated [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.8. Safety Analyses

Safety summaries and analyses will be performed on the safety population. Descriptive statistics will be presented to summarize the safety data.

4.8.1. Extent of Exposure

All patients receive one administration of investigational product. The sum of volume of investigational product injected and the volume of investigational product injected at each of the five injection sites will be summarized by treatment group using descriptive statistics (number of non-missing observations, mean, median, minimum, maximum, and standard deviation).

4.8.2. Injection Site Evaluations

The injection site evaluations will be summarized using number and percentage of patients reporting the presence of each item (Erythema, Edema, Burning or Stinging, Itching and Bruising) by treatment group and visit, as well as the number and percentage of patients with a reaction at any post-treatment visit. In addition, the number and percentage of patients reporting any injection site item will be summarized by treatment group, and by visit as well as at any post-treatment visit. Additionally, the number and percentages of patients with the specified item will be summarized according to the first visit at which the reaction was present.

4.8.3. Adverse Events

All treatment-emergent AEs (TEAEs) will be listed and summarized by treatment group, system organ class, preferred term, severity, relationship, and seriousness. Serious adverse events (SAEs) will be summarized by treatment group, severity, and relationship to study treatment and will be listed by patient separately.

Each patient will be counted only once within a system organ class or a preferred term using the event with the greatest relationship and greatest severity.

Specific AE[redacted] will be summarized by treatment group, system organ class, and preferred term. Adverse events included will be those listed in the query from Section 3.3.2.

All information pertaining to AEs noted during the trial will be listed by patient, detailing the verbatim description given by the Investigator, preferred term, system organ class, start date, stop date, severity, action taken regarding study drug, corrective treatment, outcome, and drug

relatedness. The event onset will also be shown relative (in number of days) to the date of first study treatment administration. In addition, a list of patients who prematurely discontinue from the trial due to adverse events will also be provided.

4.8.4. Laboratory Tests

4.8.4.1. Clinical Safety Laboratory Parameters

Laboratory test results will be summarized with descriptive statistics for each treatment group at Screening, Week 4, and the Final Evaluation Visit. Changes from Screening to Week 4 and to Final Evaluation Visit also will be summarized for continuous test results. For urinalysis, the number and percentage of patients within each treatment group with a normal; abnormal, clinicially significant; and abnormal, not clinically significant result will be presented.

Shift tables (low, normal, high) will be presented to summarize laboratory test results at Screening and the Final Evaluation Visit. Normal ranges established by the central laboratory will be used to determine shifts. A listing of all out-of-range or clinically significant laboratory test results at any evaluation will be provided. Determination of clinical significance for all out-of-range laboratory values were to be made by each investigator and will be included in the listing.

4.8.4.2. Pregnancy Tests

Urine pregnancy tests will be presented in data listings for all treated patients in the category of woman of child-bearing potential.

[redacted]

[redacted]

[redacted]

4.8.6. Vital Signs, Physical Examination, and ECG

Vital signs and ECG parameters will be summarized by treatment group with descriptive statistics for each treatment group by visit. Vital signs and ECG parameters will summarize the actual value as well as the change from screening for each visit using the number of non-missing observations, mean, median, minimum, maximum and standard deviation. The overall ECG assessment will be summarized for each treatment group using number and percentage of patients with a normal, abnormal and clinically significant, or abnormal and not clinically significant result.

Abnormal findings from the physical examination

4.9. Statistical/Analytical Issues

4.9.1. Adjustments for Covariates

No adjustments for covariates are planned.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.9.5. Data Handling Conventions

For all analyses, the protocol specified Treatment Day 0 will be referred to as Study Day 1.

