

NCT02010775

**Study ID:** 191622-130

**Title:** BOTOX® TREATMENT OF MASSETER MUSCLE HYPERTROPHY

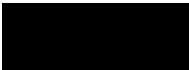
**Protocol Amendment 1 Date:** 28-Feb-2014

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## BOTOX<sup>®</sup> TREATMENT OF MASSETER MUSCLE HYPERTROPHY

Protocol Number: 191622-130  
Phase: 2  
Name of Investigational Product: BOTOX<sup>®</sup> (botulinum toxin type A) purified neurotoxin complex  
Sponsor: Allergan (North America)  
2525 Dupont Drive  
Irvine, California USA  
92612



Emergency Telephone Numbers: Refer to Study Contacts Page

Serious Adverse Event Reporting Fax Numbers: [Redacted]

Allergan Medical Safety Physician Contact Information: [Redacted]

Allergan Signatory: [Redacted]

Refer to the final page of this protocol for electronic signature and date of approval.

The following information can be found on the Study Contacts Page: name and contact information of Allergan study personnel and emergency telephone numbers; name, address, and statement of qualifications of each investigator; name of each subinvestigator working under the supervision of the investigator; name and address of the research facilities to be used; name and address of each reviewing IRB/IEC.

Approval Date: 28-Feb-2014

**INVESTIGATOR SIGNATURE PAGE**

INVESTIGATOR:

I agree to:

- implement and conduct this study diligently and in strict compliance with the protocol, good clinical practices, and all applicable laws and regulations.
- maintain all information supplied by Allergan in confidence and, when this information is submitted to an Institutional Review Board (IRB), Independent Ethics Committee (IEC) or another group, it will be submitted with a designation that the material is confidential.
- ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product, and their trial-related duties and functions.

I have read this protocol in its entirety and I agree to all aspects.

\_\_\_\_\_  
Investigator Printed Name

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

Approval Date: 28-Feb-2014

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## Protocol Summary

**Study Compound:** BOTOX® (Botulinum Toxin Type A) purified neurotoxin complex (referred to in this protocol as BOTOX)

**Phase:** 2

**Study Objective:** to evaluate the safety and efficacy of a range of doses of BOTOX for the treatment of subjects with bilateral masseter muscle hypertrophy (MMH)

**Clinical Hypotheses:** BOTOX treatment of MMH has an acceptable safety profile and is more effective than placebo, as demonstrated by a change in lower facial volume

### Study Design

*Structure:* multicenter, randomized, double-blind, placebo-controlled, up to 2-treatment, dose-escalation study

*Duration:* 12 months following randomization

*Study Treatment Groups:* BOTOX

*Controls:* placebo (saline)

*Dosage/Dose Regimen:* BOTOX or placebo will be administered intramuscularly to the bilateral masseter muscles (6 total injections, 3 injections/masseter). The initial BOTOX total dose will be 24 U (12 U/masseter) and the maximum BOTOX total dose will be 96 U (48 U/masseter). The planned dose escalation is as follows:

Cohort	Total Dose	Target Sample Size	Target Total Subjects/Cohort
1	24 U	40	50
	placebo	10	
2	48 U	40	50
	placebo	10	
3	72 U	40	50
	placebo	10	
4	96 U	40	50
	placebo	10	

Each cohort will be enrolled over an approximately 2-week period. The next cohort will be enrolled following a planned independent Data Review Committee (DRC) meeting and Allergan's written notification to proceed.

For each cohort, the DRC including Allergan nonstudy team members and non-Allergan nonstudy clinicians will meet to review safety and efficacy data through day 90. The DRC will assess if the data support study retreatment of the current cohort and/or advancement to the next cohort.

Subjects who meet the following retreatment criteria at the day 180 visit will receive a second treatment:

- Allergan written notification allowing retreatment of the current cohort
- subject has marked (grade 4) or very marked (grade 5) bilateral masseter muscle hypertrophy, as assessed by the investigator using the Masseter Muscle Prominence Scale (MMPS)
- females of childbearing potential must have a negative urine pregnancy test prior to treatment

The second treatment is only allowed at the day 180 visit. Subjects will receive the same treatment as they received at the day 1 visit.

*Randomization/Stratification:* After completion of all baseline procedures, subjects will be randomized and enrolled in cohorts of approximately 50 subjects each. Within each cohort, subjects will be randomized 4:1 to BOTOX (N = approximately 40) or placebo (N = approximately 10). Stratification will be by baseline (day 1) MMPS grade.



[REDACTED]

**Study Population Characteristics**

*Number of Subjects:* Based on 4 planned cohorts, approximately 200 subjects will be enrolled at approximately 4 to 12 investigational sites. The actual number of subjects in the study will be determined by the number of cohorts and number of subjects entering each cohort. Approximately 70% of the enrolled population in each cohort will be Asian, and subjects of Asian race will be further grouped by self-identified ethnicity (Chinese, Japanese, Korean, or other).

*Condition/Disease:* adult subjects with marked (grade 4) or very marked (grade 5) MMH, as determined by the investigator using the MMPS

*Key Inclusion Criteria:*

- adult male or female, 18 (or older if legal age of adulthood is > 18 as per local regulations) to 50 years of age, inclusive, at the time of consent
- subject has marked (grade 4) or very marked (grade 5) bilateral MMH (identical grades for left and right masseter), as determined at screening and confirmed on day 1 by the investigator using the MMPS

*Key Exclusion Criteria:*

- any medical condition that may put the subject at increased medical risk with exposure to BOTOX including diagnosed myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis, or any other condition that might interfere with neuromuscular function
- prior botulinum toxin treatment of any serotype
  - to the masseter muscle or lower face at any time or
  - to any other part of the body within the 6 months prior to study day 1

■ [REDACTED]

- history of dental or surgical procedure for lower facial shaping or masseter muscle reduction

■ [REDACTED]

- history of or current temporomandibular joint disorder (TMJD)

■ [REDACTED]

■ [REDACTED]

■ [REDACTED]

■ [REDACTED]

■ [REDACTED]

■ [REDACTED]

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**Response Measures**

*Efficacy:*

Primary

- lower facial volume (cm<sup>3</sup>) calculated from VECTRA M3 digital photography system [REDACTED]  
[REDACTED] 3D image models

Secondary

- investigator’s assessment of MMH using the MMPS (5 grades: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked, 5 = very marked)
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
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- [REDACTED]
- [REDACTED]

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**General Statistical Methods and Types of Analyses:**

Three analysis populations will be used:

- The modified intent-to-treat (mITT) population will consist of all randomized subjects who received study treatment and had at least 1 follow-up visit. The analysis will be based on the actual treatment subjects received.
- The per-protocol (PP) population will consist of randomized subjects who have no significant deviations from the protocol. Key criteria will be determined prior to database lock.
- The safety population will consist of all subjects who are treated with at least 1 injection of study treatment.

Day 1 will be considered as baseline for all measures except for the dental examination and CT imaging, for which the screening visit will be considered baseline. The primary efficacy variable will be lower facial volume at day 90. The change from baseline in lower facial volume will be analyzed by analysis of variance (ANOVA) with treatment and baseline MMPS grade as factors to assess the response between each BOTOX dose compared with placebo.

For analysis of the mITT population, the last observation carried forward (LOCF) method will be used to impute missing values. For analysis of the PP population, observed data without imputation will be used.

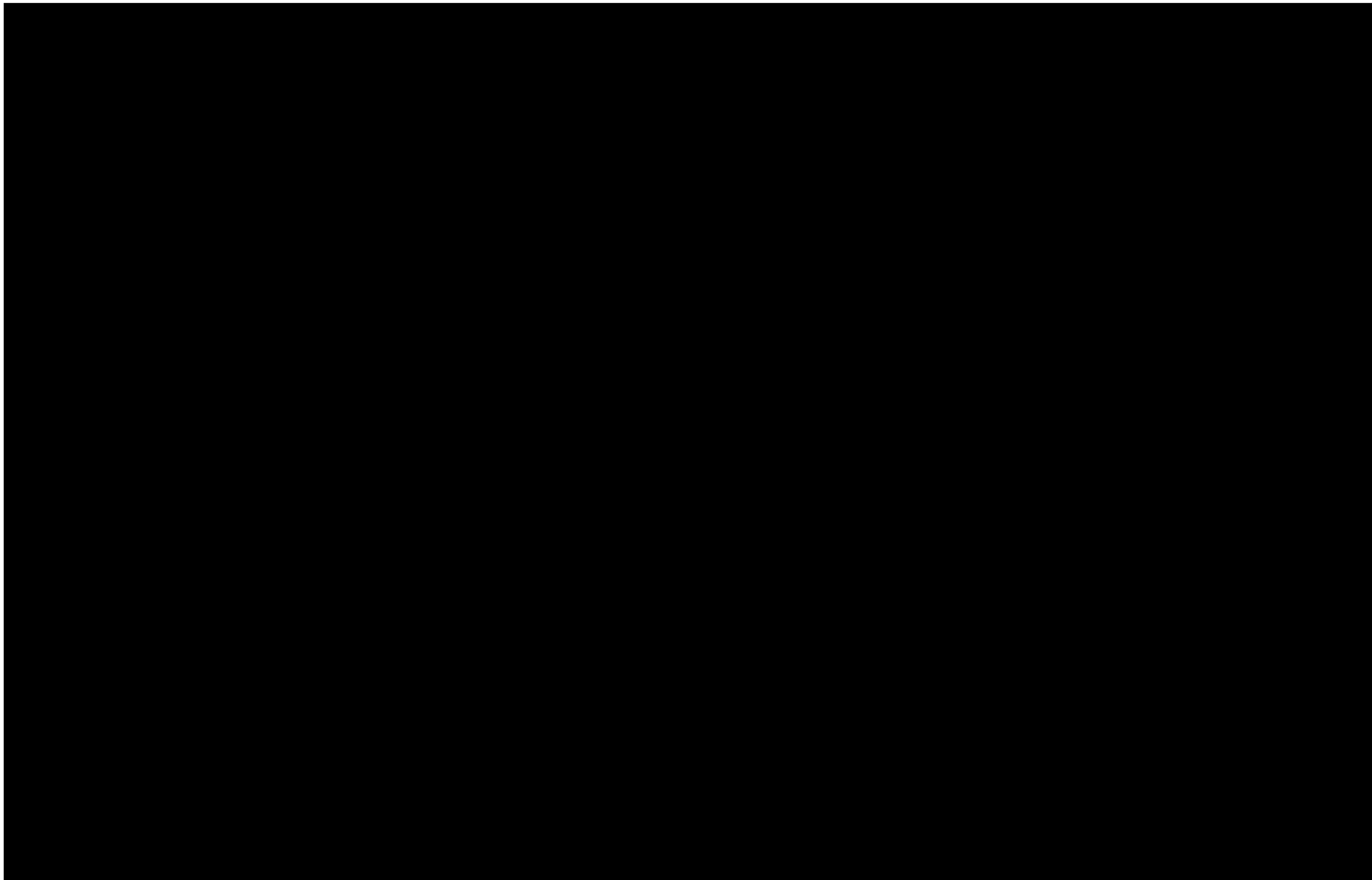
For each cohort, there will be a database snapshot with key data through the day 90 visit, for the purpose of the DRC assessment. There will be a final database lock with all study data after all subjects have completed the study (final cohort day 360). Subjects' treatment assignment will remain blinded for all site personnel, study subjects, and Allergan personnel directly involved with ongoing operational activities of the clinical study, until completion of the final database lock.

Data will be summarized with descriptive statistics, frequency tables, and data listings. Categorical variables will be analyzed using Fisher's exact tests, Pearson's chi-square tests, or Cochran-Mantel-Haenszel (CMH) tests as appropriate. Continuous variables will be analyzed using t-test, analysis of covariance (ANCOVA), or corresponding nonparametric methods.

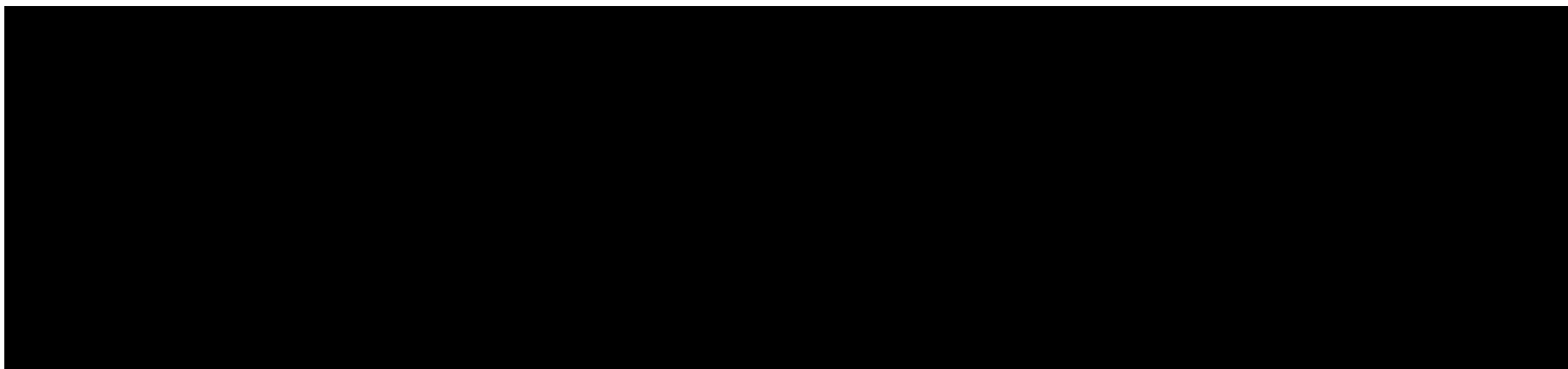
*Sample Size Calculation:*

The sample size used in this study is determined empirically. For each cohort, approximately 40 subjects will be randomized to BOTOX and approximately 10 subjects will be randomized to placebo. Assuming the VECTRA lower facial volume is a normal distribution and the effect size is 1, a 1-sided test with 0.10 significance level will have 93% power to detect a statistically significant change in the BOTOX group compared with the placebo group. The commercial software nQuery version 6.01 procedure MTT0U-1 was used for the power calculation.

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## 1 Background and Clinical Rationale

Botulinum toxin type A purified neurotoxin (BOTOX<sup>®</sup>) has been used for therapeutic and cosmetic purposes for over 2 decades and is 1 of the most common noninvasive aesthetic products in clinical use. When BOTOX is injected into a muscle, it interferes with neuromuscular transmission, producing temporary chemical denervation resulting in localized relaxation of the muscle and reduction in muscle activity. When injected into a hypertrophic masseter muscle, the effect of BOTOX has been observed as a reduction in the size of the muscle, perceived as lower facial shaping or slimming. This is the first Allergan-sponsored study of BOTOX for the treatment of masseter muscle hypertrophy (MMH), and worldwide there is no neuromodulator currently approved for treatment of this indication.

MMH may be unilateral or bilateral, and it may be idiopathic or occur in association with conditions such as bruxism, occlusal and muscular imbalances, temporomandibular joint disorder (TMJD), or excessive chewing habits (Aydil et al, 2012; Choe et al, 2005; Mischkowski et al, 2005). Aesthetically, MMH may appear as a wide, square, or trapezoidal lower face shape that is deemed undesirable, particularly in Asian countries. Individuals may seek surgical or nonsurgical alteration of prominent masseter muscles and/or mandibles to decrease a bulky or square-appearing lower face (Ahn et al, 2004; Liew and Dart, 2008).

The medical literature documenting the use of botulinum toxins, including BOTOX, for treatment of MMH dates back to 1994 (Moore and Wood, 1994; Smyth, 1994). Published cases characterize the patient population (Asian and non-Asian), injection techniques utilized, clinical results achieved, and adverse events (Ahn et al, 2004; Aydil et al, 2012; Choe et al, 2005; Liew and Dart, 2008). Due to the inherent risks associated with surgical intervention, the aesthetic procedure of treating the masseter muscle with botulinum toxin has gained popularity among physicians and patients.

In the medical literature, most side effects associated with BOTOX treatment of MMH have been local and expected, based on the well-established safety profile of BOTOX and the muscles injected. Adverse events reported in the medical literature include pain, discomfort, or muscle ache at the sites of injection; masticatory difficulties; speech disturbances; and cosmetic complaints related to the masseter and/or adjacent facial muscles. Typically, these events have been reported within 2 weeks posttreatment, were mild to moderate in severity, and resolved within 1 to 3 months. For further details regarding the safety of BOTOX treatment of MMH, including a comprehensive summary of the published literature reporting treatment in > 350 patients, please refer to the Investigator's Brochure.

This study is designed to evaluate the safety and efficacy of different doses of BOTOX for the treatment of MMH, to identify potential effects on associated structures (mandible and teeth), and to assist in the design of future clinical studies.

## 1.1 Rationale for Dose Selection and Population

A review of the medical literature of BOTOX treatment of MMH found the mean dose was approximately 36 units (U) per masseter (range: 10 U to 100 U/masseter) administered into 1 to 6 injection sites/masseter (refer to the Investigator's Brochure). In the present study, the initial dose (24 U, 12 U/masseter) will be tested to characterize the lowest threshold of potential treatment effect, whereas other planned doses (48 U, 72 U, and 96 U) are representative of total doses typical for treatment of hypertrophic masseter muscles. Subjects treated in this study are required to have marked or very marked bilateral MMH (grade 4 or 5 using Allergan's Masseter Muscle Prominence Scale [MMPS]; see Attachment 12.1.1) and will represent a variety of ethnicities, predominantly Asian.

