Title Page

Protocol Title: A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study to Evaluate the Safety and Efficacy of MT10109L (NivobotulinumtoxinA) for the Treatment of Lateral Canthal Lines With or Without Concurrent Treatment of Glabellar Lines

Protocol Number: MT10109L-006

Amendment Number: Amendment 4

Product: MT10109L (nivobotulinumtoxinA)

Brief Protocol Title: MT10109L in the Treatment of Lateral Canthal Lines With or Without Concurrent Treatment of Glabellar Lines

Development Phase: 3

Sponsor Name and Legal Registered Address:

[redacted]

Regulatory Agency Identifying Numbers: IND Number 121473;
EudraCT Number 2014-005302-38

[redacted]

[redacted]

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

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment 4	September 2020
Amendment 3	March 2019
Amendment 2	November 2018
Amendment 1	August 2018
Original Protocol	June 2018

Amendment 4 (September 2020)

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

The overall rationale of this protocol amendment was to integrate feedback and recommendations from a health authority.

Section No. and Name	Description of Change	Brief Rationale
Title Page	Updated sponsor signatory	Administrative
9.4.1.2 Primary Analyses	Added text describing imputation methods from the statistical analysis plan	Updated per recommendation by health authority
11 References	Added references	References added to Section 9.4.1.2

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[redacted]

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study to Evaluate the Safety and Efficacy of MT10109L (NivobotulinumtoxinA) for the Treatment of Lateral Canthal Lines With or Without Concurrent Treatment of Glabellar Lines

Protocol Number: MT10109L-006

Brief Title: MT10109L in the Treatment of Lateral Canthal Lines With or Without Concurrent Treatment of Glabellar Lines

Study Phase: 3

Study Rationale:

The purpose of this placebo-controlled pivotal study is to evaluate the safety and efficacy of MT10109L for the treatment of lateral canthal lines (LCL) with or without concurrent treatment of glabellar lines (GL) in participants with moderate to severe LCL and GL [redacted]

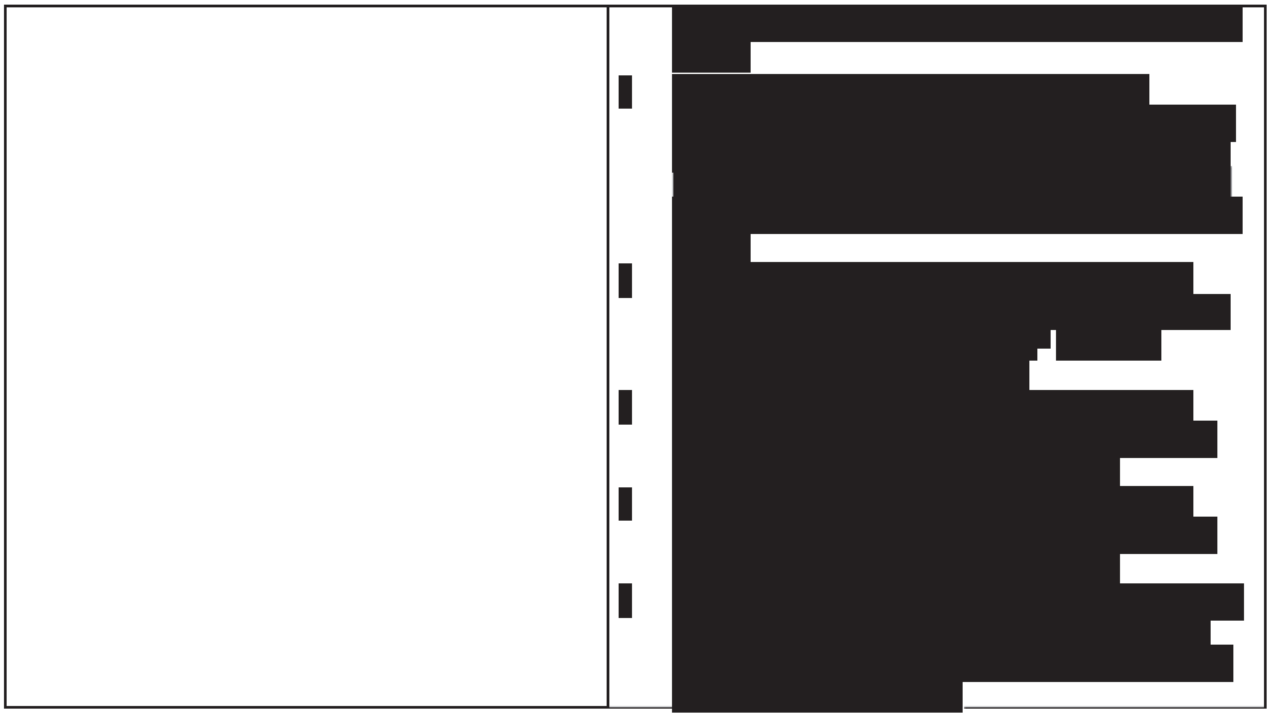
Objectives and Endpoints:

Objectives	Endpoints
Primary • To compare the efficacy between 24 U MT10109L and placebo for the treatment of LCL (with or without concurrent 20 U treatment of GL) in participants with moderate to severe LCL and GL	*For US FDA:* • Composite: The proportion of participants with a ≥ 2-grade improvement from baseline on the Facial Wrinkle Scale With Photonumeric Guide (FWS) according to investigator and participant assessments of LCL severity at maximum smile at Day 30 using the intent-to-treat (ITT) population after a single intramuscular (IM) injection of MT10109L or placebo in the LCL [redacted]

[redacted]

Secondary • To compare the efficacy between MT10109L and placebo for the treatment of LCL (with or without concurrent treatment of GL) in participants with moderate to severe LCL and GL • To compare the safety between MT10109L and placebo for the treatment of LCL (with or without concurrent treatment of GL) in participants with moderate to severe LCL and GL	*For US FDA:* • Secondary: The duration of LCL treatment effect, estimated as the median time to return to *moderate* or *severe* LCL at maximum smile in participants who achieved a rating of ≥ 2 grade improvement from baseline in LCL severity at maximum smile at Day 30 according to investigator assessments using the FWS • Secondary: The proportion of responders for investigator assessments of LCL severity at maximum smile using the FWS, where a responder is defined as achieving a ≥ 2-grade improvement from baseline at maximum smile at Day 30 • Secondary: The proportion of responders for investigator assessments of LCL severity at maximum smile using the FWS, where a responder is defined as achieving a rating of *none* or *mild* at maximum smile at Day 30 • Secondary: The proportion of participants reporting *mostly satisfied/very satisfied* on the Facial Line Satisfaction Questionnaire (FLSQ) follow-up version Item 5 for LCL at Day 60 • Secondary: The proportion of responders for investigator assessments of LCL severity at rest using the FWS among participants who were rated at least *mild* at rest at baseline, where a responder is defined as achieving a ≥ 1-grade improvement from baseline at Day 30 • Secondary: Incidence of adverse events; change from baseline in hematology/chemistry laboratory, vital signs, and electrocardiogram (ECG) parameters; and presence of binding and neutralizing antibodies [redacted]

[redacted]



Overall Study Design:

- This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group Phase 3 study to evaluate the safety and efficacy of MT10109L in treating LCL with or without concurrent treatment of GL. .
- Participants are adults ≥ 18 years of age with moderate to severe LCL at maximum smile and moderate to severe GL at maximum frown (assessed by the investigator)
- The primary efficacy measure is the investigators' and participants' assessments of LCL at maximum smile using the FWS, and the primary timepoint is Day 30 after the first intervention.
- Participants will attend a Screening Visit up to 28 days before enrollment on Day 1. All screening procedures must be completed up to 28 days prior to Day 1, and results must be available to the investigator prior to randomization on Day 1.
-
- The first treatment period (is a double-blind, randomized, placebo-controlled, parallel-group, single-treatment administration with at least a 6-month follow-up.

- On Day 1, participants will be randomly assigned in a 2:2:1 ratio to receive MT10109L 24 U (MT10109L in LCL area, placebo in GL area), MT10109L 44 U (24 U in LCL area and 20 U in GL area), or placebo (placebo in both LCL and GL areas). [redacted]
- During the retreatment period (from Day 180 through Day 330), participants who meet retreatment criteria will receive up to 2 blinded interventions of the same study intervention received in the first period (MT10109L 24 U, 44 U, or placebo). Based on individual variability in time to meet retreatment criteria, retreatment timepoints are not expected to be synchronized among all participants in this study.
- Participants who complete the study will have an exit visit at Day 360.