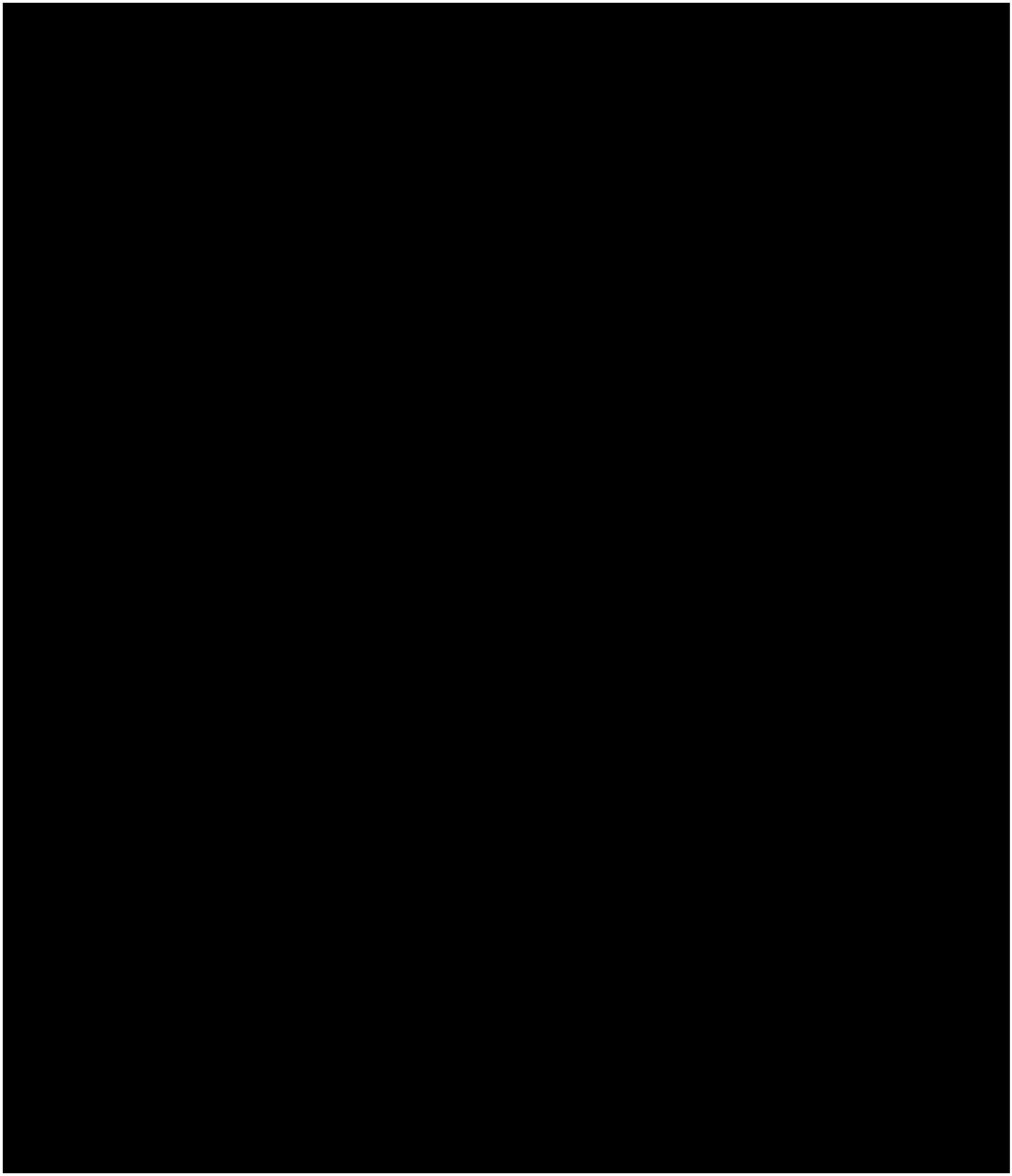
4.10. Interim Analyses and Data Monitoring

No interim analysis is planned.