## 1.2 Rationale for Efficacy Assessments

In the medical literature, various imaging methods have been used to assess effects of botulinum toxin on masseter muscle size and lower facial shape (refer to the Investigator's Brochure). Technologies used to measure quantitative changes in masseter muscle volume have included ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI). Photographic technologies developed to provide 3-dimensional (3D) quantitative analysis of facial morphology include image subtraction technique, moire topography, liquid crystal scanning, light luminance scanning, laser scanning, stereo-lithography, and passive stereophotogrammetry ([Adriaens, 2012](#); [Kim et al, 2005](#); [Tzou and Frey, 2011](#)), which all measure change to the lower facial contour. Previous studies reported peak efficacy of botulinum toxin treatment of MMH at 3 months ([Hong et al, 2005](#); [Kim et al, 2003](#); [Kim et al, 2007](#); [Park et al, 2003](#)), therefore, day 90 is the primary timepoint in the present study.

In the present study, the VECTRA M3 3D Stereophotogrammetry system [REDACTED] and CT imaging will be used to quantify the effect of BOTOX by lower facial volume (Attachment 12.1.2) and masseter muscle volume (Attachment 12.1.3), respectively. The VECTRA system has previously been validated for use in the facial region ([de Menezes, 2010](#)), and data from this study will be used to validate its use in the defined lower facial area encompassing the masseter muscle. In addition, the lower facial width (Attachment 12.1.4) and mandibular facial angle (Attachment 12.1.5) will

be calculated using 2-dimensional (2D) images projected from the VECTRA M3 3D image models.

Allergan developed the MMPS, a clinician's assessment tool for evaluation of masseter muscle prominence associated with MMH (see Attachment 12.1.1). The MMPS is to be used by trained clinicians to evaluate and grade the hypertrophy of the masseter muscle on the left and right sides of the face. The MMPS is a static measurement encompassing both visual and palpable examination of the masseter muscle both at rest and at jaw-clench state. The MMPS showed substantial inter- and intra-rater reliability in the nontreatment scale validation Study 191622-128, confirming its acceptability for use in the present study.

A reduction in masseter muscle volume may be perceived by subjects as a change in their lower facial shape at rest: specifically, narrowing of their lower facial width and change in their lower facial angle from a bulky trapezoidal or square toward a slimmer ovoid shape. Allergan developed the Lower Facial Shape Classification (LFSC; see Attachment 12.1.6), an assessment tool to be used by trained clinicians and subjects to assess a subject's lower facial shape. The LFSC to be piloted in the current study has not been tested for reliability.

### **1.3 Rationale for Safety Assessments, CT Imaging, and Dental Examination**

Safety assessments include attention to potential local and systemic effects of BOTOX treatment of MMH. Local adverse events (eg, pain, discomfort, and muscle ache at sites of injection) have been reported within the first 2 weeks posttreatment; therefore, a telephone follow-up visit is scheduled approximately 14 days following the day 1 and day 180 treatments. Because the masseter muscle is 1 of the primary muscles of mastication, masticatory difficulties (eg, transient masseter muscle fatigue after vigorous chewing and weakness on chewing) have been reported. Temporary speech disturbances have also been reported. In general, these adverse events have been reported as mild and resolved without treatment.

In the literature, nonclinical studies have reported on mandibular bone and dental changes following BOTOX treatment of the masseter muscle in animal models (Navarrete et al, 2013; Rafferty et al, 2012; Tsai and Huang, 2008; Tsai et al, 2010). However, differences in the structure and function of the mandible and dentition in animals contribute to difficulty interpreting the relevance to humans (refer to the Investigator's Brochure). One clinical study of botulinum toxin (Dysport<sup>®</sup>) injected in the masseter muscles of 10 women showed no changes in mandibular cortex thickness, mandibular bone thickness, and mandibular



volume on CT at 3 months (Chang et al, 2011). It is unknown whether BOTOX treatment of MMH may impact characteristics of the mandible and/or dentition in subjects. The medical literature does not indicate any clinically relevant change to these craniofacial structures adjacent to the masseter muscle. Therefore, Allergan has developed exploratory CT measures to determine whether any potential safety and/or efficacy signals may be detected that are not currently reported in the medical literature.

The present study includes CT and dental examinations developed by Allergan with input from consultants and specifically designed to identify potential effects of BOTOX treatment of MMH on the mandible and teeth. The CT scan captured by a CT technologist will be transferred to a central reader, who will review it to assess for changes in lower facial shape (masseter muscle volume, bigonial width, mandibular flare angle, and gonial angle) as well as relevant indicators of change in bone structure (mandibular condylar head shape, mandibular condylar cortical surface, mandibular condylar head, mandibular condylar position, glenoid fossa/eminence, and cortical thickness under the insertion point of the masseter muscle at the mandibular ramus). The dental examination will be conducted by a dentist to assess for any potential changes in dentition, occlusion, and overall oral health (Attachment 12.1.7). Both CT and dental measures will be taken at screening (considered as baseline), day 90, and at study exit (day 360 or study discontinuation).

In summary, the data obtained from this study will be used to develop a better understanding of the safety and efficacy of different dose regimens of BOTOX for the treatment of MMH.

## **2 Study Objectives and Clinical Hypotheses**

### **2.1 Study Objectives**

The study objective is to evaluate the safety and efficacy of a range of doses of BOTOX for the treatment of subjects with bilateral MMH.

### **2.2 Clinical Hypotheses**

BOTOX treatment of MMH has an acceptable safety profile and is more effective than placebo, as demonstrated by change in lower facial volume.

## **3 Study Design**

This is a multicenter, randomized, placebo-controlled, up to 2-treatment, dose-escalation study to assess a range of doses of BOTOX for the treatment of MMH. Up to 16 scheduled

visits are planned: screening (day -56 to day -1), day 1 (randomization/treatment), day 14 (telephone followup), monthly (days 30, 60, 90, 120, 150, 180 [possible retreatment]), and day 194 (telephone followup, only for subjects retreated at day 180), monthly (days 210, 240, 270, 300, and 330), and study exit (day 360).

After completion of all baseline study procedures and re-verification that the subjects meet all inclusion and exclusion criteria, subjects will be randomized and enrolled in cohorts of approximately 50 subjects each. Within each cohort, subjects will be randomized 4:1 to BOTOX (N = approximately 40) or placebo (N = approximately 10). Stratification will be by baseline (day 1) MMPS grade. Approximately 70% of the enrolled population in each cohort will be Asian, and subjects of Asian race will be further grouped by self-identified ethnicity (Chinese, Japanese, Korean, or other). Each cohort will be enrolled over approximately a 2-week period. When at least 50 subjects have been enrolled, randomization will be halted to allow observation of the cohort through the day 90 visit. The next cohort will be enrolled following a planned independent Data Review Committee (DRC) meeting (see Section 3.1) and Allergan's written notification to proceed.

On day 1, subjects will receive a single treatment of either BOTOX or placebo administered bilaterally to the masseter muscles as 3 injections/masseter in the area of maximal muscle bulge. The initial BOTOX total dose will be 24 U (12 U/masseter) and the maximum total dose will be 96 U (48 U/masseter). Table 2 shows the planned dose-escalation scheme.

**Table 2** Dose Escalation by Cohort

Cohort	Total Dose	Target Sample Size	Target Total Subjects/Cohort
1	24 U	40	50
	placebo	10	
2	48 U	40	50
	placebo	10	
3	72 U	40	50
	placebo	10	
4	96 U	40	50
	placebo	10	

Based on the DRC assessment and provisions for retreatment, subjects who meet the retreatment criteria (see Section 5.10) at the day 180 visit may receive a second study treatment. The second treatment is only allowed at the day 180 visit, and the same dose as day 1 will be administered.

### **3.1 Data Review Committee (DRC)**

For each cohort, the DRC, made up of identified Allergan nonstudy team members and non-Allergan nonstudy clinicians specializing in dentistry, radiology, and/or oral and maxillofacial surgery, will meet to review cumulative safety and efficacy data through day 90. The DRC will assess if the data support retreatment of the current cohort and/or study advancement to the next cohort.

All DRC members will be independent from the study team. Details of the DRC membership, data review procedures, timing of review, and communication between the DRC and other parties are detailed in the study DRC Charter.

## **4 Study Population and Entry Criteria**

### **4.1 Number of Subjects**

Based on the proposed doses, it is anticipated that approximately 200 subjects will be enrolled in the 4 planned cohorts. The actual number of subjects entering the study will be determined by the number of cohorts conducted and the number of subjects enrolled within each cohort.

Subjects will be enrolled at approximately 4 to 12 investigational sites.

### **4.2 Study Population Characteristics**

The study population will be adult subjects with marked (grade 4) or very marked (grade 5) MMH, as determined by the investigator using the MMPS, and who meet eligibility criteria for this protocol as specified in Sections 4.3 and 4.4. Approximately 70% of the enrolled population in each cohort will be Asian, and subjects of Asian race will be further grouped by self-identified ethnicity (Chinese, Japanese, Korean, or other).

### **4.3 Inclusion Criteria**

The following are requirements for entry into the study:

1. adult male or female, 18 (or older if legal age of adulthood is > 18 as per local regulations) to 50 years of age, inclusive, at the time of consent
2. Written informed consent has been obtained.

- 3. Written documentation has been obtained in accordance with the relevant country and local privacy requirements, where applicable.
- 4. Subject has marked (grade 4) or very marked (grade 5) bilateral MMH (identical grades for left and right masseter), as determined at screening and confirmed on day 1 by the investigator using the MMPS.

**4.4 Exclusion Criteria**

The following are criteria for exclusion from participating in the study:

[Redacted]

- 2. any medical condition that may put the subject at increased medical risk with exposure to BOTOX including diagnosed myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis, or any other condition that might interfere with neuromuscular function
- 3. prior botulinum toxin treatment of any serotype
  - a. to the masseter muscle or lower face at any time, or
  - b. to any other part of the body within the 6 months prior to study day 1

[Redacted]

[Redacted]

[Redacted]

- 7. history of or current TMJD

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**4.5 Permissible and Prohibited Medications/Treatments**

**4.5.1 Permissible Medications/Treatments**

Therapy considered necessary for the subject’s welfare may be given at the discretion of the investigator. The subject’s usual facial and orthodontic regimen (eg, topical treatments and night guard usage) should remain consistent throughout the study. If the permissibility of a specific medication/treatment is in question, please contact Allergan.

If concurrent medications may have an effect on study outcomes, these medications should be administered in dosages that remain constant throughout the course of the trial.

**4.5.1.1 Definition of Women of (Non-)Childbearing Potential and/or Acceptable Contraceptive Methods**

Women of non-childbearing potential are considered as those who are postmenopausal (at least 12 consecutive months without menstruation) or those who have had a hysterectomy or bilateral oophorectomy. For women of childbearing potential who may participate in the study, the following methods of contraception, if properly used, are generally considered reliable: oral contraceptives, patch contraceptives, injection contraceptives, male condom with intravaginal spermicide, diaphragm or cervical cap with spermicide, vaginal contraceptive ring, intrauterine device, surgical sterilization, vasectomized partner, or sexual abstinence.

Contraceptive methods using Chinese traditional medicine or other herbal remedies are not considered acceptable methods of contraception in this study.

The investigator and each subject will determine the appropriate method of contraception for the subject during the participation in the study. At each visit, the investigator should discuss compliance with contraceptive use with females of childbearing potential.

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If a female becomes pregnant during the study, the investigator will notify Allergan immediately after the pregnancy is confirmed. The investigator will (1) notify the subject's physician that the subject was being treated with an investigational drug, and (2) follow the progress of the pregnancy. The investigator must document the outcome of the pregnancy and provide a copy of the documentation to Allergan.

If a pregnancy is confirmed after the subject has received study treatment, the subject may choose to exit the study after appropriate safety followup or to remain in the study for all safety and efficacy follow-up assessments through the end-of-study visit. However, CT will not be performed and a second study treatment will not be administered for any pregnant subject or on any subject of childbearing potential who does not demonstrate a negative urine pregnancy test immediately before each CT or prior to retreatment.

#### **4.5.2 Prohibited Medications/Treatments**

The decision to administer a prohibited medication/treatment is done with the safety of the study participant as the primary consideration. When possible, Allergan should be notified before the prohibited medication/treatment is administered.

Prohibited treatments and procedures include, but are not limited to:

- facial surgery that could affect lower facial shape/appearance
- facial shaping procedures including use of fat-reducing injectables or skin-tightening laser treatments; implantation of a prosthetic device or autologous fat transplantation; use of temporary, semi-permanent, or permanent filler product in the face
- elective dental extractions, braces, implants, or reconstructive surgery
- treatment with botulinum toxin of any serotype for any indication

Co-administration of aminoglycosides or agents that could interfere with neuromuscular transmission (eg, curare-like agents) or muscle relaxants should be used with caution as the effects of the toxin, theoretically, could be potentiated.

## **5 Study Treatments**

### **5.1 Study Treatments and Formulations**

BOTOX (botulinum toxin type A) purified neurotoxin complex [REDACTED]  
[REDACTED]

[REDACTED]

## 5.2 Control Treatments

BOTOX placebo [REDACTED]

## 5.3 Methods for Masking/Blinding

All study treatments will be provided in identical vials and cartons to maintain blinding of the study.

At each study site, a designated staff member will serve as the drug reconstitutor (DR). This person will be responsible for study treatment preparation.

The DR will prepare the vial of study treatment as described in Sections 5.6 and 5.8. Once the study treatment vial is reconstituted, the DR will draw the required volume into an appropriately sized syringe and label the syringe with the subject's number. The DR will then provide the filled syringes to the investigator, who will inject the subject according to the study treatment administration instructions in Section 5.9.

For each cohort, the injection volume and treatment administration will be identical whether the subject is assigned to the BOTOX or the placebo group.

## 5.4 Treatment Allocation Ratio and Stratification

Subjects will be randomly allocated to BOTOX or placebo using the automated interactive voice response system (IVRS) or the interactive web response system (IWRS).

Subjects will be stratified by baseline (day 1) MMPS grade (4 or 5).



### **5.5 Method for Assignment to Treatment Groups/Randomization**

At the screening visit, after the subject signs informed consent, the site will call the IVRS or log on to the IWRS to obtain a subject number and coded initials that will serve as the subject identification number on all study documents.

The IVRS/IWRS will be used to manage the randomization and assignment of subjects into 1 of the 2 treatment groups for each cohort based on a central randomization schedule prepared by Allergan Biostatistics prior to day 1. The randomization will occur after all baseline procedures have been completed and the investigator has re-verified that the subject has met all inclusion and exclusion criteria. Randomization will be stratified by the subject's baseline (day 1) MMPS grade (4 or 5), as assessed by the investigator.

Study treatment will be labeled with kit numbers. The IVRS/IWRS will provide the site with the specific kit number for each randomized subject at the time of randomization (day 1). The IVRS/IWRS will also issue the specific kit number for each subject who qualifies for retreatment on day 180. Sites will dispense study treatment according to the IVRS/IWRS instructions. Sites will receive the IVRS/IWRS confirmation notifications for each transaction that will be maintained with the study source documents.

### **5.6 Treatment Regimen and Dosing**

A range of doses from 24 U (12 U/masseter) up to 96 U (48 U/masseter) will be studied in escalating dose cohorts. For each cohort, all subjects will receive 1 treatment of BOTOX or placebo on day 1. The same dose will be injected intramuscularly into the left and right masseter muscles. A total of 6 injections will be made (3 injections/masseter) into the area of maximal masseter muscle prominence at clench (mouth closed and teeth clenched).

[REDACTED]

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**Table 3 Injection Volume by Cohort**

<b>Cohort</b>	<b>Total Dose</b>	<b>Dose / Masseter</b>	<b>Total Injection Volume (mL)</b>	<b>Volume Per Injection (mL)</b>
1	24 U	12 U	0.6	0.1
	placebo	placebo		
2	48 U	24 U	1.2	0.2
	placebo	placebo		
3	72 U	36 U	1.8	0.3
	placebo	placebo		
4	96 U	48 U	2.4	0.4
	placebo	placebo		

Based on meeting retreatment criteria described in Section 5.10, subjects may receive a second treatment (same as that of day 1 [BOTOX or placebo]) administered in the same manner.

### **5.7 Storage of Study Treatment**

Study treatment must be stored in a secure area and administered only to subjects entered into the clinical study, at no cost to the subject, in accordance with the conditions specified in this protocol.

Lyophilized vials of study medication must be stored immediately upon receipt within the temperature range referenced in the Study Manual until used. Refer to the Study Manual for more detailed instructions.

### **5.8 Preparation of Study Medications/Treatments**

At each study site, a designated staff member will serve as the DR. This person will be responsible for study treatment preparation.

[REDACTED]

Detailed instructions on reconstitution and syringe preparation are provided in the Study Manual.