[redacted]

Number of Participants:

Approximately 375 participants will be enrolle [redacted]

Number of Sites:

Approximately 16 global sites

Intervention Groups and Study Duration:

- The total duration of study participation for each participant is approximately 12 months (Day 1 randomization/treatment to end of study/Day 360). Participants will attend the following visits:
  - Screening (up to 28 days prior to Day 1)
  - Randomization and treatment (Day 1)
  - Follow-up visits on Days 7 and 14 after each intervention
  - Monthly (Days 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, and 330)
  - Exit (Day 360 [completion] or early exit)
- On Day 1, participants will receive IM injections of MT10109L 24 U (MT10109L in LCL area, placebo in GL area), MT10109L 44 U (24 U in LCL area and 20 U in GL area), or placebo (placebo in both LCL and GL areas).
- During the retreatment period (from Day 180 through Day 330), participants who meet retreatment criteria will receive up to 2 blinded interventions of the same study intervention received in the first period (MT10109L 24 U, 44 U, or placebo).

Data Monitoring Committee: No

[redacted]

[redacted]

[redacted]

[redacted]

1.3. Schedule of Activities (SoA)

	All Participants						Only Participants Meeting Retreatment Criteria[a]				All Participants
Study Period	Screening[b]	Randomization Treatment (Day 1)[c]	Follow-up (Day 7 and Day 14)	Days 30, 60, 90, 120, 150	Day 180	Days 210, 240, 270, 300, 330	Retreatment 1 and Retreatment 2 (from Day 180 through Day 330)[c,d,e]	Follow-up (Day 7 and Day 14 after each retreatment)	Follow-up (Day 30 after each retreatment)[e]	Follow-up (Day 90 after each retreatment)[e]	End of Study (Day 360 or Early Exit)
Visit Windows	*Days −28 to −1*	-	*± 3 days*	*± 7 days*	*± 7 days*	*± 7 days*	-	*± 3 days*	*± 7 days*	*± 7 days*	*± 7 days*
Consent/ Authorization	X										
Demographics, Weight/ Height	X										
Inclusion/ Exclusion Criteria	X	X									
Medical/ Surgical History	X										
FLO-11©		X	X	X	X	X	X	X	X	X	X
FLSQ© (Baseline)[f]		X									
FLSQ (Follow-up)			X	X	X	X	X	X	X	X	X

	All Participants						Only Participants Meeting Retreatment Criteria[a]				All Participants
Study Period	Screening[b]	Randomization Treatment (Day 1)[c]	Follow-up (Day 7 and Day 14)	Days 30, 60, 90, 120, 150	Day 180	Days 210, 240, 270, 300, 330	Retreatment 1 and Retreatment 2 (from Day 180 through Day 330)[c,d,e]	Follow-up (Day 7 and Day 14 after each retreatment)	Follow-up (Day 30 after each retreatment)[e]	Follow-up (Day 90 after each retreatment)[e]	End of Study (Day 360 or Early Exit)
Visit Windows	*Days −28 to −1*	-	*± 3 days*	*± 7 days*	*± 7 days*	*± 7 days*	-	*± 3 days*	*± 7 days*	*± 7 days*	*± 7 days*
FWS Assessment of LCL (Investigator and Participant) and GL (Investigator Only)[f]	X[g]	X[g]	X	X	X	X	X	X	X	X	X
Standardized Facial Photography		X	X	X	X						
Physical Examination	X										
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vital Sign Measurements[i]	X	X		X[j]			X		X		X
Pregnancy Test (Urine)[k]		X					X				X
12-lead ECG[l]	X		X	X[j]	X		X		X		X

[redacted]

	All Participants						Only Participants Meeting Retreatment Criteria[a]				All Participants
Study Period	Screening[b]	Randomization Treatment (Day 1)[c]	Follow-up (Day 7 and Day 14)	Days 30, 60, 90, 120, 150	Day 180	Days 210, 240, 270, 300, 330	Retreatment 1 and Retreatment 2 (from Day 180 through Day 330)[c,d,e]	Follow-up (Day 7 and Day 14 after each retreatment)	Follow-up (Day 30 after each retreatment)[e]	Follow-up (Day 90 after each retreatment)[e]	End of Study (Day 360 or Early Exit)
Visit Windows	*Days −28 to −1*	-	*± 3 days*	*± 7 days*	*± 7 days*	*± 7 days*	-	*± 3 days*	*± 7 days*	*± 7 days*	*± 7 days*
Collection of Blood Samples for Hematology and Chemistry Testing	X			X[j]							
[redacted]		[redacted]		[redacted]			[redacted]		[redacted]	[redacted]	[redacted]
Adverse Events	X	X[n]	X	X	X	X	X[n]	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Concurrent Procedures	X	X	X	X	X	X	X	X	X	X	X
Study Intervention Injection		X					X				

Note: Participants completing this study through Day 360 will be eligible to enroll into a 2-year open-label extension study (Study MT10109L-004).

ECG = electrocardiogram; FLO-11 = 11-item Facial Line Outcomes Questionnaire; FLSQ = Facial Line Satisfaction Questionnaire; FWS = Facial Wrinkle Scale with Photonumeric Guide; GL = glabellar lines; LCL = lateral canthal lines (or crow's feet lines)

[a] Participants who meet retreatment criteria will receive up to 2 blinded study interventions of the same study intervention that they received on Day 1.

[b] All screening procedures must be completed up to 28 days before Day 1, and the results must be available to the investigator before randomization on Day 1

[c] All assessments (including photography and immunogenicity samples, if applicable) must be completed before administration of study intervention.

[d] Retreatment 1 cannot be administered earlier than the Day 180 visit; Retreatment 2 cannot be administered earlier than 84 days since administration of Retreatment 1 and no later than Day 330.

[e] If a procedure or assessment has already been performed as part of a scheduled visit, it must not be repeated.

[f] LCL at maximum smile and at rest; GL at maximum frown and at rest.

[g] To be randomized into the study, participants must meet Inclusion Criterion 2.01 both at the Screening Visit and prior to randomization at the Day 1 Visit.

[h] [redacted]

[i] Vital sign measurements are pulse rate, respiration rate, and blood pressure. Participants are to be seated for at least 2 minutes before measurements are collected.

[j] Only on Days 30 and 120

[k] Women of childbearing potential must have a negative pregnancy test. Investigator may ask participant to perform urine pregnancy test at any visit. At each visit, the investigator must discuss compliance with contraceptive use with women of childbearing potential.

[l] Single ECG traces will be taken with the participant in a semirecumbent position for ≥ 10 minutes before starting the tracing.

[redacted]

[n] Participants must be observed for ≥ 30 minutes after each study intervention for adverse events.

2. Introduction

2.1. Study Rationale

The purpose of this placebo-controlled pivotal study is to evaluate the safety and efficacy of MT10109L for the treatment of LCL with or without concurrent treatment of GL in participants with moderate to severe LCL and GL [redacted]

2.2. Background

[redacted]

Lateral canthal lines (or CFL) are horizontal *smile lines* by the sides of the eyes, and glabellar lines are deep furrows or *frown lines* in the glabellar area of the face. Both types of facial lines result from the repetitive functional action of the underlying mimetic facial musculature during animation (Blitzer 1993). When injected at therapeutic doses, MT10109L produces partial chemical denervation of the muscle, resulting in localized reduction in muscle activity. Because LCL and GL result from muscular activity, the muscle relaxation leads to a temporary relief of facial lines. While it was previously thought that these facial lines were structural and permanent, the effects of these injections demonstrate the lines are part functional and remain because of constant muscle tone (Ferreira 2004; Garcia 1996).

The development of facial lines (such as LCL and GL) is an age-related change of the face that occurs because of the repetitive muscle contractions that are associated with common facial expressions. Thus, these facial lines can be observed with contraction (dynamic rhytides) or in more severe cases in repose (static rhytides). Increasing severity in the appearance of facial lines has been associated with a patient's perception of reduced attractiveness and a negative effect on self-esteem and sense of well-being (Koblenzer 1996). Furthermore, the appearance of these facial lines can lead to a miscommunication of an emotional state of anger, anxiety, disapproval, or sadness (Khan 2001) causing distress and affecting social interactions (Finn 2003).

Evidence supports that unattractive or aging skin is indeed related to psychological and psychosocial impacts (Farage 2010). Psychological or psychosocial impacts can be characterized as changes in confidence, attractiveness, self-esteem, emotional burdensomeness, self-perceptions of appearance or age, emotional distress, and state of bother. The evaluation of psychological or psychosocial impacts associated with aging facial skin should be assessed from patients' perspectives since these impacts are dependent on their perceptions.

[redacted]

The popularity of BoNT/A cosmetic treatment of LCL and GL in adults is related to its proven efficacy for reducing moderate to severe facial lines (Beer 2006); well documented safety profile (Brin 2009); and positive impact on psychological well-being and the resulting psychosocial benefits (Finn 2003).