[redacted]

- [redacted]

[redacted]



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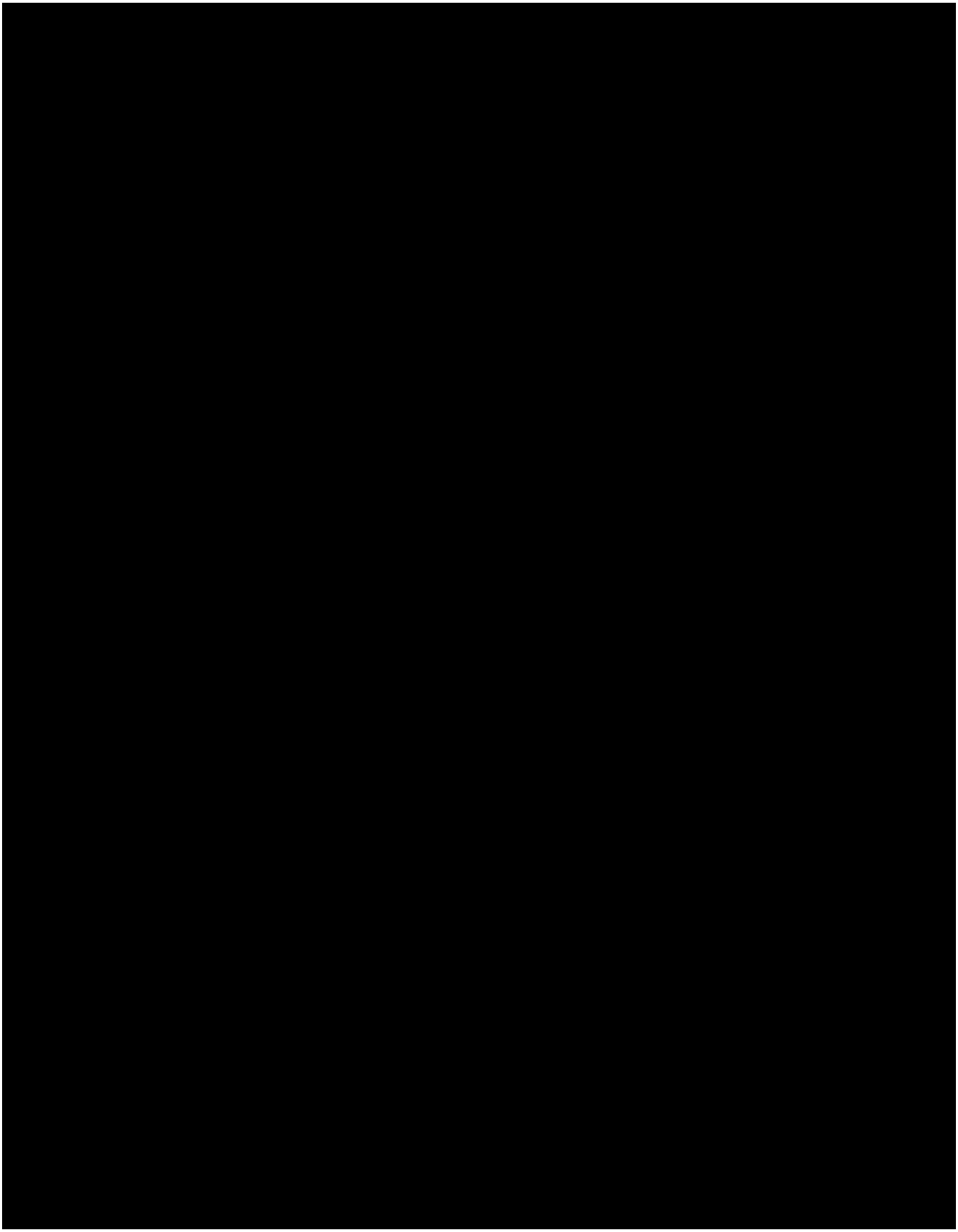