## 5.9 Treatment Administration

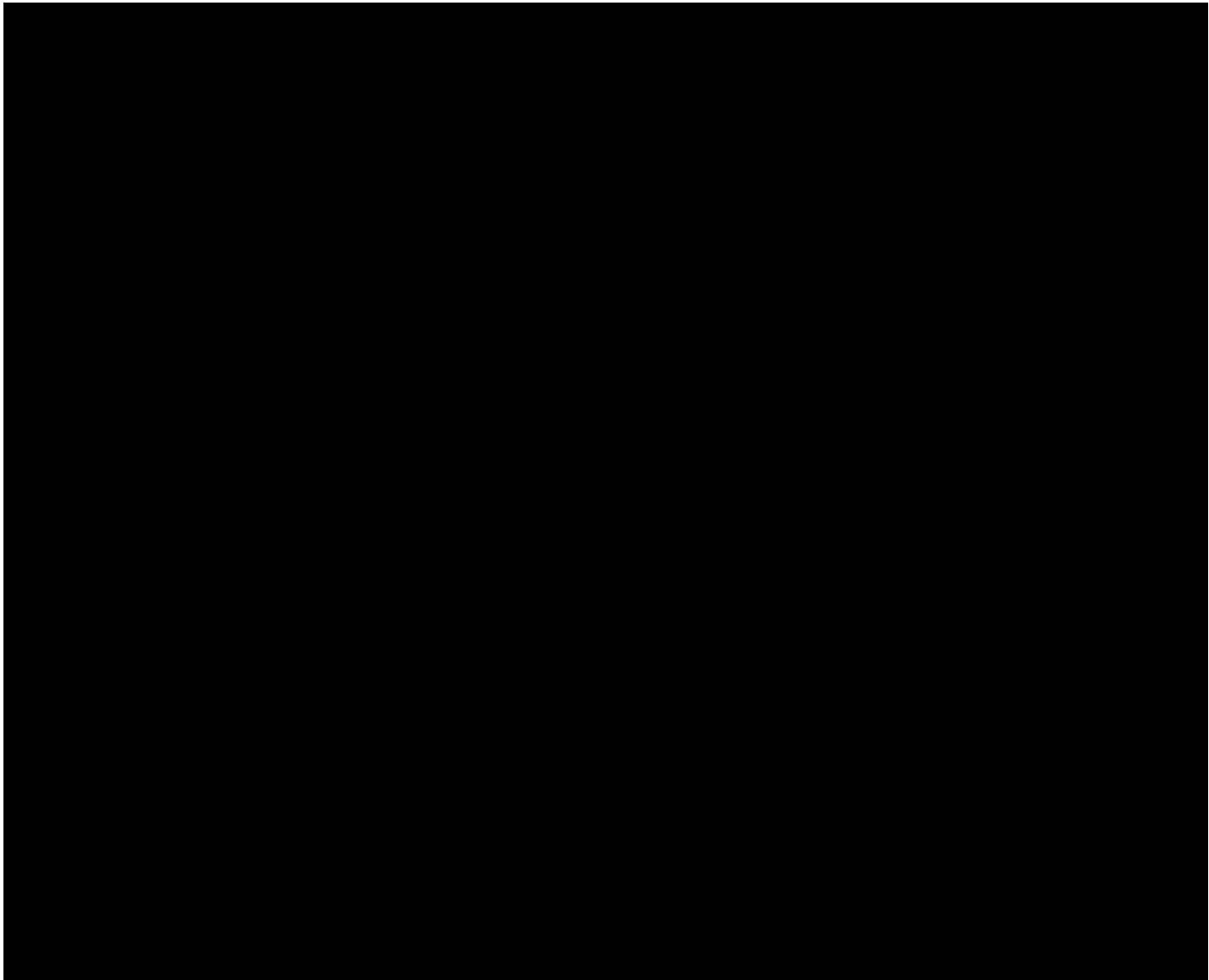
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## **5.10           Retreatment**

After treatment on day 1, subjects will receive a second treatment based on meeting the following criteria at the day 180 visit:

- Allergan decision and written notification to study sites allowing a second treatment
- Subject has presence of bilateral masseter muscle hypertrophy of at least marked (grade 4), as measured by the investigator using the MMPS.
- Females of childbearing potential must have a negative urine pregnancy test prior to treatment.

The second treatment is only allowed at the day 180 visit. Retreatment is prepared and administered in the same manner as described in Sections 5.1 to 5.9. Subjects will receive the same treatment at day 180 as they received at day 1.

## 6 Response Measures and Summary of Data Collection Methods

### 6.1 Efficacy Measures

#### 6.2 Primary Efficacy Measure

- lower facial volume (cm<sup>3</sup>) calculated from VECTRA M3 digital photography system 3D image models [REDACTED] (see Attachment 12.1.2)

#### 6.3 Secondary Efficacy Measure

- investigator’s assessment of MMH using the MMPS (5 grades: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked, 5 = very marked; see Attachment 12.1.1)

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### 6.5 Other Study Supplies

The following will be provided by Allergan:

- temperature recording device for monitoring refrigerator’s temperature

[REDACTED] will provide the photography system for the dental photographs to the dentists and the VECTRA M3 digital photography system and corresponding equipment.

The following will be provided by the site:

- cotton pads and makeup remover
- alcohol wipes
- medical gloves
- urine pregnancy test kits with minimum sensitivity of 25 IU/mL
- sterile surgical marker pens
- appropriately sized sterile needles and syringes for study treatment reconstitution and injection

- sterile saline (0.9% without preservative)
- refrigerator to store study treatment kits according to the Study Manual
- covered container for discarded medical waste materials (sharps box)
- internet connection (high-speed connection for electronic case report form completion)

## 6.6 Summary of Methods of Data Collection

This protocol will use electronic case report forms (eCRFs) using remote electronic data capture (EDC) through a qualified third party vendor. The data will be entered on the eCRFs on an ongoing basis throughout the study.

## 7 Statistical Procedures

A detailed statistical analysis plan will be generated and finalized prior to the first cohort day 90 database snapshot.

For each cohort, there will be a database snapshot with key data through the day 90 visit, for the purpose of the DRC. There will be a final database lock with all study data after all subjects have completed the study (final cohort day 360). Subjects' treatment assignment will remain blinded for all site personnel, study subjects, and Allergan personnel directly involved with ongoing operational activities of the clinical study, until completion of the final database lock.

### 7.1 Analysis Populations

All efficacy analyses will be performed on the modified intent-to-treat (mITT) population as treated, consisting of all randomized subjects who received study treatment and had at least 1 follow-up visit. A per-protocol (PP) analysis will also be performed on the primary endpoint. The PP population will be defined prior to database lock. Criteria used as a guideline in determining the exclusion of subjects or data from the PP analysis include violation of key inclusion and exclusion criteria, taking prohibited medication, and receiving the incorrect treatment.

The safety analyses will be based on the safety population, which will include all subjects who receive at least 1 injection of treatment. All safety analyses will be performed with subjects analyzed by their actual treatment or regimen received on day 1.

## 7.2 Collection and Derivation of Primary and Secondary Efficacy Assessments

Efficacy results for all study visits will be summarized based on time since injection. Visit windows for all timepoints will be described in the statistical analysis plan.

Pairwise comparisons will be done between each BOTOX group and the placebo group. A pairwise comparison will also be done between a BOTOX group and the next higher dose BOTOX group. For interim analyses, subjects in the placebo group(s) from previous cohort(s) will be pooled with the placebo group from the current cohort for analysis if the results for the placebo groups are combinable. For final analysis, all subjects who received placebo will be pooled together as a total placebo group if the results for the placebo groups are combinable. Details will be specified in the Analysis Plan.

The primary efficacy variable will be the lower facial volume at day 90. The change from baseline in lower facial volume will be analyzed by analysis of variance (ANOVA) with treatment and baseline (day 1) MMPS grade as factors to assess the response between groups.

For analysis of the mITT population, the last observation carried forward (LOCF) method will be used to impute missing values. For analysis of the PP population, observed data without imputation will be used.

### 7.2.1 Primary Efficacy Variable

The primary efficacy variable, change from baseline in lower facial volume (cm<sup>3</sup>), is calculated from VECTRA M3 digital photography system 3D image models [REDACTED]

### 7.2.2 Secondary Efficacy Variable

The secondary efficacy variable is the investigator's assessment of MMH using the MMPS (1 = minimal, 2 = mild, 3 = moderate, 4 = marked, 5 = very marked).



### 7.3 Hypothesis and Methods of Analysis

#### 7.3.1 Primary Efficacy Analyses

Descriptive statistics for change from baseline in lower facial volume for each study visit (sample size, mean, standard deviation, median, minimum, and maximum) will be provided by treatment regimen for all scheduled visits.

The primary efficacy analysis will be based on the mITT population. Day 90 is the primary timepoint.

The following set of hypotheses will be used to compare the BOTOX groups with placebo:

- Null hypothesis: BOTOX and placebo are equally effective in changing lower facial volume at day 90.
- Alternative hypothesis: BOTOX and placebo are not equally effective in changing lower facial volume at day 90.

The change from baseline in lower facial volume at each visit will be analyzed using an ANOVA model with treatment and baseline (day 1) MMPS grade as factors. In addition, 2-sided 95% confidence intervals for the treatment differences will be provided.

Analysis will be performed for the PP population and also based on observed data (ie, strictly data that falls within the visit windows) for the mITT population.

#### 7.3.2 Secondary Efficacy Analyses

The proportion of responders will be analyzed with a responder defined as subjects who achieve an MMPS grade of  $\leq 3$ . The proportion of responders will be analyzed using Cochran-Mantel-Haenszel (CMH) tests stratified by baseline (day 1) MMPS grade.

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#### 7.4 Subgroup Analyses

Subgroup analyses of the primary efficacy variable will be provided by subgroups of race (Asian and non-Asian), gender, age (18 to 35 years and 36 to 50 years), and baseline (day 1) MMPS grade (4 and 5).

#### 7.5 Sample Size Calculation

The sample size used in this study is determined empirically.

For each cohort, 40 subjects will be randomized to BOTOX, and 10 subjects will be randomized to placebo. Assuming the VECTRA lower facial volume is a normal distribution and the effect size is 1, a 1-sided test with 0.10 significance level will have 93% power to detect a statistically significant change in the BOTOX group compared with the placebo group. The commercial software nQuery version 6.01 procedure MTT0U-1 was used for the power calculation.

#### 7.6 Interim Analyses

An interim database lock may be performed to support a regulatory filing, if needed. The treatment assignments will be unblinded to selected individuals for interim analyses. Unblinded data will be disseminated only to Allergan personnel who are directly involved in submission-related activities. These data will remain blinded for all Allergan personnel who are directly involved with the ongoing operational activities of the clinical study, all subjects,

and all site personnel until the final database lock. Further details regarding an interim analysis will be provided in the analysis plan.

## **7.7 Final Analyses**

A final database lock will be performed following the last subject's completion of the day 360 (study exit or early discontinuation) visit. All study data, from every subject and every visit, will be included in this final analysis.

## **8 Study Visit Schedule and Procedures**

Please see Table 1 for a schematic of the schedule of visits and procedures.

### **8.1 Subject Entry Procedures**

#### **8.1.1 Overview of Entry Procedures**

Prospective subjects as defined by the criteria in Sections 4.3 and 4.4 (inclusion and exclusion criteria, respectively) will be considered for entry into this study.

#### **8.1.2 Informed Consent and Subject Privacy**

The study will be discussed with the subject, and a subject wishing to participate must give informed consent prior to any study-related procedures or change in treatment. The subject must also give authorization and other written documentation in accordance with the relevant country and local privacy requirements (where applicable) prior to any study-related procedures or change in treatment.

Each subject that provides informed consent will be assigned a subject number that will be used on subject documentation throughout the study.

### **8.2 Washout Intervals/Run-in**

Subjects taking prohibited medications, agents that could interfere with neuromuscular transmission, or muscle relaxants must undergo a washout of the medication(s) for at least 28 days prior to entering the study. If washout is required for the purposes of this study then the subject must sign the informed consent before the washout is commenced.

For subjects who have undergone facial shaping procedures (eg, use of fat-reducing injectables or skin-tightening laser treatments; implantation of a prosthetic device or autologous fat transplantation; use of temporary, semi-permanent, or permanent filler product in the face) prior to screening, the procedure must have occurred at least 6 months prior to entering the study.

### **8.3 Procedures for Final Study Entry**

A subject is considered to have enrolled in the study upon randomization to treatment on day 1 after completion of all pre-treatment and randomization procedures and after the investigator re-verifies the subject has met all the inclusion and exclusion criteria for study



entry. Some inclusion and exclusion criteria will require verification by the dentist, radiologist, or CT technologist. Prior to day 1, [REDACTED], must approve each subject's VECTRA photos; 1 retake will be allowed before day 1 if the photos are not acceptable.

See Section 5.5 for the method for assignment to treatment groups/randomization.

## **8.4 Visits and Associated Procedures**

### ***Training***

The investigator performing MMPS and LFSC assessments will be trained on the appropriate use of the MMPS and LFSC prior to screening study subjects. Documentation of investigator training will be maintained in the study center regulatory binder with a copy sent to Allergan.

On day 1, enrolled subjects will view a training presentation on how to use the LFSC to assess their own lower facial shape. Each subject will choose the lower facial shape grade that best matches the contour of the lower portion of his/her face (1, 2, 3, or 4).

### ***Screening, Treatment, and Follow-up Visits***

For a summary of the procedures to be performed at scheduled visits, see Table 1 (Schedule of Visits and Procedures).

Evaluations should be performed by the same evaluator throughout the study whenever possible. If it is not possible to use the same evaluator to follow the subject, then evaluations should overlap (examine the subject together and discuss findings) for at least 1 visit.

## **8.5 Instructions for the Subjects**

Once their VECTRA photos have been approved by [REDACTED], subjects will be instructed to maintain their baseline weight (remain within 10% of baseline) and, for males, maintain a clean-shaven lower face for study visits.

## **8.6 Unscheduled Visits**

Unscheduled visits can be performed if safety concerns arise and at the discretion of the investigator. If a subject is seen for an unscheduled visit, an assessment and record of

adverse events should be completed. Additional evaluations should be performed, as necessary, and the appropriate case report forms should be completed.

## **8.7 Compliance with Protocol**

Enrolled subjects should be able to attend all clinic visits for treatment administration and followup.

## **8.8 Early Discontinuation of Subjects**

Subjects may voluntarily withdraw from the study at any time. Notification of early subject discontinuation from the study and the reason for discontinuation will be made to Allergan and will be clearly documented on the appropriate case report form. All day 360/study exit procedures should be performed (Table 1), including an exit CT scan, unless the investigator proposes a medical reason to waive the exit CT scan.

## **8.9 Withdrawal Criteria**

Subjects should be discontinued from the study if any of the following criteria are met.

- Subject develops (or has an exacerbation of) any medical condition that, in the opinion of the investigator, would put the subject at an unacceptable medical risk or compromises the subject's ability to participate in the study.
- Subject is unable/unwilling to comply with study procedures.

Where possible, the decision to withdraw a subject from the study should be discussed with Allergan.

## **8.10 Study Termination**

The study may be stopped at his/her study site at any time by the site investigator. Allergan may stop the study (and/or the study site) for any reason with appropriate notification.

## **9 Adverse Events**

Adverse events occurring during the study will be recorded on an adverse event case report form. If adverse events occur, the first concern will be the safety of the study participants.

## **9.1 Definitions**

### **9.1.1 Adverse Event**

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. In addition, during the screening period, adverse events will be assessed regardless of the administration of a pharmaceutical product.

Note: Adverse events must be collected once informed consent has been obtained, regardless of whether or not the subject has been administered study drug.

Progression of treatment indication including new or worsening of anticipated clinical signs or symptoms, which are collected as clinical efficacy variables and assessed as unequivocally associated with the disease progression and/or lack of efficacy, should NOT be reported as adverse events unless the disease progression is greater than anticipated in the natural course of the disease.

Adverse events will be assessed, documented, and recorded in the case report forms throughout the study (ie, after informed consent has been obtained). At each visit, the investigator will begin by querying for adverse events by asking each subject a general, non-directed question such as “How have you been feeling since the last visit?” Directed questioning and examination will then be done as appropriate. All reported adverse events will be documented on the appropriate case report form.

### **9.1.2 Serious Adverse Event**

A serious adverse event is any adverse event occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (See Section 9.3 for procedures for reporting a serious adverse event.)

Allergan considers all cancer adverse events as serious adverse events. In addition, Allergan considers any abortion (spontaneous or nonspontaneous) as a serious adverse event.

Pre-planned surgeries or procedures for pre-existing, known medical conditions for which a subject requires hospitalization is not reportable as a serious adverse event.

Any pre-planned surgery or procedure should be clearly documented in the site source documents by the medically qualified investigator at the time of the subject's entry into the study. If it has not been documented at the time of the subject's entry into the study, then it should be documented as a serious adverse event and reported to Allergan.

### **9.1.3 Severity**

A clinical determination will be made of the intensity of an adverse event. The severity assessment for a clinical adverse event must be completed using the following definitions as guidelines:

Mild	Awareness of sign or symptom, but easily tolerated.
Moderate	Discomfort enough to cause interference with usual activity.
Severe	Incapacitating with inability to work or do usual activity.
Not applicable	In some cases, an adverse event may be an 'all or nothing' finding that cannot be graded.

### **9.1.4 Relationship to Study Drug or Study Procedure**

A determination will be made of the relationship (if any) between an adverse event and the study drug or study procedure, as applicable. A causal relationship is present if a determination is made that there is a reasonable possibility that the adverse event may have been caused by the drug or study procedure.

## **9.2 Procedures for Reporting Adverse Events**

Any adverse event must be recorded on the appropriate case report form.

All adverse events that are drug-related and unexpected (not listed as treatment-related in the current Investigator's Brochure) must be reported to the governing Institutional Review Board/Independent Ethics Committee (IRB/IEC) as required by the IRB/IEC, local

regulations, and the governing health authorities. Any adverse event that is marked “ongoing” at the exit visit must be followed-up as appropriate.