2.3. Benefit/Risk Assessment

Generally, the popularity of BoNT/A cosmetic treatment of LCL and GL in adults is related to its proven efficacy for reducing moderate to severe facial lines (Beer 2006); well documented safety profile (Brin 2009); and positive impact on psychological well-being and the resulting psychosocial benefits (Finn 2003).

[redacted]

In some cases, botulinum toxin effect may be observed beyond the site of local injection. The symptoms may include asthenia, generalized muscle weakness, diplopia, eyelid ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. Swallowing and breathing difficulties can be life threatening, and there have been reports of death related to distant spread of toxin effects with other BoNT/A treatments for noncosmetic indications. The risk of symptoms is probably greatest in children treated for spasticity, but symptoms can also occur in adults treated for spasticity and other conditions.

Reduced blinking after BoNT/A product injection to the orbicularis muscle can lead to corneal exposure, persistent epithelial defect, and corneal ulceration with perforation. In the use of another BoNT/A product for treatment of blepharospasm, 1 case of corneal perforation in an aphakic eye requiring corneal grafting has occurred because of this effect.

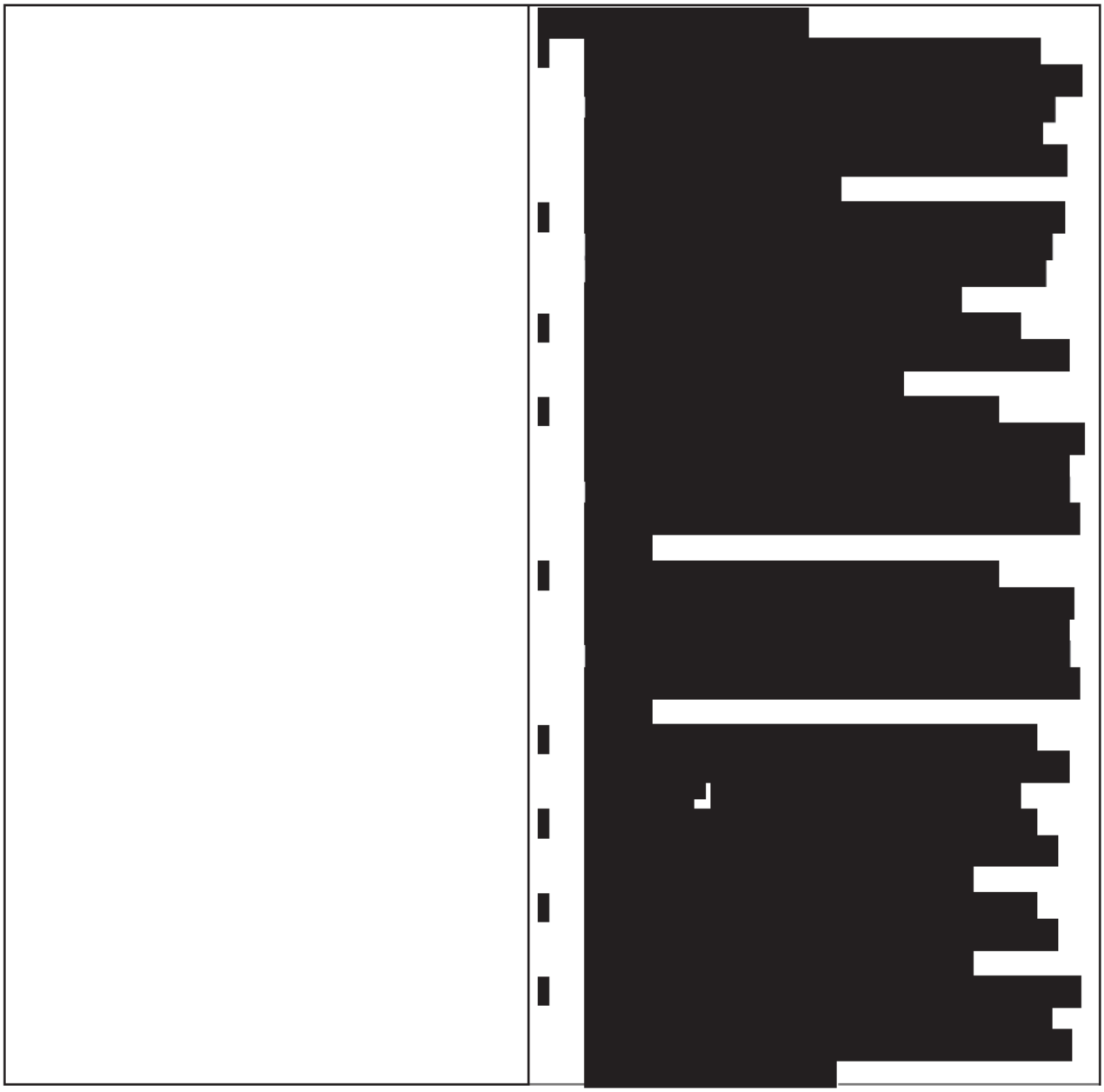
[redacted]

[redacted]

3. Objectives and Endpoints

Objectives	Endpoints
Primary • To compare the efficacy between 24 U MT10109L and placebo for the treatment of LCL (with or without concurrent 20 U treatment of GL) in participants with moderate to severe LCL and GL	*For US FDA:* • Composite: The proportion of participants with a ≥ 2-grade improvement from baseline on the FWS according to investigator and participant assessments of LCL severity at maximum smile at Day 30 using the ITT population after a single IM injection of MT10109L or placebo in the LCL [redacted]
Secondary • To compare the efficacy between MT10109L and placebo for the treatment of LCL (with or without concurrent treatment of GL) in participants with moderate to severe LCL and GL • To compare the safety between MT10109L and placebo for the treatment of LCL (with or without concurrent treatment of GL) in participants with moderate to severe LCL and GL	*For US FDA:* • Secondary: The duration of LCL treatment effect, estimated as the median time to return to *moderate* or *severe* LCL at maximum smile in participants who achieved a rating of ≥ 2 grade improvement from baseline in LCL severity at maximum smile at Day 30 according to investigator assessments using the FWS • Secondary: The proportion of responders for investigator assessments of LCL severity at maximum smile using the FWS, where a responder is defined as achieving a ≥ 2-grade improvement from baseline at maximum smile at Day 30 • Secondary: The proportion of responders for investigator assessments of LCL severity at maximum smile using the FWS, where a responder is defined as achieving a rating of *none* or *mild* at maximum smile at Day 30 • Secondary: The proportion of participants reporting *mostly satisfied/very satisfied* on the FLSQ follow-up version Item 5 for LCL at Day 60 • Secondary: The proportion of responders for investigator assessments of LCL severity at rest using the FWS among participants who were rated at least *mild* at rest at baseline, where a responder is defined as achieving a ≥ 1-grade improvement from baseline at Day 30 • Secondary: Incidence of adverse events; change from baseline in hematology/chemistry laboratory, vital signs, and ECG parameters; and presence of binding and neutralizing antibodies

[redacted]



Additional exploratory efficacy assessments of MT10109L versus placebo are described in Section 9.4.1.5.

4. Study Design

4.1. Overall Design

- This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group Phase 3 study conducted across approximately 16 global sites to evaluate the safety and efficacy of MT10109L in treating LCL with or without concurrent treatment of GL. Participants may receive up to 3 study interventions.
- Participants are adults ≥ 18 years of age with bilaterally symmetrical moderate to severe LCL at maximum smile on both sides of the face [redacted] and moderate to severe GL at maximum frown (assessed by the investigator)
- The primary efficacy measure is the investigators' and participants' assessments of LCL at maximum smile using the FWS, and the primary timepoint is Day 30 after the first intervention.
- Participants will attend a Screening Visit up to 28 days before enrollment on Day 1. All screening procedures must be completed up to 28 days prior to Day 1, and results must be available to the investigator prior to randomization on Day 1.
- [redacted]
- The first treatment period (Day 1 with follow-up to Day 180) is a double-blind, randomized, placebo-controlled, parallel-group, single-treatment administration with at least a 6-month follow-up.
- On Day 1, participants will be randomly assigned in a 2:2:1 ratio to receive MT10109L 24 U (MT10109L in LCL area, placebo in GL area), MT10109L 44 U (24 U in LCL area and 20 U in GL area), or placebo (placebo in both LCL and GL areas). [redacted].
- MT10109L 24 U, 44 U, or placebo will be administered as 11 IM injections: 6 to the bilateral LCL areas (3 in each orbicularis oculi) and 5 to the GL complex (2 in each corrugator muscle, 1 in the procerus muscle), 0.1 mL (4 U MT10109L or 0 U placebo) per injection.
- During the retreatment period (from Day 180 through Day 330), participants who meet retreatment criteria will receive up to 2 blinded interventions of the same study intervention received in the first period (MT10109L 24 U, 44 U, or placebo). Based on individual variability in time to meet retreatment criteria, retreatment timepoints are not expected to be synchronized among all participants in this study.