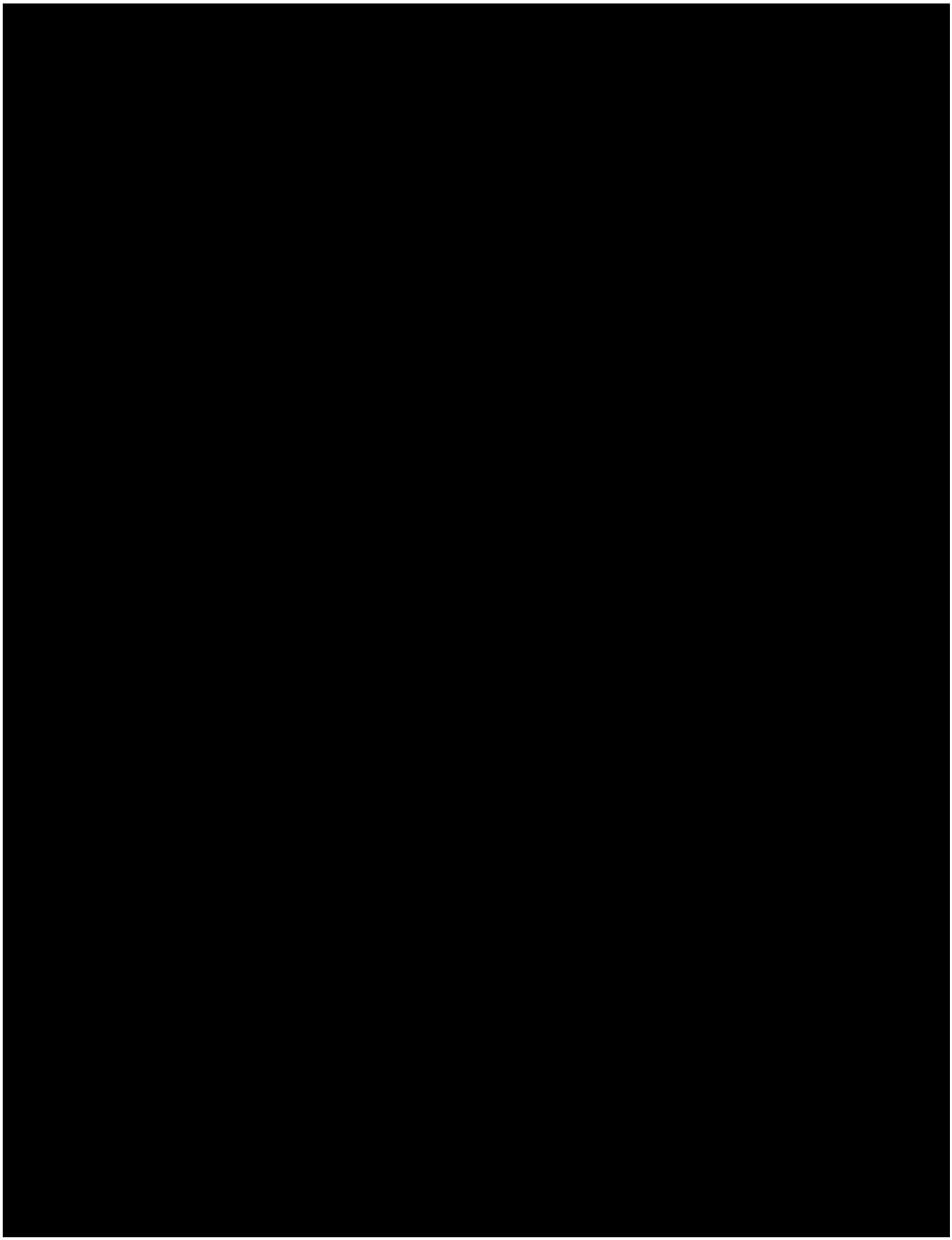