### **9.3 Procedures for Reporting a Serious Adverse Event**

Any serious adverse event occurring during the study period (beginning with informed consent) and for at least 28 days after the last dose of study drug must be immediately reported but no later than 24 hours after learning of a serious adverse event. Serious adverse events must be reported to Allergan as listed on the Allergan Study Contacts Sheet and recorded on the serious adverse event form. All subjects with a serious adverse event must be followed up and the outcomes reported. The investigator must supply Allergan and the IRB/IEC with any additional requested information (eg, autopsy reports and discharge summaries).

In the event of a serious adverse event, the investigator must:

1. Notify Allergan immediately by fax or email using the serious adverse event form (contact details can be found on page 1 of the serious adverse event form); phone numbers and relevant Allergan personnel contacts are also on the Study Contacts Page.
2. Obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and followup of the subject.
3. Provide Allergan with a complete, written description of the adverse event(s) on the serious adverse event form describing the event chronologically, including any treatment given (eg, medications administered, procedures performed) for the adverse event(s). Summarize relevant clinical information about the event: signs, symptoms, diagnosis, clinical course and relevant clinical laboratory tests, etc. Include any additional or alternative explanation(s) for the causality which includes a statement as to whether the event was or was not related to the use of the investigational drug.
4. Promptly inform the governing IRB/IEC of the serious adverse event as required by the IRB/IEC, local regulations, and the governing health authorities.

## **9.4 Procedures for Unmasking of Study Medication**

When necessary for the safety and proper treatment of the subject, the investigator can unmask the subject's treatment assignment to determine which treatment has been assigned and institute appropriate follow-up care. When possible, the sponsor (Allergan Medical Safety Physician) should be notified prior to unmasking study medication. The investigator should inform the sponsor (Allergan Medical Safety Physician) of the unmasking if there is no notification prior to the unmasking.

The treatment assignment for the subject can be determined by designated site personnel calling into the IVRS or IWRS system via password protected access. The reason for breaking the code must be recorded in the subject's source documents.

## **10 Administrative Items**

This protocol is to be conducted in accordance with the applicable Good Clinical Practice (GCP) regulations and guidelines, eg, the International Conference on Harmonisation (ICH) Guideline on GCP.

### **10.1 Protection of Human Subjects**

#### **10.1.1 Compliance with Informed Consent Regulations (US 21 CFR Part 50) and Relevant Country Regulations**

Written informed consent is to be obtained from each subject prior to any study-related activities or procedures in the study, and/or from the subject's legally authorized representative. If the subject is under the legal age of consent, the consent form must be signed by the legally authorized representative in accordance with the relevant country and local regulatory requirements.

#### **10.1.2 Compliance With IRB or IEC Regulations**

This study is to be conducted in accordance with IRB regulations (US 21 CFR Part 56.103) or applicable IEC regulations. The investigator must obtain approval from a properly constituted IRB/IEC prior to initiating the study and re-approval or review at least annually. Allergan is to be notified immediately if the responsible IRB/IEC has been disqualified or if proceedings leading to disqualification have begun. Copies of all IRB/IEC correspondence with the investigator should be provided to Allergan.

### **10.1.3 Compliance With Good Clinical Practice**

This protocol is to be conducted in accordance with the applicable GCP regulations and guidelines.

### **10.1.4 Compliance With Electronic Records; Electronic Signatures Regulations (US 21 CFR Part 11)**

This study is to be conducted in compliance with the regulations on electronic records and electronic signature.

## **10.2 Changes to the Protocol**

The investigator must not implement any deviation from or changes of the protocol without approval by Allergan and prior review and documented approval/favorable opinion from the IRB/IEC of a protocol amendment, except where necessary to eliminate immediate hazards to study subjects, or when the changes involve only logistical or administrative aspects of the study (eg, change in monitors or change of telephone numbers).

## **10.3 Subject Confidentiality**

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the study drug may ultimately be marketed, but the subject's name will not be disclosed in these documents. The subject's name may be disclosed to the Sponsor of the study, Allergan, or the governing health authorities or the US Food and Drug Administration (FDA) if they inspect the study records. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

### **10.3.1 Subject Privacy**

Personal information protection authorization, privacy documentation, and other documentation in accordance with the relevant country and local privacy requirements (where applicable) are to be obtained from each subject prior to enrollment into the study, and/or from the subject's legally authorized representative in accordance with the applicable privacy requirements (eg, the Personal Information Protection and Electronic Documents Act [PIPEDA]).

In accordance with local personal information protection authorization or privacy documentation requirements, additional purposes of this study include publishing anonymous subject data from the study.

## **10.4 Documentation**

### **10.4.1 Source Documents**

Source documents may include a subject's medical records, hospital charts, clinic charts, the investigator's subject study files, as well as the results of diagnostic tests such as X-rays, laboratory tests, and electrocardiograms. The investigator's copy of the eCRFs serves as part of the investigator's record of a subject's study-related data.

The following information should be entered into the subject's medical record:

- subject's name
- subject's initials (coded)
- subject's age
- subject number
- subject's contact information
- the date that the subject entered the study, subject number, and subject randomization (or medication kit) number
- the study title and/or the protocol number of the study and the name of Allergan
- a statement that informed consent, local personal information protection authorization or privacy documentation, or other country and local subject privacy required documentation for this study has been obtained (including the dates)
- dates of all subject visits
- all concurrent medications (List all prescription and non-prescription medications being taken at the time of enrollment. At each subsequent visit, changes to the list of medications should be recorded.)
- occurrence and status of any adverse events



- the date the subject exited the study, and a notation as to whether the subject completed the study or reason for discontinuation
- results of urine pregnancy tests
- key study variables

#### **10.4.2 Case Report Form Completion**

The investigator is responsible for ensuring that data are properly recorded on each subject's eCRFs and related documents. An investigator who has signed the protocol signature page should personally sign the eCRFs (as indicated in the eCRF) to ensure that the observations and findings are recorded on the eCRFs correctly and completely. The eCRFs are to be completed in a timely manner at the completion of the study, or as otherwise specified by Allergan.

#### **10.4.3 Study Summary**

An investigator's summary will be provided to Allergan within a short time after the completion of the study, or as designated by Allergan. A summary is also to be provided to the responsible IRB/IEC.

#### **10.4.4 Retention of Documentation**

All study related correspondence, subject records, consent forms, subject privacy documentation, records of the distribution and use of all investigational products, and copies of eCRFs should be maintained on file.

For countries falling within the scope of the ICH guidelines, Allergan-specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by the applicable regulatory requirement(s) or if needed by Allergan.

In addition, for countries not falling within the scope of the ICH guidelines, local regulatory requirements should be followed regarding the retention of clinical study documentation.

Allergan requires that it be notified in writing if the investigator wishes to relinquish ownership of the data so that mutually agreed-upon arrangements can be made for transfer of ownership to a suitably qualified, responsible person.

## **10.5 Labeling, Packaging, and Return or Disposal of Study Medications/Treatments**

### **10.5.1 Labeling/Packaging**

The investigational materials will be packaged and labeled in identically appearing vials. The study treatment will be identified as an investigational compound. The study number and kit number will be identified on the unit label.

### **10.5.2 Clinical Supply Inventory**

The investigator must keep an accurate accounting of the number of investigational units received from Allergan, dispensed to the subjects, the number of units returned to the investigator by the subject, and the number of units returned to Allergan during and at the completion of the study. A detailed inventory must be completed for the study medication. The study medication must be dispensed only by an appropriately qualified person to subjects in the study. The medication is to be used in accordance with the protocol by subjects who are under the direct supervision of an investigator. A unit is defined as a study medication vial.

### **10.5.3 Return or Disposal of Study Medications/Treatments and/or Supplies**

All clinical study medications/treatments and/or supplies will be returned to Allergan or Allergan designee for destruction.

## **10.6 Monitoring by the Sponsor**

A representative of Allergan will monitor the study on a periodic basis. The determination of the extent and nature of monitoring will be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the study.

Authorized representatives of Allergan or regulatory authority representatives will conduct on-site visits to review, audit and copy study-related documents. These representatives will

meet with the investigators and appropriate staff at mutually convenient times to discuss study-related data and questions.

## 10.7 Publications

Allergan, as the sponsor, has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and Allergan personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with Allergan.

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## **12 Attachments**

### **12.1 Examination Procedures, Tests, Equipment, and Techniques**

#### **12.1.1 Masseter Muscle Prominence Scale (MMPS)**

##### *Instructions*

Using visual inspection and palpation, you will rate the masseter muscle prominence during rest and function, by separately evaluating the right and left side of the subject's face.

- Sit directly in front of the subject and inspect the contour of the face in the clenched and unclenched state.
- Define the posterior and anterior border of each masseter, as well as the superior and inferior margins.
- While the subject clenches and relaxes, use your fingers to feel the dimensions and surface texture of each masseter.
- Have the subject repeat the sequence of clenching and relaxing at least twice. As best as possible, distinguish masseter muscle from bone and other non-muscular soft tissue (eg, fat).
- Rate each masseter separately, and record your ratings. In the presence of discordant assessment between rest and clenched states, the subject's masseter prominence assessment noted in the clenched state should factor most significantly in determining the overall rating for each side of the face.

Rating	Clinical Evaluation
Minimal (1)	<p>AT REST: With mouth closed and no clenching, surface overlying masseter is concave. There is no contour contributed by masseter muscle. Masseter is not palpable.</p> <p>AT CLENCH: No visible difference in contour compared with when mouth is closed, no clenching. Masseter is minimally palpable and difficult to define.</p>
Mild (2)	<p>AT REST: With mouth closed and no clenching, surface overlying masseter is flat or slightly concave. The contour contributed by masseter muscle may or may not be visible. Masseter is minimally palpable.</p> <p>AT CLENCH: With clenching, minimal difference in lower facial contour compared with when mouth is closed, no clenching. Portion of masseter bulk may be visible and palpable.</p>
Moderate (3)	<p>AT REST: With mouth closed and no clenching, surface overlying masseter is flat or convex. The contour contributed by masseter muscle may or may not be visible. Masseter is palpable.</p> <p>AT CLENCH: With clenching, the lower face is more convex in contour compared with when mouth is closed, no clenching. Masseter bulk is easily identifiable, palpable, and firm.</p>
Marked (4)	<p>AT REST: With mouth closed and no clenching, surface overlying masseter is convex. The masseter muscle, in conjunction with the chin and jawline, creates a square lower facial contour. Masseter is palpable and firm.</p> <p>AT CLENCH: With clenching, the lower face is wider and squarer compared with when mouth is closed, no clenching. Masseter is palpable and firm or hard.</p>
Very Marked (5)	<p>AT REST: With mouth closed and no clenching, surface overlying masseter is convex. The masseter muscle, in conjunction with the chin and jawline, creates a trapezoidal lower facial contour. Masseter is palpable and firm.</p> <p>AT CLENCH: With clenching, the lower face is more trapezoidal compared with when mouth is closed, no clenching. Masseter is palpable and hard.</p>

### 12.1.2 Lower Facial Volume Measurement

The lower facial volume measurement (cm<sup>3</sup>) will be performed by [REDACTED]

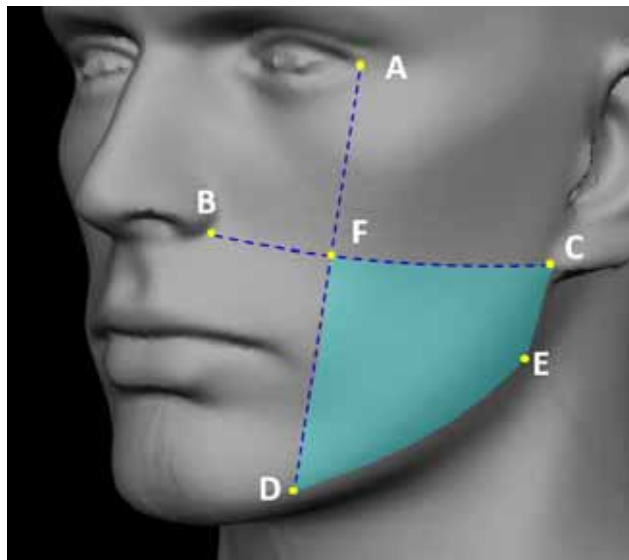
To measure the difference in volume between two 3D surface models from different timepoints (ie, baseline and posttreatment), the models are first registered in 3D space such that relative surfaces unrelated to the treatment regions are correspondingly aligned. The analysis region is then defined using a series of anatomical landmarks placed on the baseline surface that are then projected mathematically to the posttreatment surface and verified by the analysis technician.

In Figure 2, the green-shaded region represents the defined measurement selection area created by the perimeter formed using landmarks (C-F-D-E). Anatomical landmarks are located at: Lateral canthus (A), Alar recess (B), Earlobe attachment point (C), Prejowl sulcus (D), Mandible point (E). A single interpolated landmark (F) is also used at the intersection point of surface lines between points (A)-(D) and (B)-(C).

The difference in volume is then measured between the select region of the baseline surface and the select region of the posttreatment surface. The lower facial volume is the summed volumes for both the left side and the right side of the face, which will be compared between each paired baseline/posttreatment timepoint for the study.

In response to treatment, the region is expected to decrease in volume.