[redacted]

- Participants who complete the study will have an exit visit at Day 360.
- The total duration of study participation for each participant is approximately 12 months (Day 1 randomization/treatment to end of study/Day 360). Participants will attend the following visits:
  - Screening (up to 28 days prior to Day 1)
  - Randomization and treatment (Day 1)
  - Follow-up visits on Days 7 and 14 after each intervention
  - Monthly (Days 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, and 330)
  - Exit (Day 360 [completion] or early exit)
- [redacted]
- Approximately 375 participants will be enrolled at approximately 16 sites [redacted]
- Participants who prematurely discontinue from the study will not be replaced.

4.1.1. Clinical Hypotheses

MT10109L 24 U is more effective than placebo in treating LCL, measured by both investigators' and participants' assessments of LCL at maximum smile using the FWS.

MT10109L 24 U (for LCL) and 44 U (24 U for LCL and 20 U for GL) have an acceptable safety profile after single and repeat interventions.

[redacted]

[redacted]

[redacted]

4.4. End of Study Definition

The end of the study is defined as the date of the last scheduled procedure shown in the SoA for the last participant in the study globally.

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the SoA.

5. Study Population

Participants in the current study have moderate to severe LCL at maximum smile and moderate to severe GL at maximum frown as specified in Section 5.1.

Sites may recruit from existing patient databases and/or clinic referrals. To aid with recruitment, the sponsor has developed study-level advertising templates (eg, flyers, pamphlets), which the sites may choose to adapt for use. Alternatively, sites may develop their own study advertising materials. All advertising/recruitment materials for participants must receive IRB/EC and sponsor approval before use in the study.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1.	**Age**
1.01	Participant must be ≥ 18 years of age and considered to be an adult in her/his local jurisdiction at the time of signing the informed consent.
2.	**Type of Participant and Characteristics**
2.01	Bilaterally symmetrical *moderate* to *severe* LCL at maximum smile [redacted] nd *moderate* to *severe* GL at maximum frown (assessed by the investigator only), using the FWS
2.02	Participants must have sufficient visual acuity without the use of eyeglasses (contact lens use acceptable) to accurately assess their facial lines, in the opinion of the investigator.
3.	**Sex**
3.01	Male and female
4.	**Contraceptives**
4.01	Female participants willing to minimize the risk of inducing pregnancy for the duration of the clinical study and follow-up period

[redacted]

4.02	Female participants of childbearing potential must have a negative urine pregnancy test before each study intervention. A female is considered NOT to be of childbearing potential if she is premenarchal, postmenopausal (at least 12 consecutive months without menstruation), or permanently sterilized (eg, tubal occlusion, hysterectomy, bilateral oophorectomy).
5.	**Informed Consent**
5.01	Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol
5.02	Written informed consent from the participant has been obtained prior to any study-related procedures.
5.03	Written documentation has been obtained in accordance with the relevant country and local privacy requirements, where applicable (eg, Written Authorization for Use and Release of Health and Research Study Information [US sites] and written Data Protection consent [EU sites]).
6.	**Other**
6.01	Ability to follow study instructions, including completing study assessment tools without any assistance or alteration to the assessment tools and likely to complete all required visits

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1.	**Medical Conditions**
1.01	Any condition which precludes a participant's ability to comply with study requirements, including completion of the study visits or inability to read, understand, and/or self-assess LCL severity using the FWS
1.02	Known immunization or hypersensitivity to any botulinum toxin serotype
[redacted]	[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
1.09	Any uncontrolled systemic disease
1.10	Recent history of alcohol or drug abuse based on the investigator's judgment
[redacted]	[redacted]
1.12	Anticipated need for surgery or overnight hospitalization during the study
2.	**Prior/Concomitant Therapy/Procedures**
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
3.	**Prior/Concurrent Clinical Study Experience**
3.01	Current enrollment in an investigational drug or device study or participation in such a study within 30 days of entry into this study
4.	**Other**
4.01	Females who are pregnant, nursing, or planning a pregnancy during the study
4.02	Participants who plan for an extended absence away from the immediate area of the study site that would preclude them from returning for all protocol-specified study visits
4.03	Participants who, in the investigator's opinion, are unable or unwilling to maintain their standardized skin care regimen throughout the study period
4.04	The participant has a condition or is in a situation which, in the investigator's opinion, may put the participant at significant risk, may confound the study results, or may interfere significantly with the participant's participation in the study.

[redacted]

5.3. Lifestyle Considerations

No restrictions are required.

[redacted]

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from health authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Screen failures can occur during the screening period up to the Day 1 Visit. [redacted]

[redacted]

6. Study Intervention

Study intervention is defined as any investigational intervention(s), marketed product(s), or placebo intended to be administered to a study participant according to the study protocol.

Retreatment criteria are described in Section 6.6.

6.1. Study Interventions Administered

Study Intervention Name	MT10109L	Placebo
Dosage Formulation	Sterile injectable solution	Sterile injectable solution
[redacted]	[redacted]	[redacted]
Route of Administration	Intramuscular	Intramuscular
[redacted]	[redacted]	[redacted]
Packaging and Labeling	Study intervention will be provided in identical appearing vials and cartons. Each vial and carton will be labeled as required per country requirement.	Study intervention will be provided in identical appearing vials and cartons. Each vial and carton will be labeled as required per country requirement.
Blinding	Study intervention will be supplied in identical appearing vial or other mechanism of maintaining blinding.	Study intervention will be supplied in identical appearing vial or other mechanism of maintaining blinding.
Number and Timing of Interventions	Initial treatment Day 1, up to 2 additional treatments	Initial treatment Day 1, up to 2 additional treatments

[redacted]

6.1.1. Study Supplies

The following will be provided by the sponsor:

- Study intervention
- Syringe labels
- Temperature recording devices for monitoring refrigerator and freezer temperatures (if applicable)
- Mirror for participant assessment of FWS
- FWS Photonumeric Guides (investigator and participant versions)

[redacted]

- Photographic equipment (including headbands and drapes) will be provided by a qualified third-party vendor
- Laboratory sample kits (for immunogenicity and hematology/chemistry sampling) will be provided by a qualified third-party vendor
- Electrocardiogram equipment and supplies will be provided by a qualified third-party vendor
- Tablets for electronic PRO administration will be provided by a qualified third-party vendor

The following will be provided by the investigator:

- Urine pregnancy test kits (sensitivity of 25 mIU/mL)
- Cotton pads and make-up remover
- Appropriately sized sterile needles fitted to 1 mL sterile syringes with 0.01 mL demarcations for extraction of liquid study intervention from vial
- Half-inch 30-gauge sterile needles for study intervention injection
- Alcohol wipes
- Protective gloves
- Penlight
- Covered container for medical waste (sharps box)
- Refrigerator to store study intervention with a temperature between 2° and 8°C
- Internet connection (high speed connection for eCRF completion)
- Monitor and DVD player for viewing participant instructions
- Centrifuge for separation of serum
- Freezer, that does not automatically defrost, to store blood samples at a temperature of −20°C or colder

6.1.2. Instructions for Use and Administration

Only trained and medically qualified physicians experienced with BoNT/A injections are authorized to administer the study interventions. Study-specific training for LCL and GL injections are provided to investigators via a video recording from a board-certified plastic surgeon with injection demonstration, and review of injection techniques as outlined in the protocol. The video is available on the training portal for injectors to access at any time as a refresher course. The investigator must maintain documentation of training records for all study personnel.

There will be up to 3 treatments in the study. In the first treatment period (Day 1 to Day 180), all participants will receive blinded treatment on Day 1, either MT10109L 24 U, 44 U, or placebo. In the retreatment period (from Day 180 through Day 330), all participants will receive up to

MT10109L

2 interventions of MT10109L 24 U, 44 U, or placebo (same as blinded Treatment 1) based on meeting the retreatment criteria.

The LCL study interventions will be administered as bilaterally symmetrical IM injections at 3 injection sites in the lateral aspect of each orbicularis oculi (Figure 6-1A). The GL study interventions will be administered as IM injections at 5 injection sites in the glabellar complex, 2 in each corrugator muscle and 1 in the procerus (Figure 6-3A). Lateral canthal lines and GL will be treated together, following the appropriate injection technique for each area, as described below.

Participants must be observed for adverse events for ≥ 30 minutes after each study intervention.