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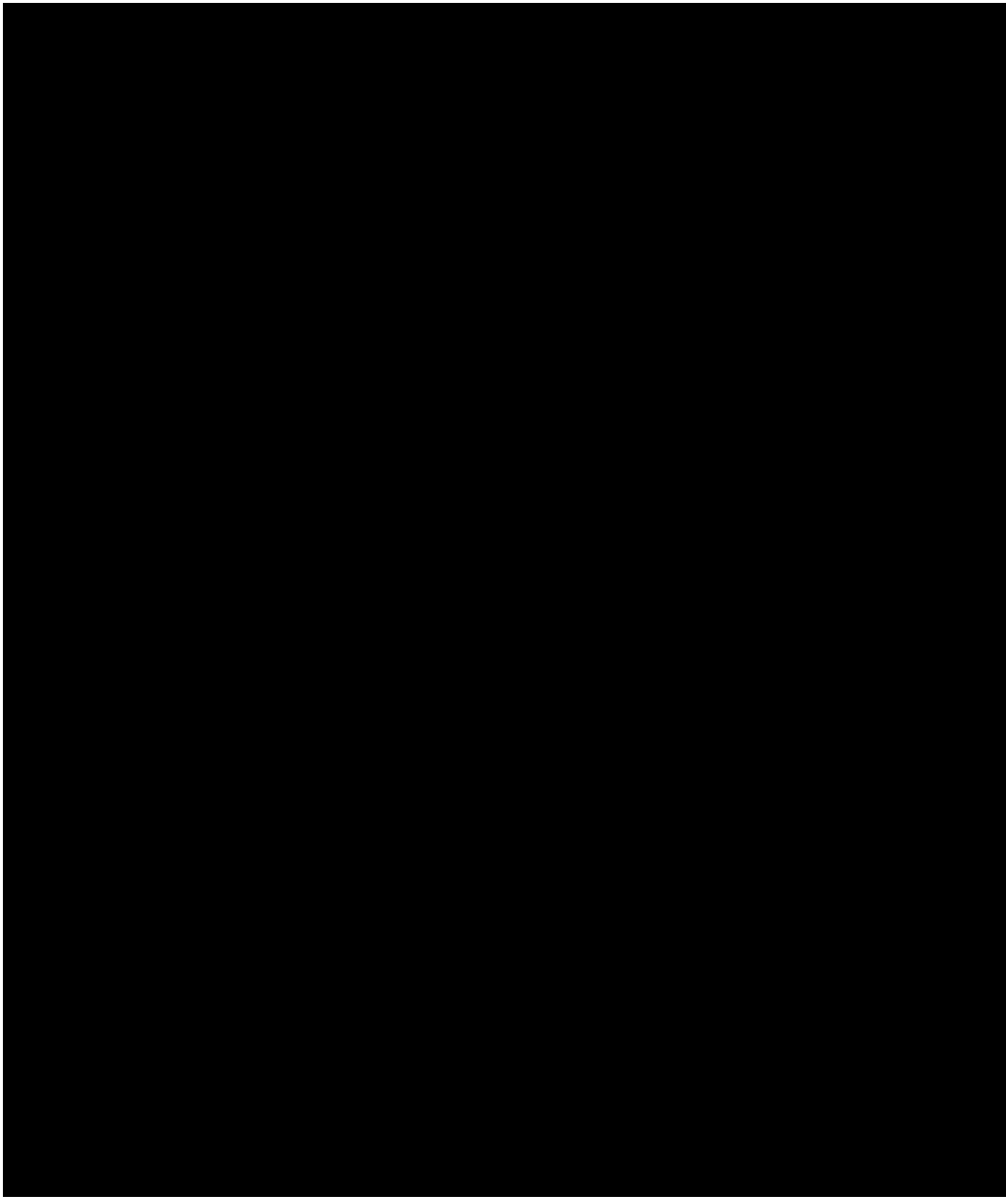