**Figure 2** Lower Facial Volume Measurement





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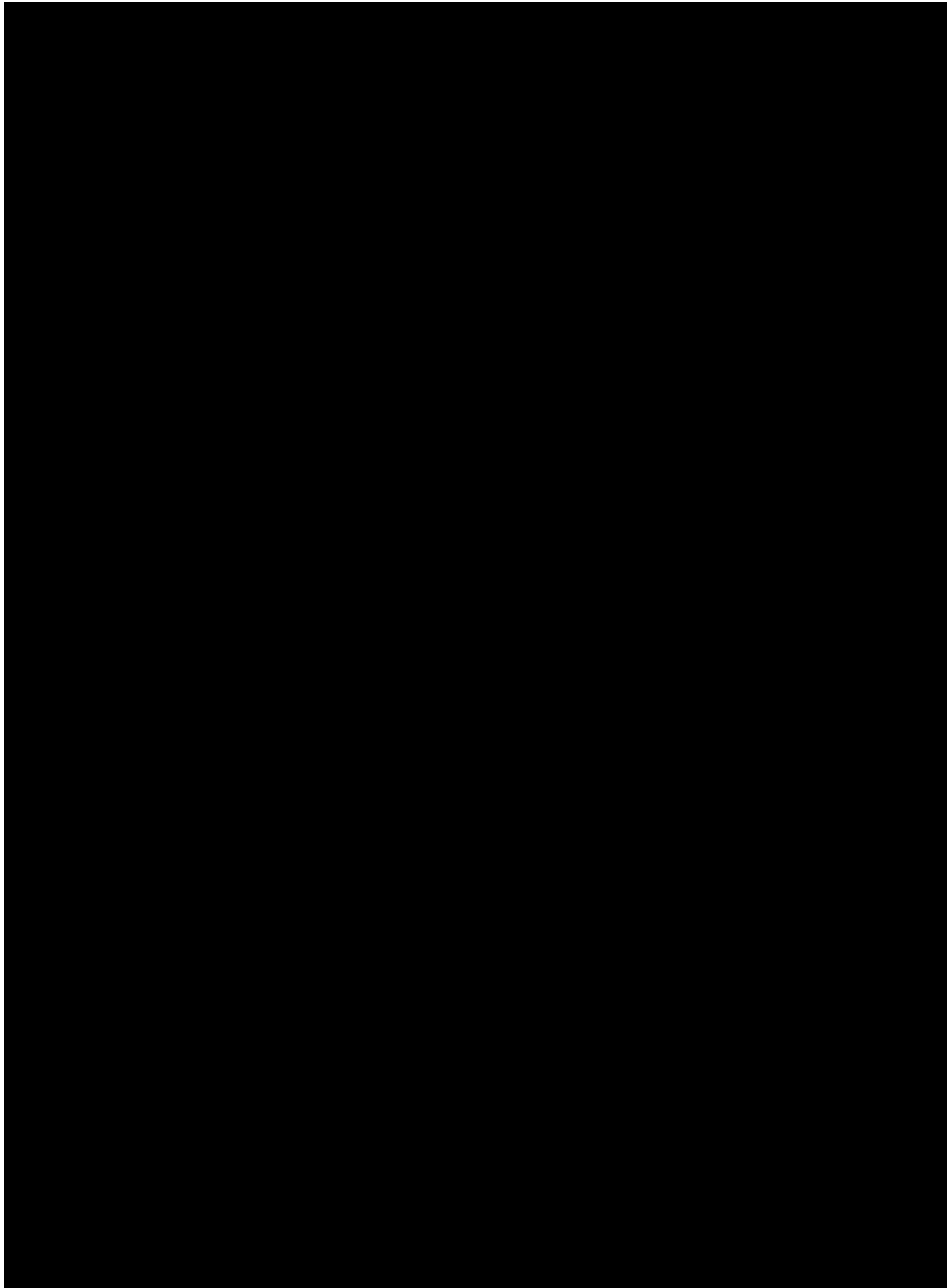
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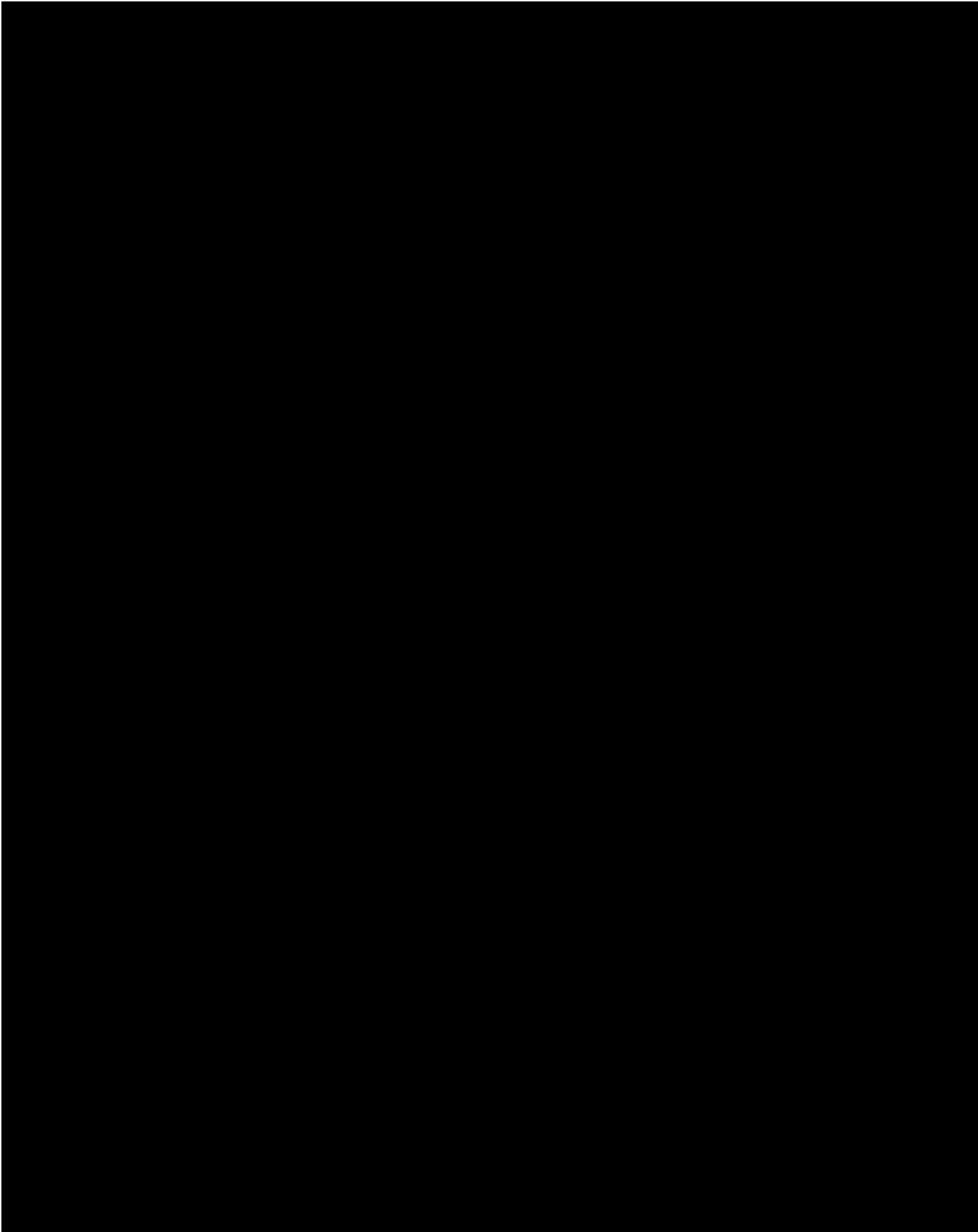
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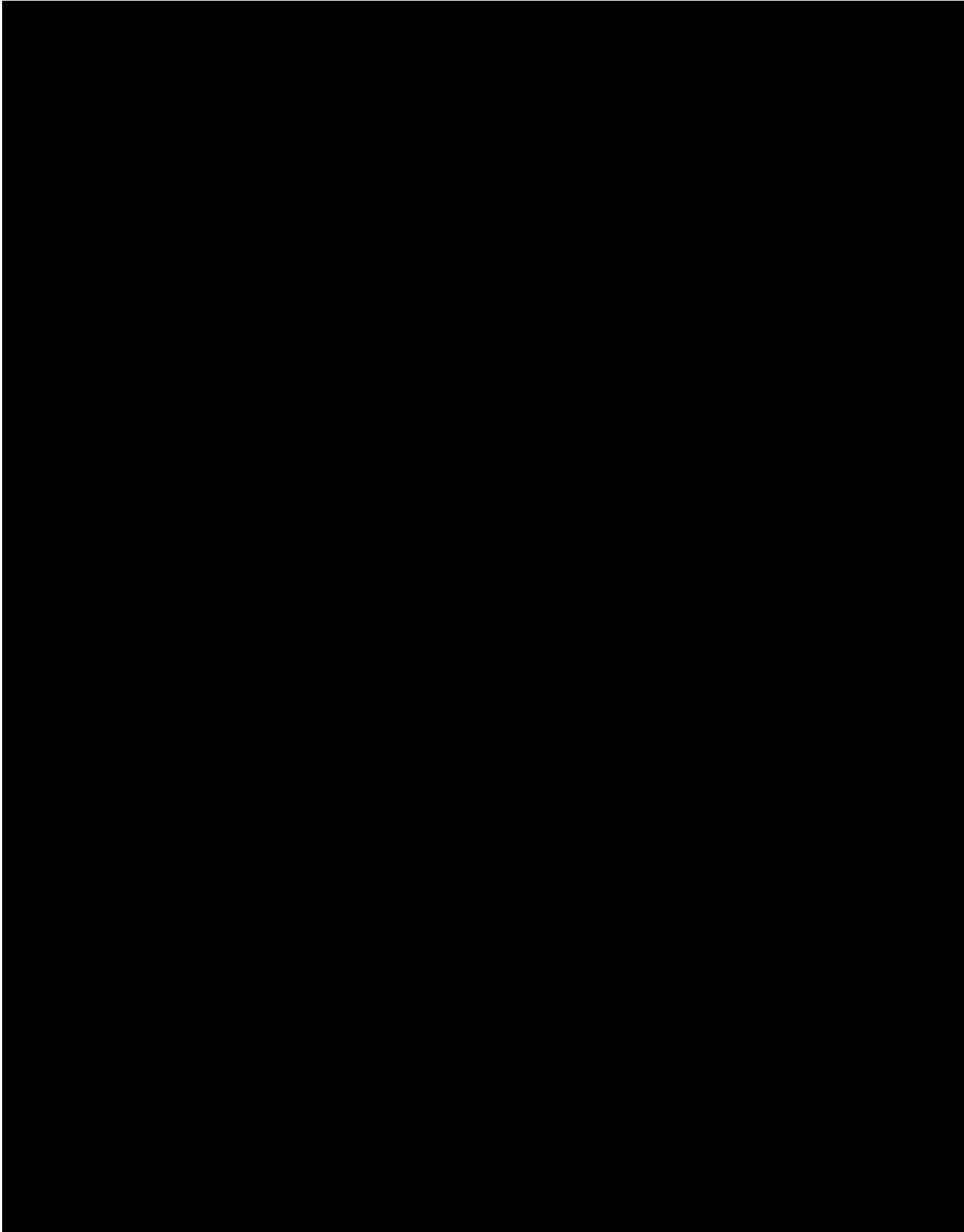
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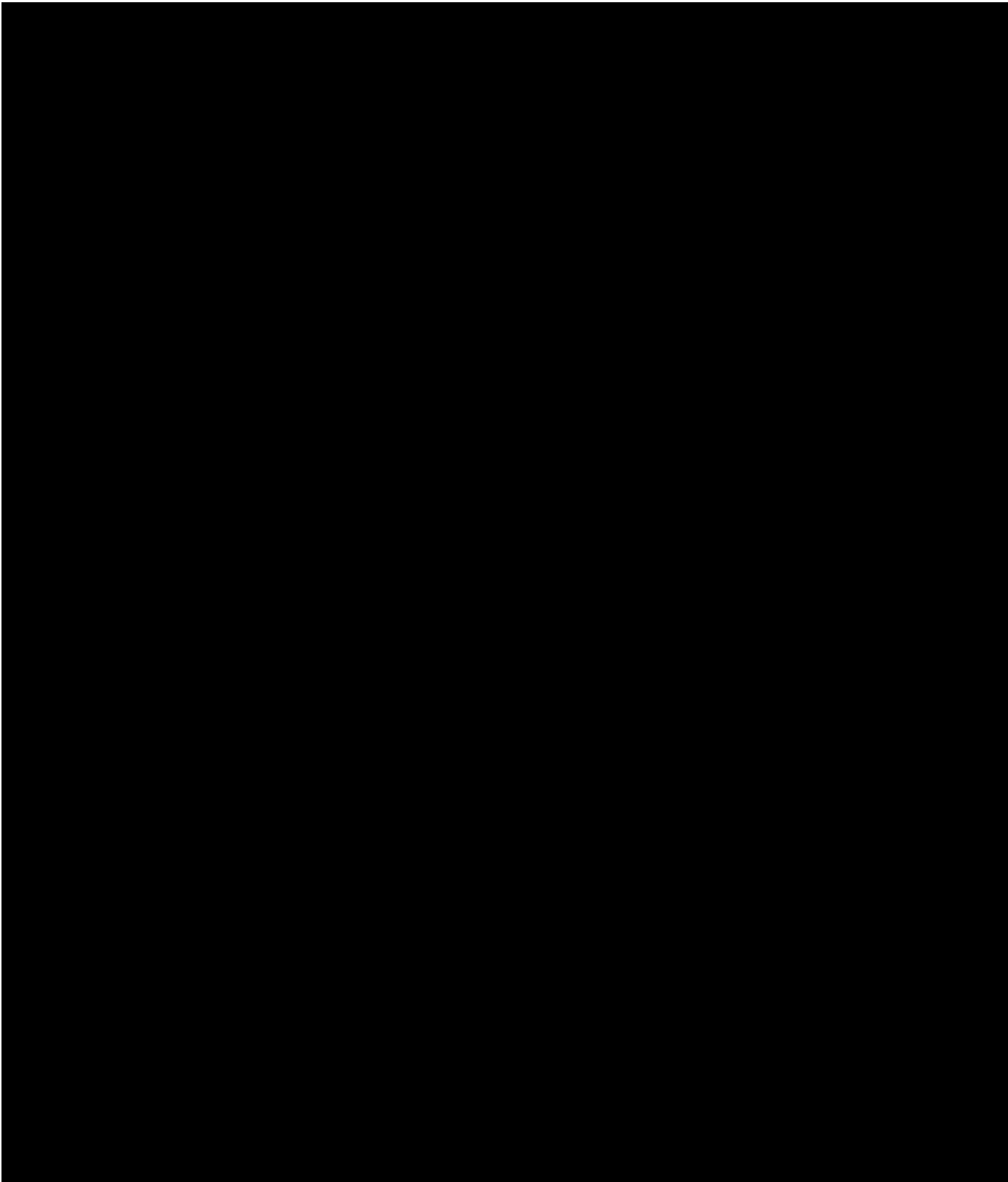
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[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
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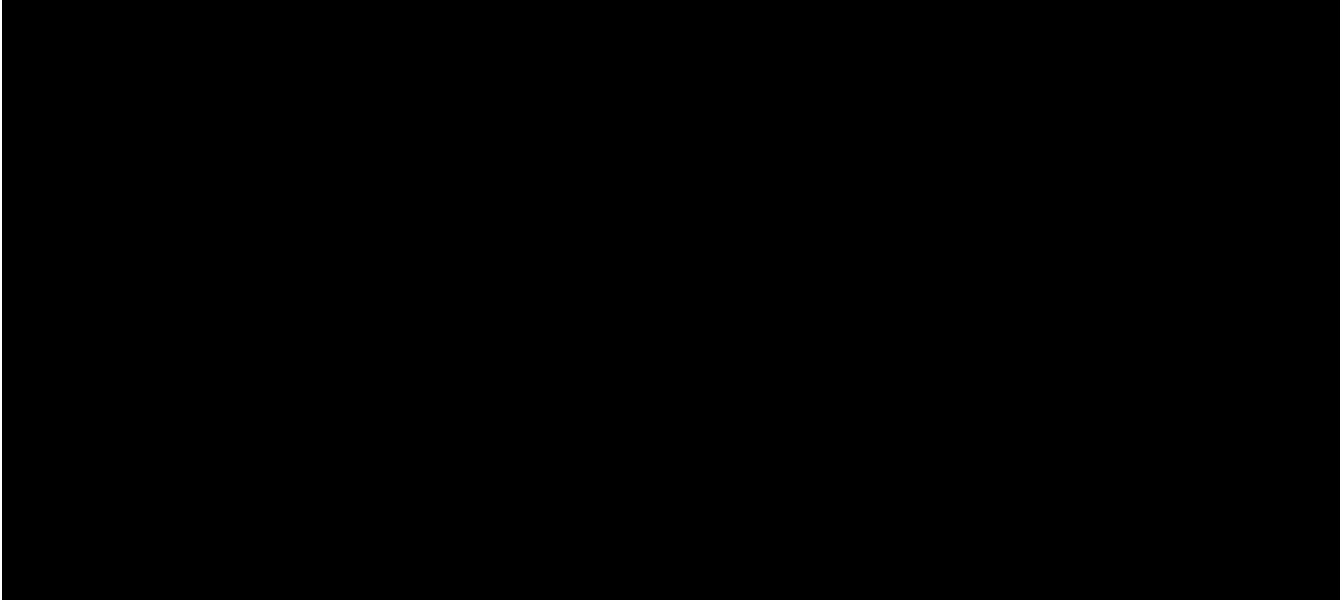


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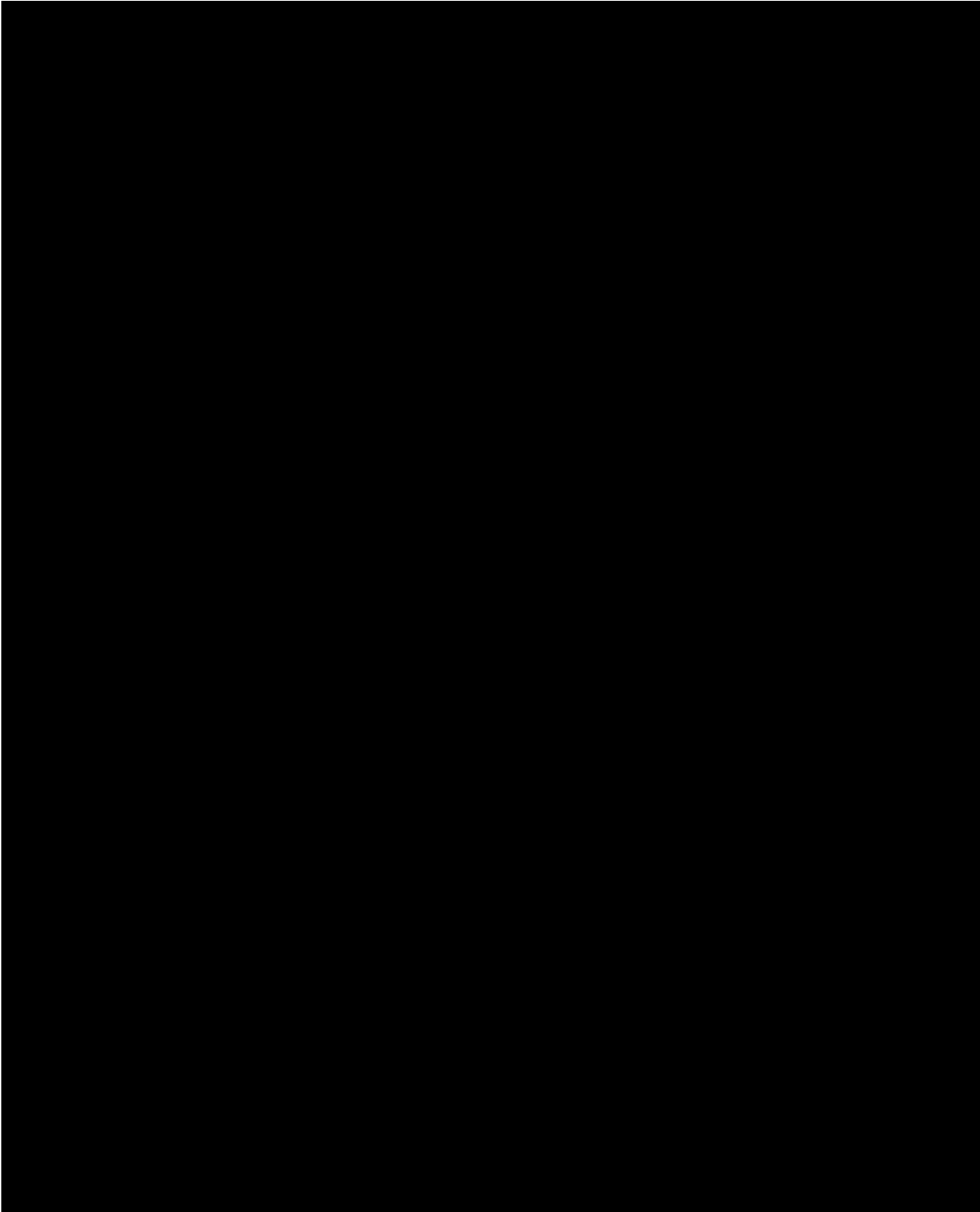