Lateral Canthal Line Injection Technique

Each injection volume is 0.1 mL, for a total of 0.6 mL. Lateral canthal lines injections must be given with the needle-tip bevel up and oriented away from the eye. The first injection will be made into the orbicularis oculi at the level of the lateral canthus, ≥ 1.5 to 2.0 cm temporal to the lateral canthus and just temporal to the lateral orbital rim (Figure 6-1B, Point A). The second and third injections will be made 1.0 to 1.5 cm above and below the first injection site, each at an approximate 30° angle medially. Repeat this procedure for the contralateral side.

If the lines in the lateral canthal area are primarily below the lateral canthus, injection sites may be given in a line that angles from anteroinferior to superposterior, but the most anterior injection will be lateral to a line drawn vertically from lateral canthus, and the most inferior injection will be superior to the maxillary prominence (Figure 6-2). Repeat this procedure for the contralateral side.

Figure 6-1 **(A) The Orbicularis Oculi (Lateral Canthal Line Area) on 1 Side of the Face and (B) Injection Pattern when Lateral Canthal Lines are Distributed Above and Below the Lateral Canthus**

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Glabellar Line Injection Technique

Each injection volume is 0.1 mL. Glabellar lines injections must be given with the bevel oriented superiorly and laterally. The first injection will be made in the procerus muscle in the midline. The next 4 injections will be made bilaterally (ie, 2 injections per side) into each corrugator muscle (Figure 6-3B). The corrugators will be injected inferomedially near the origin of the supratrochlear nerve and superolaterally into the superior middle aspect ≥ 1 cm above the bony orbital rim.

[redacted]

[redacted]

[redacted]

[redacted]

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention, and only authorized site personnel may administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site personnel.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided in the study manual.

All unused study intervention and empty vials must be returned to the sponsor at the termination of the study. Unit counts will be performed when the study intervention is returned, and all study intervention must be accounted for. Unused drug supplies and empty vials will be returned to the sponsor.

6.3. Measures to Minimize Bias: Randomization and Blinding

At the Screening Visit, each participant who provides informed consent will be assigned a participant number that will serve as the participant identification number on all study documents.

An automated IWRS will be used to manage the randomization and study intervention assignment based on a randomization scheme prepared by the sponsor's biostatistics department. Before administering study intervention, the site must contact the IWRS and enter the site number and the participant's enrollment stratification information [redacted] The IWRS will then randomly assign participants to receive MT10109L 24 U, 44 U, or placebo in a 2:2:1 ratio. Once a randomization number has been assigned, it must not be re-assigned. In addition, withdrawn study participants cannot be replaced.

Study intervention will be labeled with study kit numbers. The IWRS system will provide the site with the specific medication kit numbers for each randomized participant at the time of randomization. Study sites will dispense study intervention according to IWRS instructions. Study sites will also contact the IWRS at subsequent retreatment visits (if applicable) to obtain study kit numbers for dispensing study intervention. Study sites will receive the IWRS confirmation notifications for each transaction. All notifications are to be maintained with the study source documents.

[redacted]

The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's study intervention assignment unless this could delay emergency treatment of the participant. If a participant's study intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation.

6.4. Study Intervention Compliance

Participants will receive all doses under the direct supervision of study site personnel. Study intervention compliance will not be calculated.

The study site will keep an accurate drug disposition record that specifies the amount of study intervention administered to each participant and the date of administration.

6.5. Concomitant Therapy

The use of any concomitant medication or vaccine (including prescription or over-the-counter medication, vitamins, and/or herbal supplements) is to be recorded on the participant's eCRF at each visit along with the reason the medication is taken.

At screening and end of study and upon admission to and discharge from the study site, study site personnel will question each participant specifically on the use of concomitant medications. Study site personnel must notify the sponsor immediately if a participant consumes any concomitant medications not permitted by the protocol. Participants who admit to using prohibited concomitant medications may be discontinued from the study at the discretion of the investigator or sponsor.

6.5.1. Prohibited Interventions

The decision to administer a prohibited medication/treatment is done with the safety of the participant as the primary consideration. When possible, the sponsor must be notified before the prohibited medication/treatment is administered. Co-administration of aminoglycosides or agents that could interfere with neuromuscular transmission (eg, curare-like agents) or muscle relaxants must be used with caution as the effects of the toxin, theoretically, could be potentiated.

No other facial cosmetic procedures or treatments are to be performed throughout the duration of the study. Prohibited treatments and procedures include, but are not limited to:

- Oral retinoids
- New or changes to regimen of topical hormone cream to the face
- New or changes to regimen of topical retinoids to the face
- Microdermabrasion to the face

- Medium depth to deep facial chemical peels (ie, TCA and phenol)
- Laser treatment, ultrasound treatment, or resurfacing to the face
- Facial lift (mid or full face)
- Blepharoplasty
- Synthetic implantation (eg, Gore-Tex) to the upper half of the face
- Autologous fat transplantation to the face
- Dermal fillers to the face
- Permanent make-up to the face
- Concurrent treatment with botulinum toxin of any serotype for any indication (other than the study intervention) is prohibited.

6.5.2. Permitted Interventions

Any medication or vaccine (including prescription or over-the-counter medication, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Indication
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Therapy considered necessary for the participant's welfare may be given at the discretion of the investigator. If the permissibility of a specific medication/intervention is in question, please contact the sponsor.

The sponsor must be contacted if there are any questions regarding concomitant or prior therapy.

Any medication taken during the study between the date of the first dose of study intervention and the date of the end of study visit will be recorded in the eCRF as a concomitant medication; any medication started after the end of study visit will not be considered a concomitant medication and should not be captured in the eCRF.

6.5.3. Rescue Medicine

Rescue medicine is not applicable.

6.6. Dose Modification

This protocol does not allow for alteration from the currently outlined dosing schedule.

[redacted]

[redacted]

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

A premature discontinuation will occur if a participant who signs the ICF and is randomized ceases participation in the study, regardless of circumstances, before the completion of the protocol-defined study procedures.

Notification of early participant discontinuation from the study and the reason for discontinuation will be made to the sponsor and will be clearly documented on the appropriate eCRF.

Definitions of the standard terms are provided in Appendix 5.

Reasons for discontinuation from the study intervention and/or the study may include the following commonly used terms:

Commonly Used Terms
Adverse event
Lost to follow-up
Lack of efficacy
Other
Physician decision
Pregnancy
Protocol deviation
Site terminated by sponsor
Study terminated by sponsor
Withdrawal by subject

7.1. Discontinuation of Study Intervention

Study intervention should be discontinued for the following reasons:

- Pregnancy (see Appendix 7 and Section 8.3.5)
- Other safety criteria (eg, hypersensitivity to the study intervention, failure to continue to meet randomization criteria)

Women who test positive for urine pregnancy test will NOT receive further treatment and will be discontinued from the study. They should complete study exit procedures and be followed up for pregnancy outcome. See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

[redacted]

7.2. Participant Discontinuation/Withdrawal From the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- See the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The study site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- The amount of blood collected from each participant throughout this 12-month study will be approximately 220 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- Blood samples may be stored for a maximum of 5 years following finalization of the study's final CSR. Samples will then be disposed.
- All assessments, including photography, must be completed after the participant removes their make-up (if wearing any) and before administration of study intervention.

8.1. Efficacy Assessments

8.1.1. Facial Wrinkle Scale With Photonumeric Guide (FWS)

Investigators' and participants' assessments of the severity of LCL at rest and maximum smile and investigators' assessments of the severity of GL at rest and maximum frown using the validated FWS, based on the following scale:

0 = None

1 = Mild

2 = Moderate

3 = Severe

The FWS with investigator-oriented instructions and the FWS with participant-oriented instructions will be provided by the sponsor to each study site. Both versions of the FWS provide photographic examples of LCL severity at rest and at maximum smile and GL severity at rest and maximum frown. Prior to enrolling participants, investigators and appropriate site personnel will be trained in grading LCL and GL severity using the FWS to ensure that severity is graded consistently at each site and across all sites.

[redacted]

Participants will also be provided standardized training by the study site personnel in grading LCL severity using the FWS with participant-oriented instructions to ensure that severity is scored consistently. Instructions on using the FWS will be provided prior to assessment. Mirrors will be used by the participants to aid in self-assessments.

Investigators and participants will assess LCL and investigators will assess GL severity using the FWS independently of each other, and these assessments will be the basis for several efficacy measures described in this section. The investigator and participant must grade the severity of LCL at the same time, first at rest, then at maximum smile, using the FWS. The investigator and participant must not discuss their results with each other. When completing the FWS, investigators and participants must rate the severity of LCL at rest prior to rating severity at maximum smile. The investigator must grade the severity of GL at rest prior to rating severity at maximum frown. See Appendix 9.1 for a sample FWS Patient Answer Sheet for LCL.