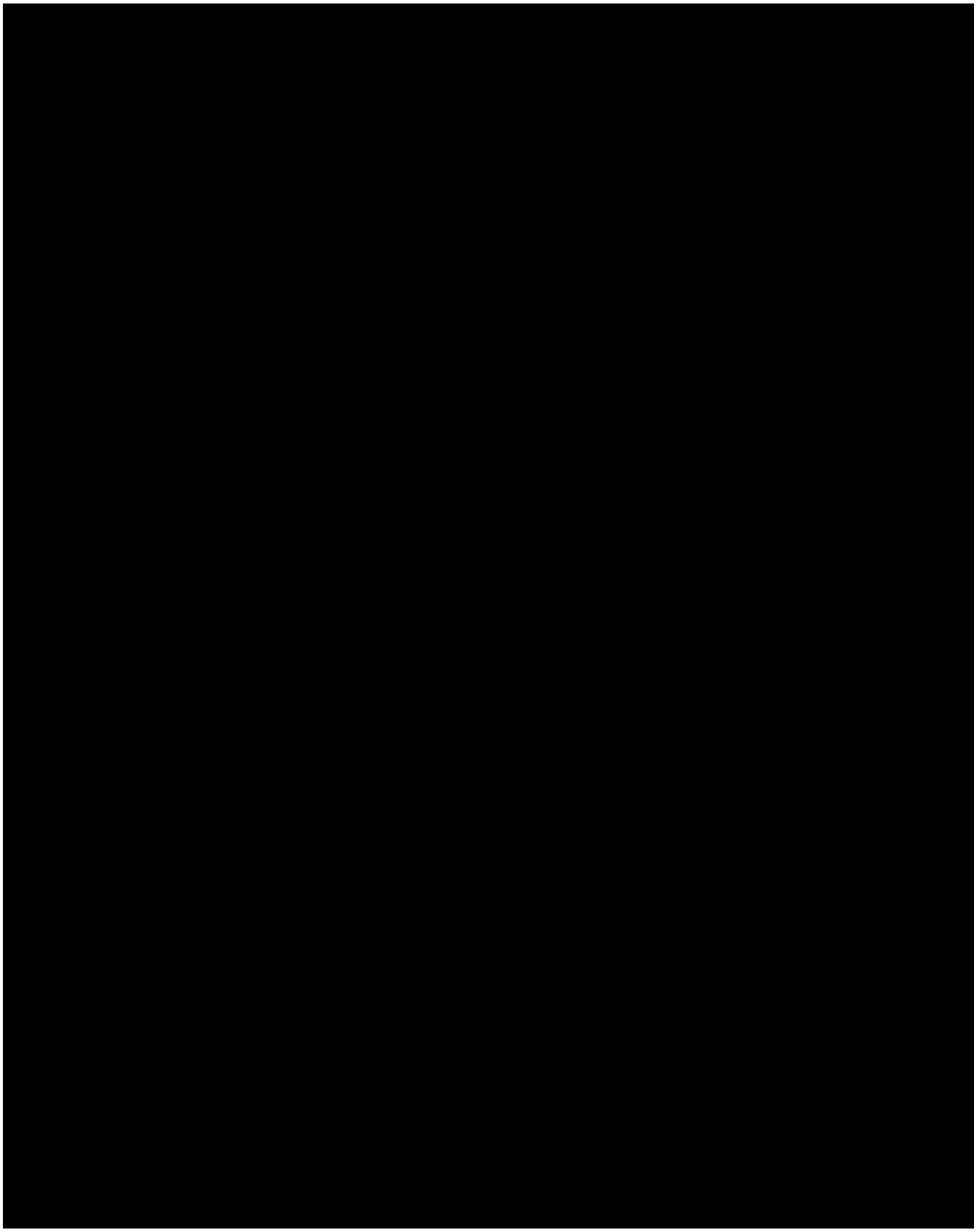

[redacted]

[redacted]