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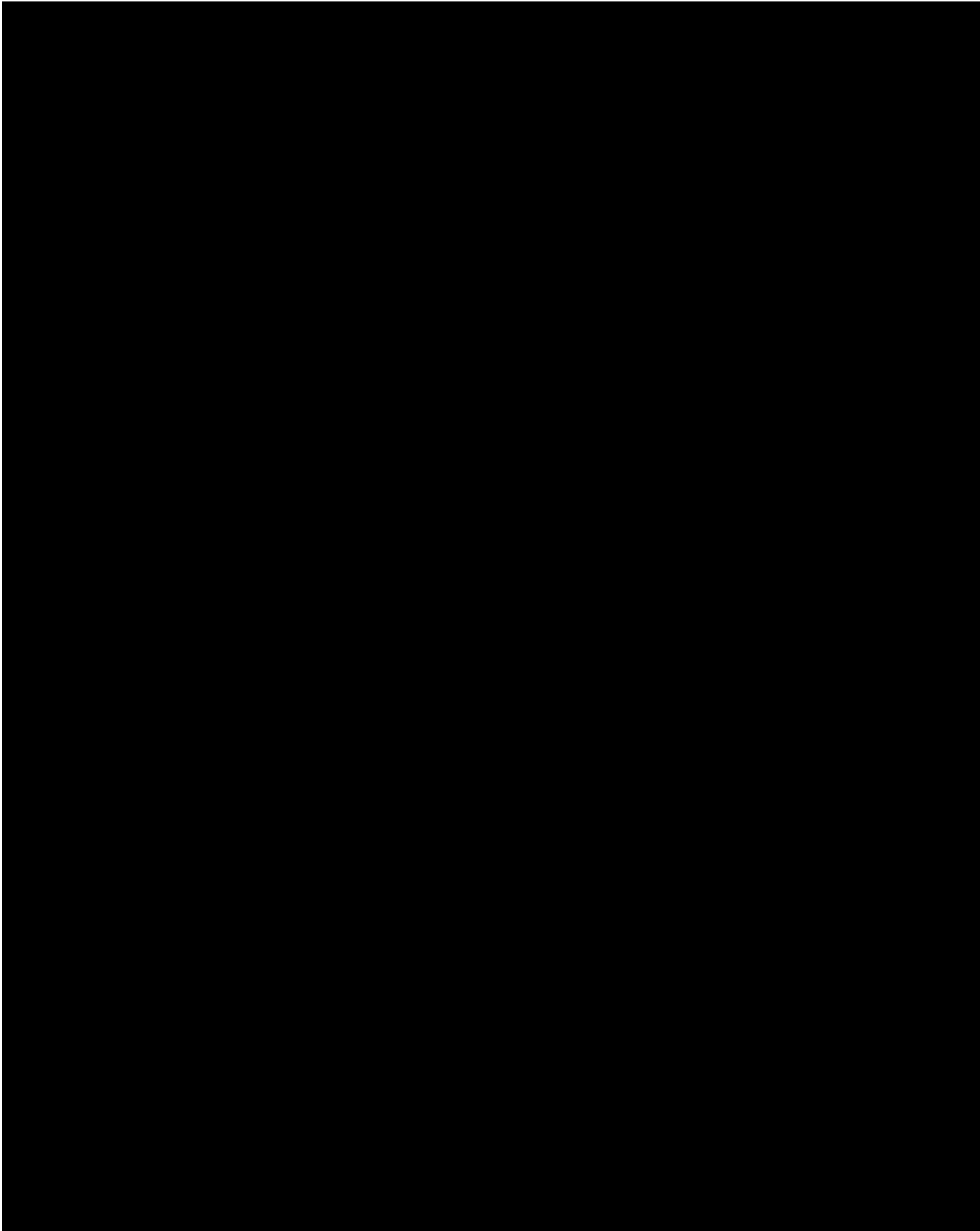




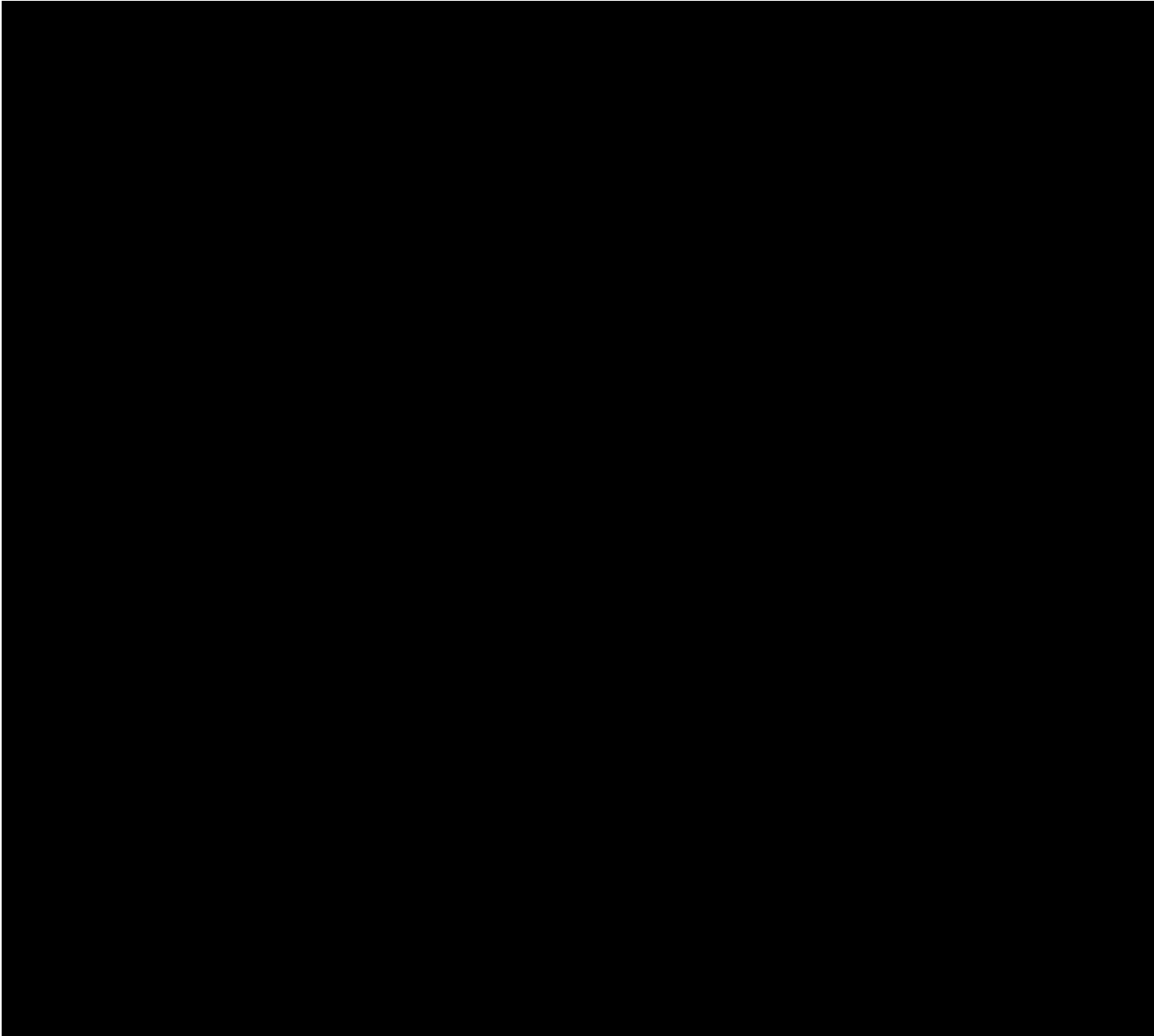
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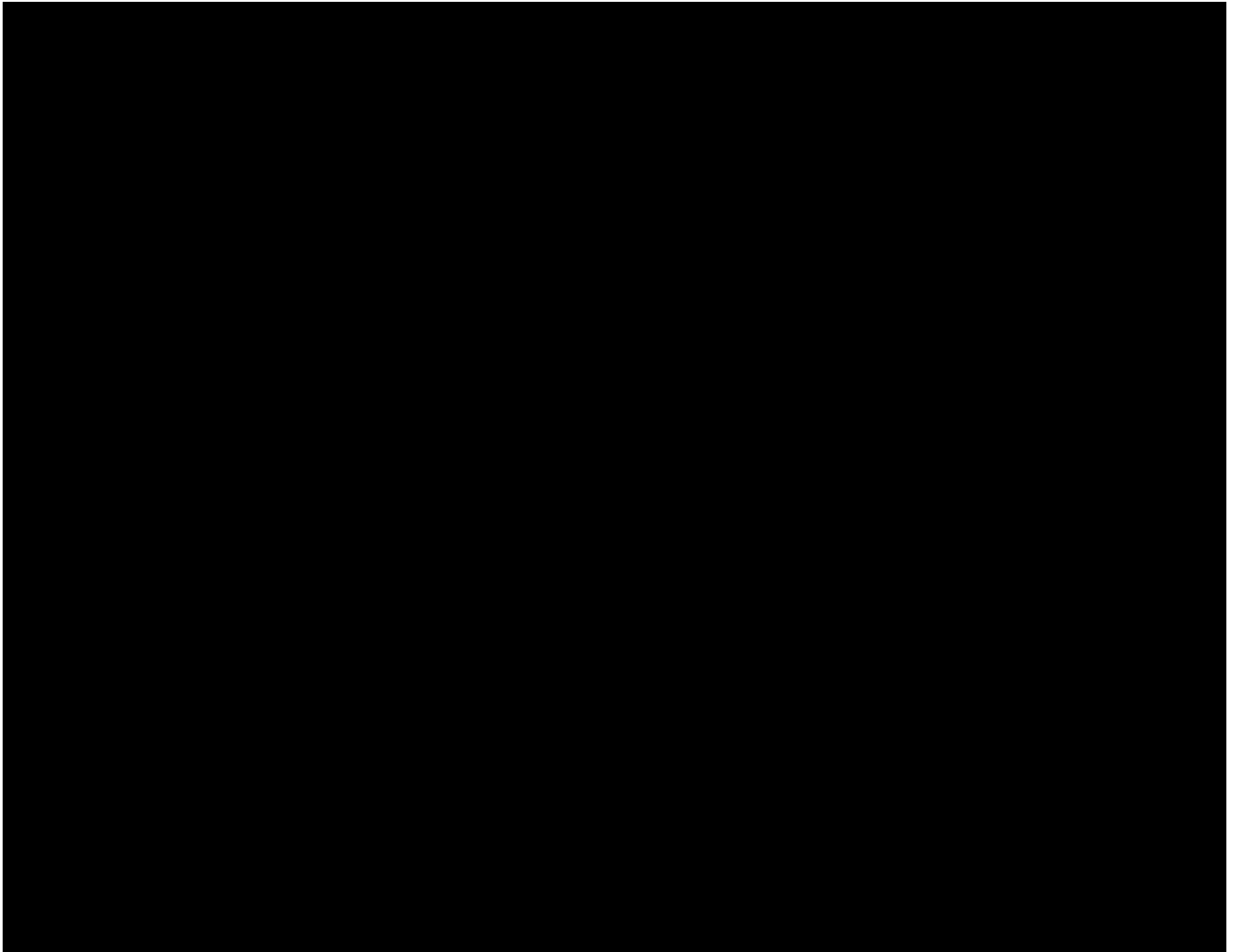
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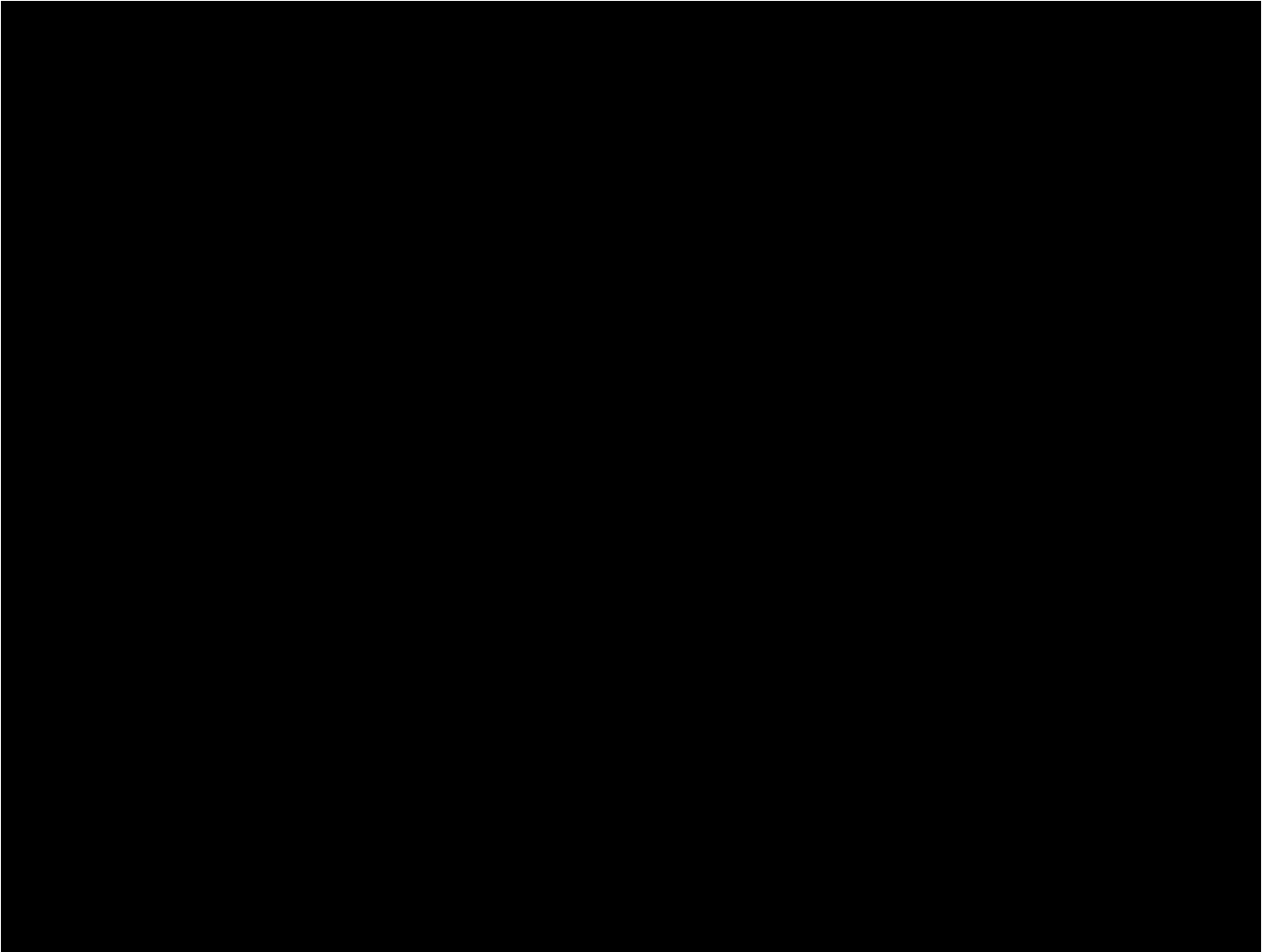
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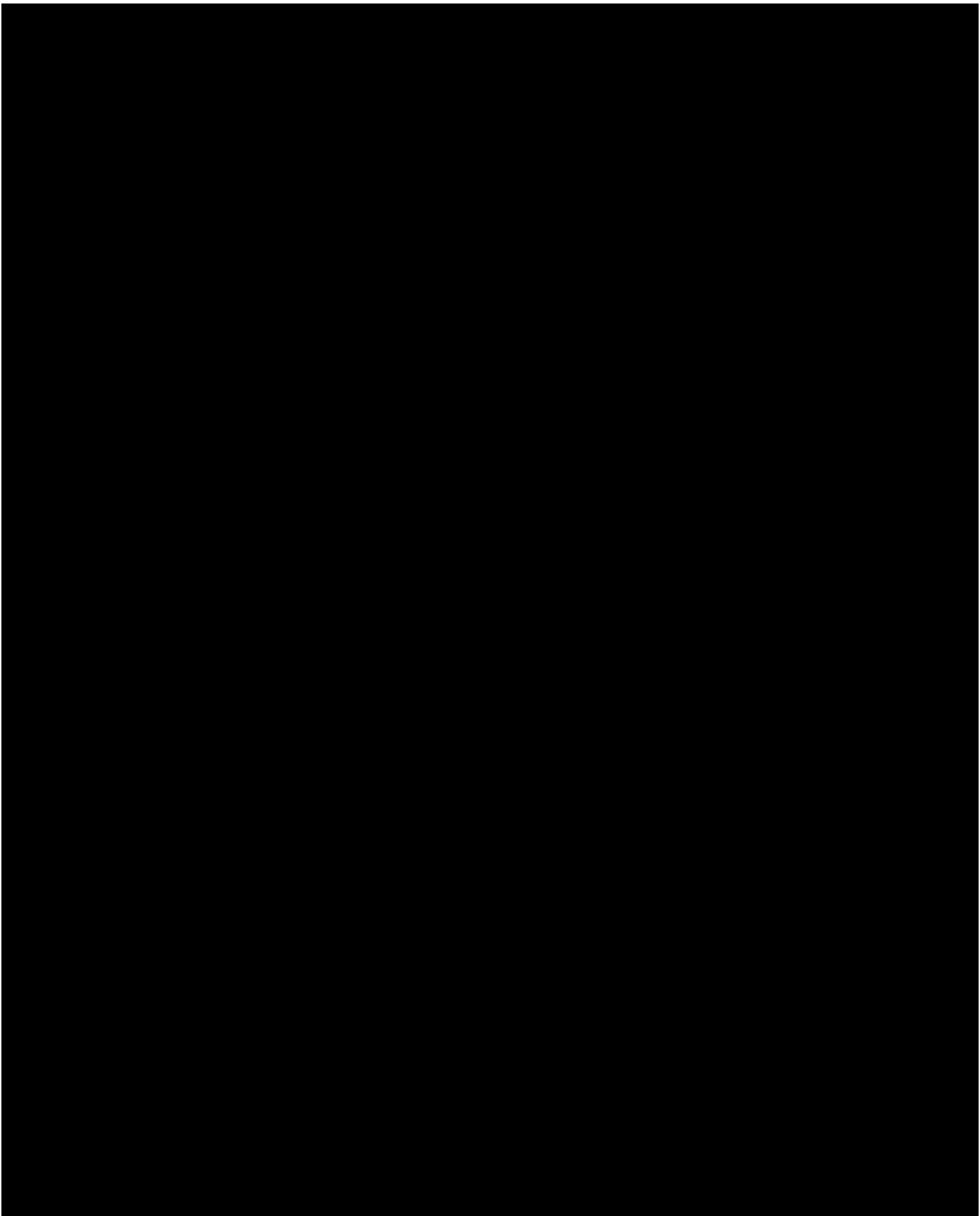
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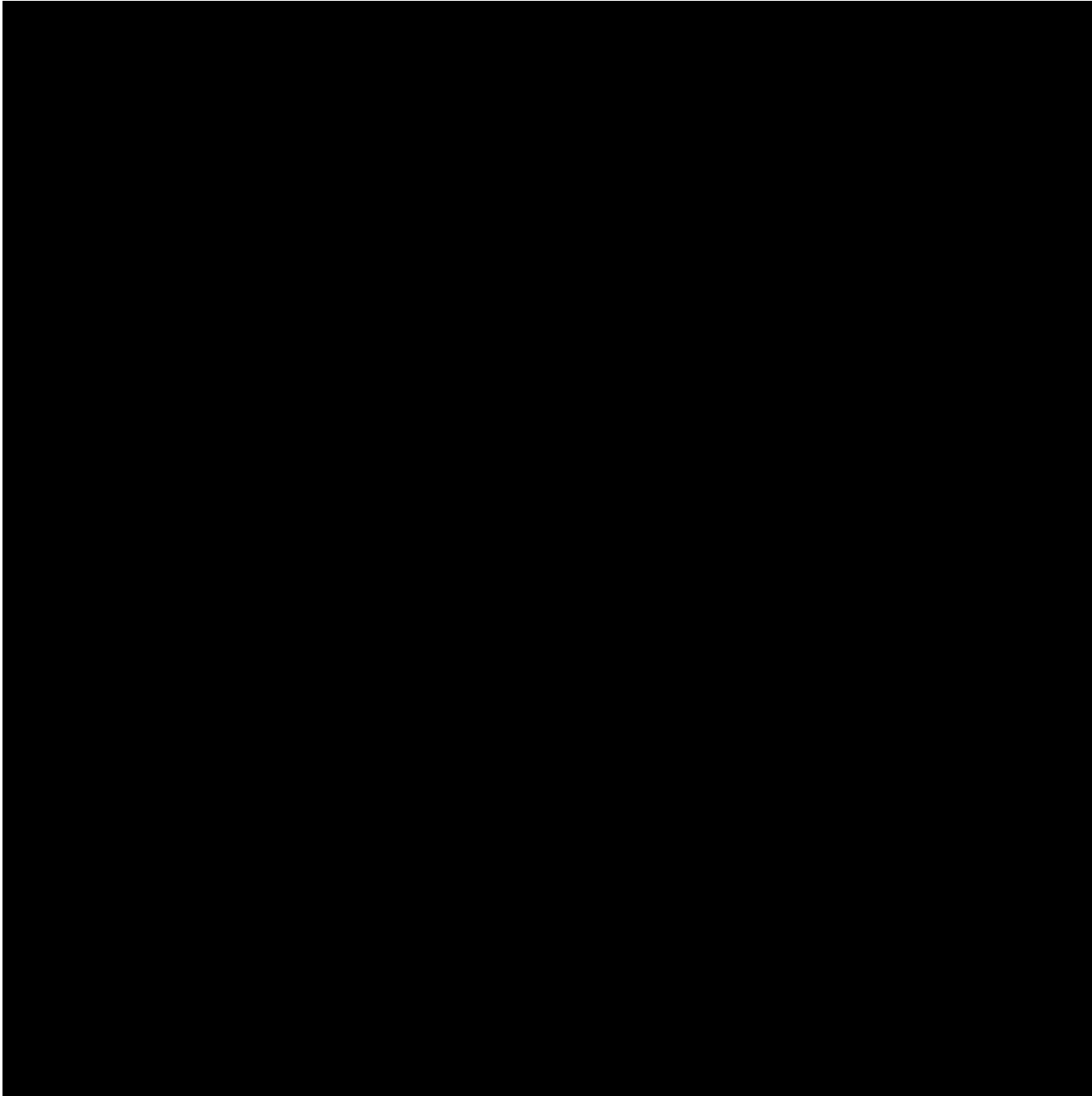
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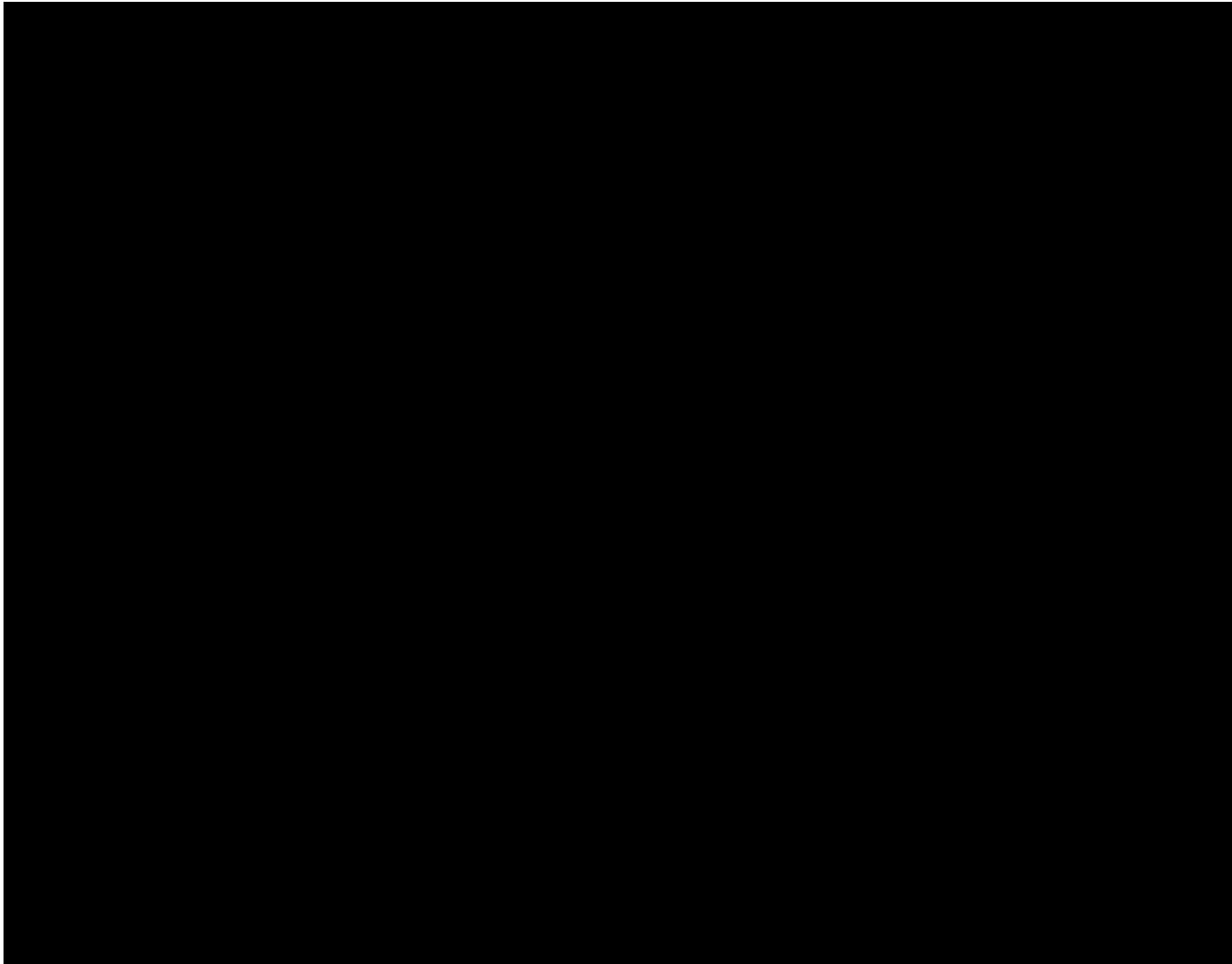