8.1.2. Facial Line Outcomes (FLO-11) Questionnaire and Facial Line Satisfaction Questionnaire (FLSQ) LCL Versions

Participant-reported LCL impact and satisfaction with study intervention will be assessed using the FLO-11 LCL version, and FLSQ baseline and follow-up LCL versions. Answers to the items on the questionnaires must come from the participant directly, not from family, friends, or the study site personnel. The questionnaires must be given to participants to complete in as quiet an area as possible. The instructions for completion of each of the PRO questionnaire will be reviewed with participants at the Day 1 visit, and participants must be alerted that they are expected to complete the PRO questionnaires at Day 1 and all future visits.

Upon completion of the questionnaires, the study site personnel must review them to assure completeness. The study site personnel must also confirm that each questionnaire is dated.

The participant questionnaires for a specific study visit must only be completed at that specific study visit. Therefore, if the participant refuses to complete any questionnaires at a particular visit, or if the study site personnel inadvertently forget to administer any questionnaires at a particular visit, no attempt must be made at any subsequent visit to administer the missed questionnaires. The study site personnel must also not attempt to correct any omissions, errors, or discrepancies on any questionnaires completed at any previous study visits.

- [redacted]

[redacted]

[redacted]

- [redacted]

8.2. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA.

8.2.1. Adverse events

The investigator will question the participant to ascertain whether any adverse events were experienced since the previous visit. Additionally, at treatment visits, the participants will be observed for ≥ 30 minutes following study intervention. All pertinent information regarding adverse events (ie, date of onset and stop, duration, outcome, severity, relationship to study intervention, action or treatment required) will be obtained and recorded in the source documents and appropriate eCRF page.

8.2.2. Physical Examination

Physical examination will be conducted at the Screening Visit and will include the investigator assessment of general appearance, HEENT, heart/cardiovascular, lungs, abdomen, extremities, back, musculoskeletal, lymphatic, and skin.

[redacted]

[redacted]

[redacted]

8.2.4. Vital Signs

- Pulse rate (beats per minute): Participants are to be seated for at least 2 minutes, and pulse rate will be counted over 60 seconds and recorded in the source document and eCRF as beats per minute.
- Blood pressure (mm Hg): Participants are to be seated for at least 2 minutes, and systolic/diastolic blood pressure will be measured.
- Respiration rate (breaths per minute): Participants are to be seated for at least 2 minutes, and breaths will be counted for 30 seconds and multiplied by 2.

8.2.5. Electrocardiograms

- All participants will undergo conventional 12-lead ECG using standardized equipment and electrode placement at the visits outlined in the SoA. Participants are to be in a semirecumbent position for at least 10 minutes prior to starting the tracing. During screening, a single ECG trace will be taken to assess entry eligibility.
- A qualified third-party vendor will read the ECGs and report the findings as normal, abnormal, or unable to evaluate.
- For screening ECGs, prespecified significant abnormal findings will be flagged as exclusion alerts, and a third-party vendor will generate an exclusion alert for the site and the sponsor. For all subsequent ECGs, a qualified third-party vendor will also report the appearance of any new, prespecified significant abnormal findings and generate a protocol alert for the site and the sponsor.
- The cardiologists will be blinded to participant study intervention assignments. If the ECG finding is abnormal, they will specify the abnormality or give a diagnosis, whenever it is possible. Electrocardiogram reports will be provided to the investigator and the sponsor via a secure portal within 24 hours of screening and within 72 hours for all other visits.
- Before study intervention, if the ECG finding is clinically significant, the investigator must capture the finding in the medical history eCRF. After study intervention, if the pre-existing finding becomes worse and is clinically significant or the new ECG finding is clinically significant, the investigator must capture the adverse event in the adverse event eCRF. Hard copies of the ECG tracings will be kept in the study files at the investigator's site.
- The ECG will be assessed for the following measures: heart rate, QRS duration, QT interval, QTcB interval, QTcF interval, ST segment, RR interval, PR interval, and qualitative results.

[redacted]

8.2.6. Hematology and Chemistry

- See Appendix 2 for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.
- Hematology and nonfasting blood chemistry assays will be performed by a central laboratory.
- During the Screening Period, the investigator or subinvestigator will assess the clinical significance of any values outside the reference ranges provided by the laboratory, and participants with abnormalities judged to be clinically significant will be excluded from the study.

8.2.7. Urine Pregnancy Test

Urine dipstick kits will be used to conduct pregnancy tests at the timepoints specified in the SoA, or more frequently at the investigator's discretion.

8.2.8. Suicidal Risk Monitoring

Suicidal risk monitoring is not applicable for this study.

8.3. Adverse Events and Serious Adverse Events

The definitions of an adverse event or SAE can be found in Appendix 3.

Adverse events will be reported by the participant.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an adverse event or SAE and remain responsible for following up adverse events that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section 7).

Adverse drug reactions for MT10109L have not been established. [redacted]

The following expected adverse drug reactions are based on BOTOX clinical trial data for the treatment of LCL and GL (Tables 8-1 and 8-2, respectively).

Table 8-1 Expected Adverse Reactions for Treatment of Lateral Canthal Lines

Expected Adverse Reactions[a]	Incidence
Eyelid oedema	1%

[a] Data are based on BOTOX lateral canthal lines clinical trial data (BOTOX Cosmetic US Package Insert, 2017)

[redacted]

Table 8-2 Expected Adverse Reactions for Treatment of Glabellar Lines

Expected Adverse Reactions[a]	Incidence
Eyelid ptosis	3%
Facial pain	1%
Facial paresis	1%
Muscular weakness	1%

[a] Data are based on BOTOX glabellar lines clinical trial data (BOTOX Cosmetic US Package Insert, 2017)

The adverse drug reactions of eyelid oedema, eyelid ptosis, facial pain, facial paresis, and muscular weakness with BOTOX usually are mild in severity, reversible, and have a low incidence. Therefore, no treatment for these reactions is recommended. If these reactions are moderate or severe, medical help should be sought as needed.

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

[redacted]

Medical occurrences that begin before the start of study intervention, but after obtaining informed consent will be recorded in the adverse event section of the eCRF.

All SAEs from the signing of the ICF until at least 12 weeks after the last administration of study intervention will be collected at the timepoints specified in the SoA (Section 1.3), and as observed or reported spontaneously by study participants.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek adverse event or SAE information after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

The method of recording, evaluating, and assessing causality of adverse events and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

[redacted]

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about adverse event occurrences.

8.3.3. Follow-up of Adverse Events and Serious Adverse Events

After the initial adverse event/SAE report, the investigator is required to proactively follow each participant who received study intervention at subsequent visits/contacts. All TEAEs/SAEs, including AESIs (see Section 8.3.6) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the adverse event or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any postmortem findings including histopathology.

New or updated information will be recorded in the originally completed eCRF.

The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ IECs, and investigators.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the investigator's brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

- Urine pregnancy testing will be conducted for women of childbearing potential prior to each study intervention and at the study exit visit. See Appendix 7 for detailed information on definition of women of childbearing potential, use of contraceptives, and pregnancy.
- To minimize the risk of pregnancy, all women of childbearing potential must agree to use a highly effective or acceptable contraception method (Appendix 7) consistently and correctly throughout the duration of the study. For participants of childbearing potential in Germany, only highly effective contraception methods are allowed for this study.
- Women who test positive for urine pregnancy test will NOT receive further treatment and will be discontinued from the study.
- Women who test positive for urine pregnancy test should complete end-of-study procedures and be followed up for pregnancy outcome.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 7.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) or genetic abnormalities (whether leading to an elective abortion or not) are considered SAEs.

[redacted]

8.3.7. Medication Errors

Medication error refers to any unintended error in the dosing and/or administration of the study intervention as per instructions in the protocol. Medication errors generally fall into 4 categories as follows:

- Wrong study intervention
- Wrong dose (including dosing regimen, strength, form, concentration, amount)
- Wrong route of administration
- Wrong participant (ie, not administered to the intended participant)

Medication errors include occurrences of overdose and underdose of the study intervention.

Overdose: Unintentional administration of a quantity of the study intervention given per administration or per day that is above the maximum recommended dose according to the

[redacted]

reference safety information or protocol for the study intervention or comparator as applicable. See Section 8.4 for information of treatment of overdose.

Underdose: Unintentional administration of a quantity of the study intervention given per administration or per day that is under the minimum recommended dose according to the reference safety information or protocol.

8.4. Treatment of Overdose

Overdose of MT10109L is a relative term and depends upon dose, site of injection, and underlying tissue properties. Signs and symptoms of overdose are not likely to be apparent immediately postinjection. Excessive doses may produce local or distant, generalized and profound neuromuscular paralysis.