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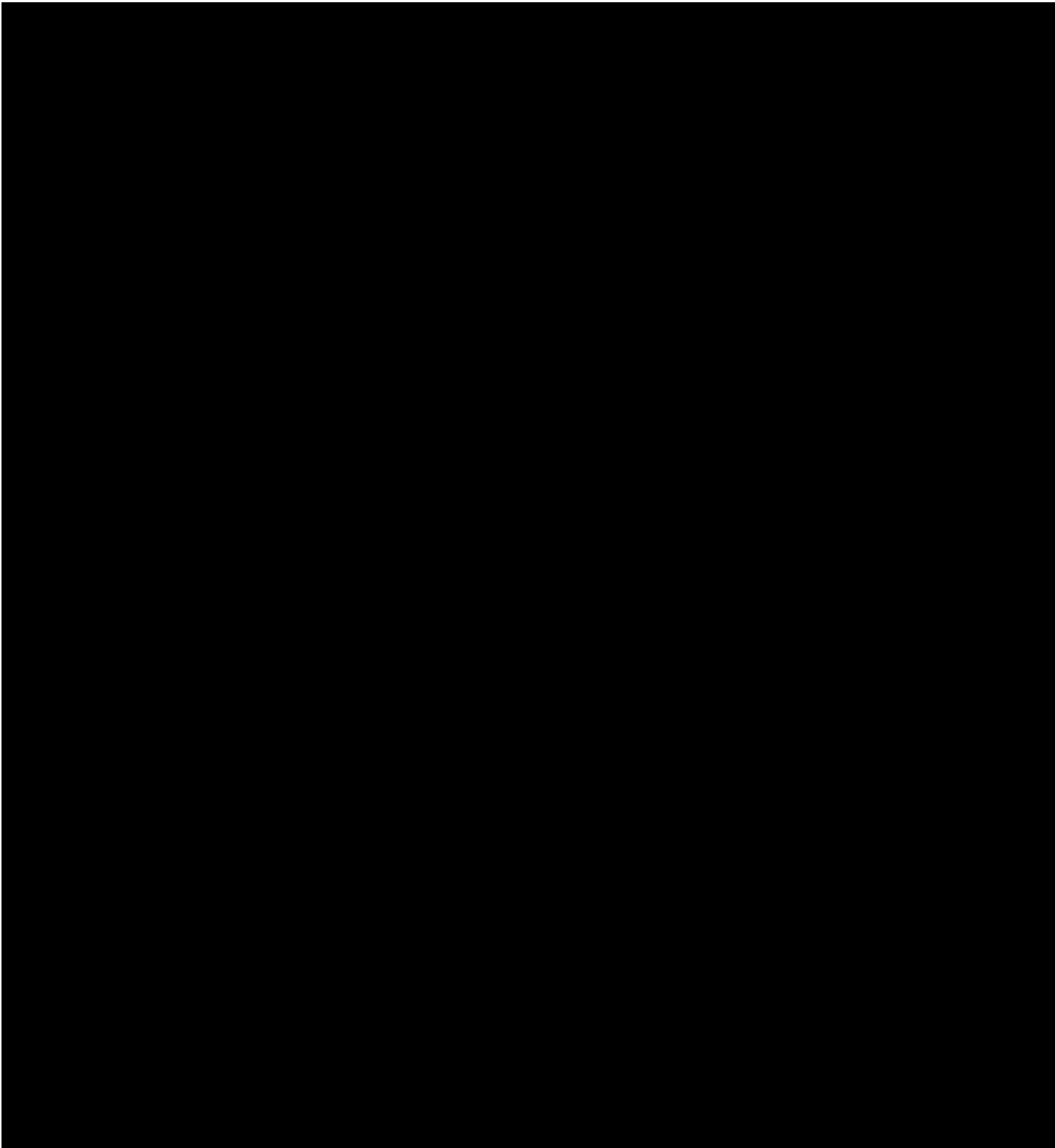


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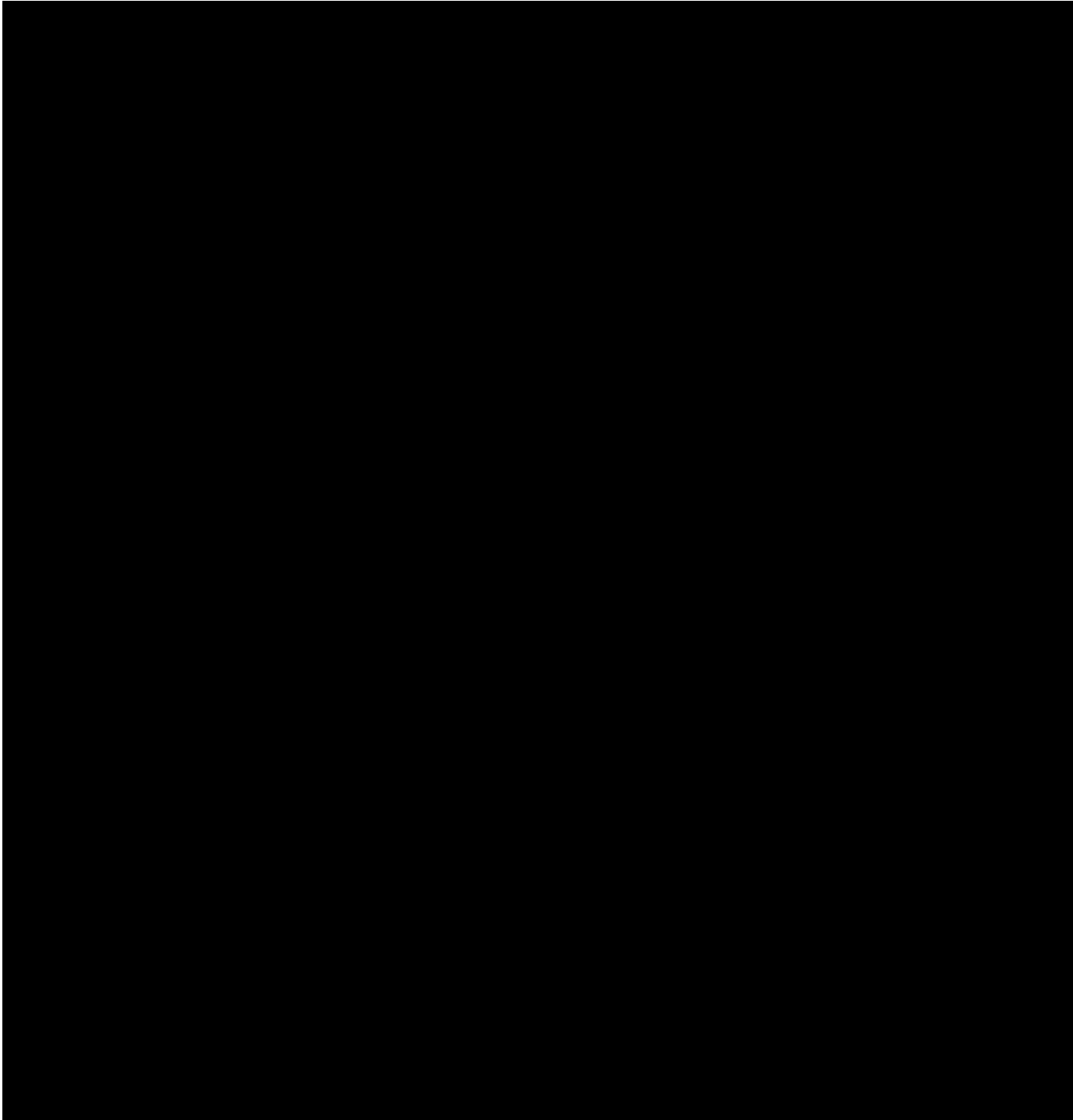