Because MT10109L is administered as injections by physicians for this study, the chance of overdose is extremely low. Should accidental injection or oral ingestion occur or overdose be suspected, the participant should be medically monitored for up to several weeks for progressive signs or symptoms of systemic muscular weakness that could be local or distant from the site of injection, which may include ptosis, diplopia, dysphagia, dysarthria, generalized weakness, or respiratory failure. For GL or LCL, ptosis, diplopia, or vision blurred are known local effects of the toxin. These participants should be considered for further medical evaluation and appropriate medical therapy immediately instituted, which may include hospitalization.

If the musculature of the oropharynx and esophagus is affected, aspiration may occur, which may lead to development of aspiration pneumonia. If the respiratory muscles become paralyzed or sufficiently weakened, intubation and assisted respiration may be necessary until recovery takes place. Supportive care could involve the need for a tracheostomy and/or prolonged mechanical ventilation, in addition to other general supportive care.

In the event of an overdose, the investigator should educate the participant, monitor the course of overdose, contact the medical safety physician as needed, document the quantity of the excess dose, associated adverse events as well as the duration of the overdose in the eCRF.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers and Other Assessments

Immunogenicity Assessments

The presence of antidrug antibodies, including binding antibodies and neutralizing antibodies to MT10109L, will be assessed during the course of the study using validated assays.

Blood samples for immunogenicity testing will be collected from each participant at the Day 1 visit, and Day 30 and Day 90 after treatment. For any of the retreatments, blood samples for immunogenicity testing will be taken before eligible participants receive each retreatment [redacted]

A 2-stage assay approach will be used for the detection of binding antibodies against MT10109L and neutralizing antibodies against MT10109L in participants' serum. In Stage 1, serum samples will be screened for the presence of binding antibodies using the validated ELISA in a 3-tier format (screening, confirmation, and titering). The screen positive serum samples will be subsequently immunodepleted to confirm that the binding antibodies are specific to MT10109L and titered to assess the extent of antibodies present. [redacted]

8.9. Medical Resource Utilization and Health Economics

Medical resource utilization and health economics parameters are not evaluated in this study.

[redacted]

9. Statistical Considerations

9.1. Statistical Hypotheses

For US FDA:

The primary efficacy analysis will be performed on the ITT population, which consists of all randomized participants. The following hypotheses will be used to compare MT10109L 24 U and placebo:

- Null hypothesis: MT10109L 24 U and placebo are equally effective in reducing LCL severity at maximum smile as measured by the proportion of responders with ≥ 2-grade improvement from baseline based on both the investigator- and participant-rated FWS at Day 30.
- Alternative hypothesis: MT10109L 24 U and placebo are not equally effective in reducing LCL severity at maximum smile as measured by the proportion of responders with ≥ 2-grade improvement from baseline based on both the investigator- and participant-rated FWS at Day 30.

[redacted]

[redacted]

9.2. Sample Size Determination

Approximately 375 participants will be randomized into the study in a 2:2:1 ratio yielding approximately 150 participants in each of the MT10109L 24 U and 44 U groups and 75 participants in the placebo group in the first treatment period. The sample size of 375 allows for an adequate safety database of participants treated with MT10109L for these indications.

[redacted]

For the US FDA primary analysis, an estimated sample size of 214 participants will give a power of greater than 95% to detect a difference in responder rates between the MT10109L 24 U and placebo groups, assuming a 5% drop-out rate by Day 30. The MT10109L 24 U and placebo responder rates are assumed to be 25.7% and 1.3% respectively (based on the data from BOTOX Study 191622-098, LCL on maximum smile), where a responder is defined as having a ≥ 2-grade improvement from baseline on the FWS, assessed by both the investigator and participant at Day 30.

[redacted]

9.3. Populations for Analyses

Primary and secondary efficacy analyses for US FDA will be performed on the ITT population, consisting of all randomized participants.

[redacted]

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

[redacted]

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock and unblinding and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary, secondary, and exploratory endpoints. [redacted]

9.4.1. Efficacy Analyses

9.4.1.1. Primary Efficacy Endpoints

For the US FDA, the composite efficacy endpoints are the proportion of participants with ≥ 2-grade improvement from baseline on the FWS according to both investigator and participant assessments of LCL severity at maximum smile at Day 30 using the ITT population after the single IM injection of MT10109L or placebo in the LCL.

[redacted]

9.4.1.2. Primary Analyses

The primary efficacy analysis will be based on the comparison of LCL efficacy for MT10109L 24 U versus placebo at the primary timepoint of Day 30 of the first treatment period. The evaluation of the equality of the proportions of responders will be based on CMH test stratified by investigator-assessed baseline LCL severity at maximum smile. Relative risk and 95% CI for relative risk will be presented. Missing values will be imputed up to Day 180 using multiple imputation methods. SAS Proc MI procedure will be used to generate 5 imputation data sets. Seed for all Proc MI procedure is prespecified as [redacted]. Primary measures up to Day 180 for Treatment Cycle 1 will be imputed, and the imputation will be stratified by treatment group using the MCMC method. Although the MCMC method assumes multivariate normality, inferences based on multiple imputation can be robust to departures from the multivariate normality if the amount of missing information is not large. [redacted] The imputed values will then be rounded to integer values.

[redacted]

The following is a sample SAS code to impute missing data for FWS score.

[redacted]

by trtcd;

[redacted]

run;

Proc MIANALYZE procedure will be used to combine the 5 imputation data sets to generate the final results. For CMH, relative risk and corresponding variance will be used as input for Proc MIANALYZE. The p-value for testing the relative risk of MT10109L versus placebo (Col 1 risk from SAS output) equal to 1 will be presented. The relative risk in SAS output is a logit value, log of the output relative risk will be used as the input for Proc MIANALYZE procedure. A test for relative risk equal to 1 will be equivalent to a test of log relative risk equal to 0. The 95% CI (L, U) for relative risk will be used to calculate the variance for the relative risk [variance=((log(U)-log(L))/2*1.96)**2] using normal approximation.

For the CMH test, the Wilson-Hilferty transformation (Wilson 1931, O'Kelly 2014) will be used. Under the null hypothesis, the transformed statistic is approximately normally distributed:

$$\text{wh\_CMH}^{(m)} = \sqrt[3]{\frac{cmh^{(m)}}{k}} \sim \text{Normal}\left(1 - \frac{2}{9k}, \frac{2}{9k}\right)$$

Where $cmh^{(m)}$ is the chi-square statistics each with k degrees of freedom from m = 1, … . , M imputed datasets. In this case, k=1. This statistic will be passed to PROC MIANALYZE to obtain the combined p-value for CMH test.

[redacted]

[redacted]

Sensitivity analyses of the primary efficacy variables will be performed to establish their consistency and robustness as well as to further characterize the extent of participants' responses. Observed data analysis, missing as nonresponder analysis, and stratification based on both baseline LCL severity and site analysis are planned for sensitivity analyses.

9.4.1.3. Secondary Efficacy Endpoints

For US FDA:

- The duration of LCL treatment effect, estimated as the median time to return to *moderate* or *severe* LCL at maximum smile in participants who achieved a rating of ≥ 2 grade improvement from baseline in LCL severity at maximum smile at Day 30 according to investigator assessments using the FWS
- The proportion of responders for investigator assessments of LCL severity at maximum smile using the FWS, where a responder is defined as achieving a ≥ 2-grade improvement from baseline at maximum smile at Day 30
- The proportion of responders for investigator assessments of LCL severity at maximum smile using the FWS, where a responder is defined as achieving a rating of *none* or *mild* at maximum smile at Day 30
- The proportion of participants reporting *mostly satisfied/very satisfied* on the FLSQ follow-up version Item 5 for LCL at Day 60
- The proportion of responders for investigator assessments of LCL severity at rest using the FWS among participants who were rated at least *mild* at rest at baseline, where a responder is defined as achieving a ≥ 1-grade improvement from baseline at Day 30

[redacted]

[redacted]

[redacted]

9.4.1.4. Secondary Analyses

All secondary variables will be evaluated for all study visits with the prespecified primary timepoint given above, except for duration of treatment effect. The duration of LCL treatment effect is defined as the time to return to moderate or severe LCL at maximum smile in those participants achieving a responder status (for US FDA, responder is defined as participants who achieved a rating of ≥ 2-grade improvement from baseline in LCL severity at maximum smile; [redacted] Day 30 according to investigator assessments using the FWS. It will be estimated using the Kaplan-Meier method. The 25th percentile, median, and 75th percentile estimates will be calculated. Duration of effect is a key secondary efficacy variable; however, as it is not part of the hypothesis testing, it will not be included in the hierarchical testing strategy for multiplicity control.

[redacted]

The proportion of responders will be analyzed using the CMH test stratified by baseline LCL severity at maximum smile as assessed by the clinician (investigator or subinvestigator). The continuous variables and ordinal variables will be analyzed using ANCOVA with treatment as the main effect, baseline LCL severity, and corresponding baseline value as factors.