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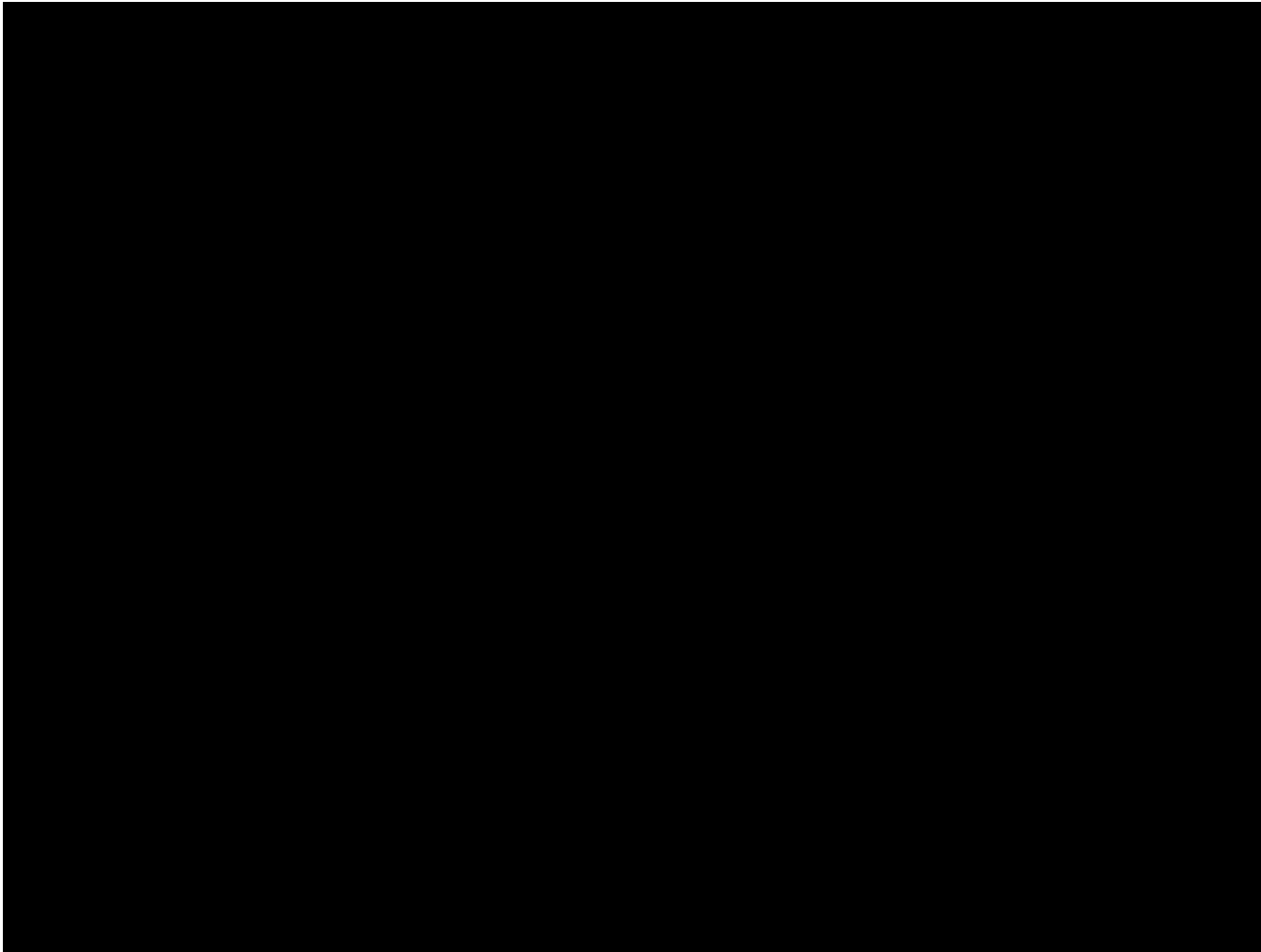
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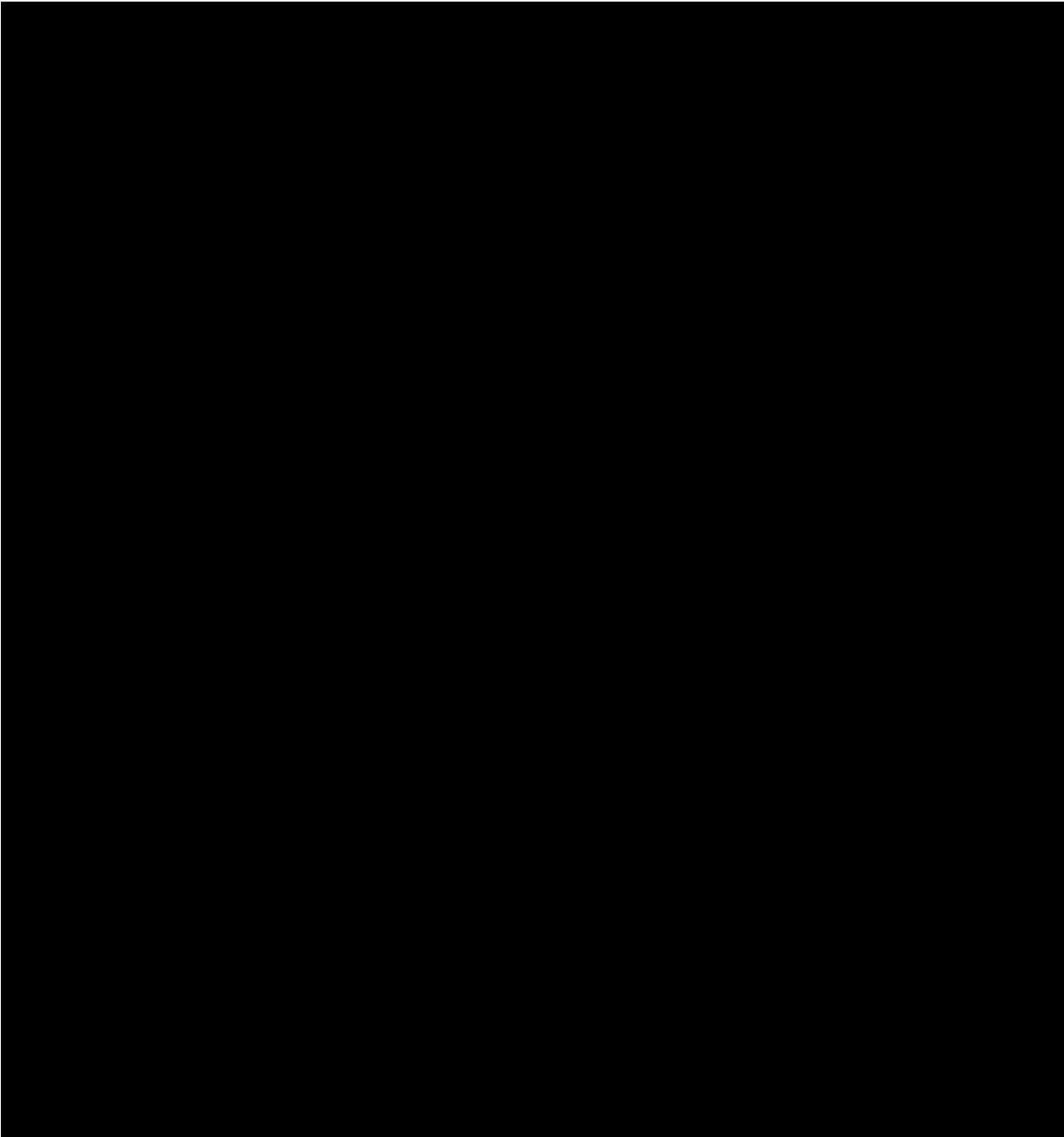
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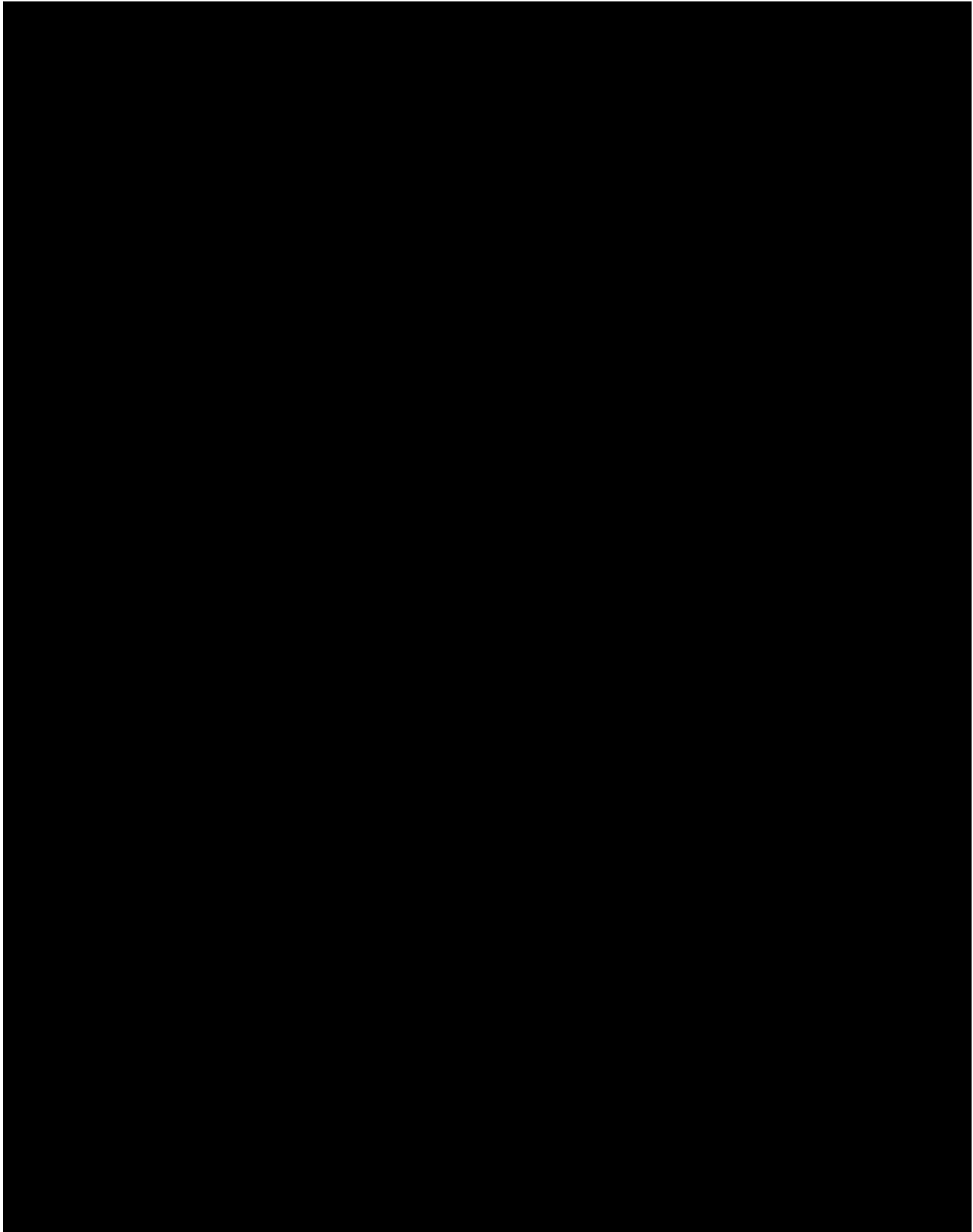
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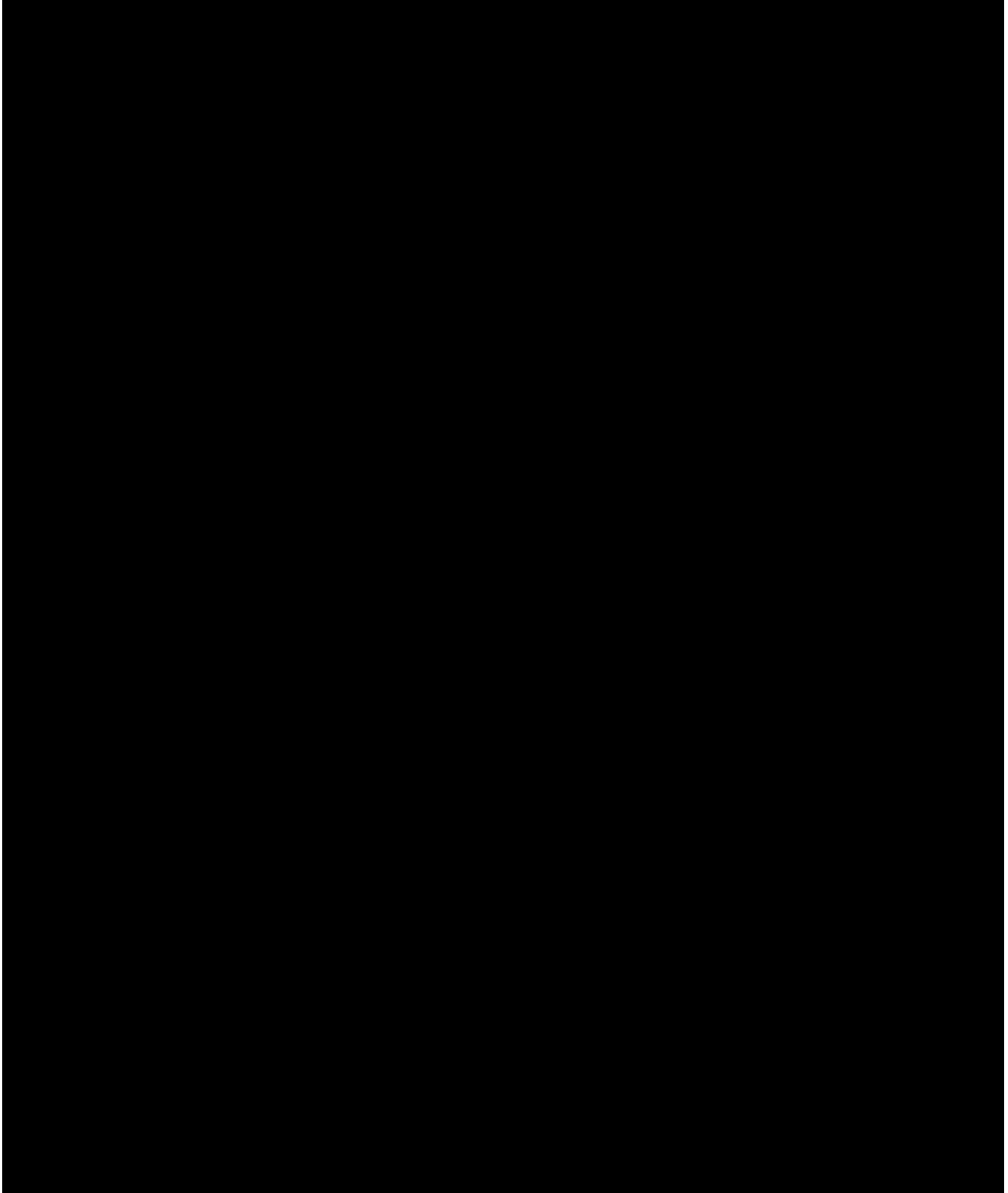
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## 12.2 Glossary of Abbreviations

<b>Term/Abbreviation</b>	<b>Definition</b>
2D	2-dimensional
3D	3-dimensional
ANCOVA	analysis of covariance
ANOVA	analysis of variance
CMH	Cochran-Mantel-Haenszel
CPAP	continuous positive airway pressure
CT	computed tomography
DR	drug reconstitutor
DRC	data review committee
eCRF	electronic case report form
EDC	electronic data capture
GCP	Good Clinical Practices
ICH	International Conference on Harmonisation
ID	identification
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IVRS	interactive voice response system
IWRS	interactive web response system
LFSC	Lower Facial Shape Classification
LFSQ	Lower Facial Shape Questionnaire
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMH	masseter muscle hypertrophy
MMPS	Masseter Muscle Prominence Scale
MRI	magnetic resonance imaging
OA	osteoarthritis
PP	per(-)protocol
ROI	region of interest
TMJD	temporomandibular joint disorder
US(A)	United States (of America)

### 12.3 Protocol Amendment Summary

Title: BOTOX® Treatment of Masseter Muscle Hypertrophy

Protocol 191622-130 Amendment 1

Date of Amendment: February 2014

#### Amendment Summary

This summary includes changes made to Protocol 191622-130 (18 October 2013). Based on input from study dentists and radiologists, this protocol was amended to: 1) revise and clarify the CT assessments; and 2) revise and clarify specific measurements and analyses.

Following is a summary of content-oriented changes that were made to each section of the protocol, and a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized.

Section	Revision	Rationale
Protocol Summary; Section 3	Added that approximately 50 subjects will be enrolled in each cohort: approximately 40 will receive BOTOX and approximately 10 will receive placebo	Clarification
Protocol Summary; Table 1; Section 3; Section 5.5	Clarified that baseline MMPS grade is from day 1 assessment and that randomization and enrollment will not occur until after all baseline procedures are performed and the investigator has re-verified that subjects meet the inclusion and exclusion criteria	Clarification
[REDACTED]	[REDACTED]	[REDACTED]
Protocol Summary; Section 4.1	Updated that “Subjects will be enrolled at approximately 4 to 12 investigational sites”	To allow for at least 4 investigational sites

Approval Date: 28-Feb-2014

<b>Section</b>	<b>Revision</b>	<b>Rationale</b>
Protocol Summary; Section 4.3  [REDACTED]	Added “or older if legal age of adulthood is > 18 as per local regulations” as minimum age for enrollment  [REDACTED]	To clarify that the minimum age of enrollment is 18 years or older if the country-specific legal age of adulthood is > 18 years  [REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
Protocol Summary; Sections 7.2, 7.3.1	Changed ANCOVA to ANOVA method of analysis of primary endpoint, removal of baseline value	Primary measure (based on VECTRA 3D images) does not produce a baseline value; change will be measured at later time points relative to the subject’s own baseline image.
Figure 1	Updated figure to raise Line A  [REDACTED]	Correction  [REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

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Section	Revision	Rationale
[REDACTED]	[REDACTED]	[REDACTED]
Section 8.2	Removed paragraph separation between and reordered the first 2 sentences	Timing of informed consent in relation to washout is relevant to neuromuscular agents and muscle relaxants but not to the procedures specified for 6 months prior to study entry.
Section 8.8 and Table 1	Updated to indicate that if a subject discontinues from the study early, an exit CT scan should be performed, unless the investigator proposes a medical reason to waive	To allow for a final CT scan of the subject
Section 10.4.2	Removed the statement that eCRFs will be maintained in a central data repository	Update
Section [REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

Approval Date: 28-Feb-2014

# ALLERGAN

Protocol 191622-130 Amd 1

Date (DD/MMM/YYYY)/Time (PT)

████████████████████

Signed by:

██████████

Justification

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