[redacted]

9.4.1.5. Exploratory Efficacy Endpoints

[redacted], analyses for exploratory efficacy endpoints will be performed on the ITT population.

[redacted]

[redacted]

[redacted]

9.4.1.6. Exploratory Efficacy Analyses

The proportion of responders will be analyzed using the CMH test [redacted]

9.4.2. Safety Analyses

The safety analysis will be performed using the safety population and are fully defined in the SAP. The safety parameters will include:

- Adverse events
- [redacted]
- Vital signs
- Electrocardiogram
- Immunogenicity analyses
- Hematology and chemistry laboratory tests

9.4.2.1. Adverse Events

An adverse event will be considered a TEAE if:

- The adverse event began on or after the date of the first dose of study intervention; or
- The adverse event was present before the date of the first dose of study intervention, but increased in severity or became serious on or after the date of the first dose of study intervention

[redacted]

[redacted]

An adverse event will be considered a TESAE if it is a TEAE that additionally meets any SAE criteria.

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

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

If more than 1 adverse event is coded to the same preferred term for the same participant, the participant will be counted only once for that preferred term using the most severe and most related occurrence for the summarizations by severity and by relationship to study intervention.

The number and percentage of participants reporting TEAEs that are included in the PDSOT term list will be tabulated by study intervention. The PDSOT term list will be provided by the MSP.

The PDSOT will be reviewed by the MSP in a timely fashion for monitoring severity, frequency, and trending.

Summary tables will be provided for participants with SAEs and participants with adverse events leading to discontinuation if 5 or more participants reported such events. Listings of all adverse events, SAEs, and adverse events leading to discontinuation by participant will be presented.

The definitions of an adverse event and SAE can be found in Appendix 3.

9.4.2.2. Vital Signs

Descriptive summaries (n, mean, SD, median, minimum, and maximum) of actual values and changes from baseline will be calculated for vital signs (systolic and diastolic blood pressure, pulse and respiration rate). These summaries will be presented by study intervention and by visit.

9.4.2.3. Electrocardiograms

Descriptive statistics for ECG parameters (eg, heart rate, QRS duration, QT interval, QTc intervals, RR interval, and PR interval) at baseline, and changes from baseline at all postbaseline timepoints will be presented by study intervention and by visit. For each parameter, only participants who had both baseline postbaseline assessments will be included in the summary. QTc interval will be calculated using both Bazett ($QTcB = QT/[RR]^{1/2}$) and Fridericia ($QTcF = QT/[RR]^{1/3}$) corrections; if RR is not available, it will be replaced with 60/heart rate in the correction formula.

Data listings, which include ECG basic parameters and ECG abnormalities, will be produced.

9.4.2.4. Hematology/Chemistry Laboratory Testing

Descriptive statistics (n, mean, SD, median, minimum, and maximum) for clinical laboratory values at baseline and change from baseline at postbaseline visits will be summarized in SI units by study intervention and by visit.

9.4.3. Other Analyses

9.4.3.1. Immunogenicity Analyses

Immunogenicity results, manifested as the presence of binding antibodies and neutralizing antibodies to MT10109L, will be summarized in a table.

9.5. Interim Analyses

No interim analysis is planned.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH/ISO GCP guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, investigator's brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the overall conduct of the study at the site and adherence to requirements of applicable local regulations, for example 21 CFR, ICH guidelines, the IRB/IEC, and European regulation 536/2014 for clinical studies (if applicable)

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Participants who are rescreened are required to sign a new ICF.

10.1.4. Data Protection

- Participants will be assigned a unique identifier. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by clinical quality assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Posting Clinical Study Data

- Study data and information may be published in nonpromotional, peer-reviewed publications either by or on behalf of the sponsor.
- Clinical study reports, safety updates, and annual reports will be provided to regulatory authorities as required.
- Company-sponsored study information and tabular study results will be posted on the US National Institutes of Health's website www.ClinicalTrials.gov and other publicly accessible sites.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or eCRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator as stated in the clinical trial agreement. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study.
- Definition of what constitutes source data can be found in Section 4.0 of ICH E6, Good Clinical Practice: Consolidated Guidance and must follow ALCOA, ie, records must be attributable, legible, contemporaneous, original, and accurate.

10.1.8. Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

[redacted]

10.1.10. Compliance with Protocol

The investigator is responsible for compliance with the protocol at the investigational site and will ensure the availability of appropriate study personnel and compliance with GCP regulations and procedures. Trainings are provided by the sponsor to discuss the protocol procedures and study requirements. A representative of the sponsor will make frequent contact with the investigator and his/her research staff and will conduct regular monitoring visits at the site to review participant and study intervention accountability records for compliance with the protocol. Protocol deviations will be discussed with the investigator upon identification. The use of the data collected for the participant will be discussed to determine if the data are to be included in the analysis. The investigator will enter data that may be excluded from analysis as defined by the protocol deviation specifications. Significant protocol deviations will be reported to the IRB/IEC according to the IRB/IEC's reporting requirements.

[redacted]

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 10-1 will be performed by the central laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 10-1 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters	
Hematology	Platelets RBC count Hemoglobin Hematocrit RBC morphology	WBC count with differential (absolute): Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry	BUN Potassium AST Total, direct and indirect bilirubin Creatinine Sodium ALT Total protein	Glucose Calcium Alkaline phosphatase Chloride, albumin Magnesium Phosphorus Bicarbonate (carbon dioxide content) Uric acid

Investigators must document their review of each laboratory safety report.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

[redacted]

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease); for example:
  - The test result is associated with accompanying symptoms, and/or
  - The test result requires additional diagnostic testing or medical/surgical intervention, and/or
  - The test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or

[redacted]

- The test result is considered to be an AE by the investigator or sponsor.

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE or SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AEs or SAEs if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.
- The disease/disorder being studied or expected progression, signs, or symptoms (clearly defined) of the disease/disorder being studied, unless more severe than expected for the participant's condition
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

Definition of SAE

SAEs must meet both the AE criteria described above and the seriousness criteria listed below.

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life threatening The term *life threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or intervention that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. Hospitalization for elective intervention of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive intervention in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and Follow-Up of AEs and/or SAEs

AE and SAE Recording

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE or SAE information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor in lieu of completion of the AE or SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

MILD	A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
MODERATE	A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
SEVERE	A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

An event is defined as *serious* when it meets at least one of the predefined outcomes as described in the definition of an SAE/SADE, NOT when it is rated as severe.

Assessment of Causality
• The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE. • A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. • The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment. • For each AE or SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE or SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.** • The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Reporting of SAEs

SAE Reporting
[redacted] [redacted] • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE form, sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE form within the designated reporting time frames. • [redacted]

[redacted]

10.4. Appendix 4: Abbreviations

AESI	adverse event of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BoNT/A	botulinum toxin type A
BUN	blood urea nitrogen
CFL	crow's feet lines
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CMH	Cochran-Mantel-Haenszel
CONSORT	Consolidated Standards of Reporting Trials
DVD	digital versatile disc
ECG	electrocardiogram
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
EU	European Union
FDA	US Food and Drug Administration
FHL	forehead lines
FLO-11	11-Item Facial Line Outcomes questionnaire
FLSQ	Facial Line Satisfaction Questionnaire
FSH	follicle-stimulating hormone
FWS	Facial Wrinkle Scale With Photonumeric Guide
GCP	Good Clinical Practice
GL	glabellar lines
HEENT	head, eyes, ear, nose, and throat
HIPAA	Health Insurance Portability and Accountability Act
HRT	hormonal replacement therapy
IB	investigator's brochure
ICF	informed consent form

MT10109L	
ICH	International Conference on Harmonisation
IEC	institutional ethics committee
IM	intramuscular
IND	investigational new drug application
IRB	institutional review board
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IWRS	interactive web response system
LCL	lateral canthal lines
LD_{50}	median lethal intraperitoneal dose
LLN	lower limit of normal value provided by the laboratory
MCMC	Markov chain Monte Carlo
mITT	modified intent-to-treat
MSP	medical safety physician
PDSOT	possible distant spread of toxin
PRO	patient-reported outcome
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SI	Le Système International d'Unités (International System of Units)
SoA	schedule of activities
SUSAR	serious adverse reactions
TCA	trichloroacetic acid
U	unit
UFL	upper facial lines
ULN	upper limit of normal value provided by the laboratory
WBC	white blood cell
WOCBP	woman of childbearing potential

10.5. Appendix 5: Standard Discontinuation Criteria

CDISC Submission Value	CDISC Definition
Adverse event	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any 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. For further information, see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (modified from ICH E2A) Synonyms: side effect, adverse experience. See also serious adverse event, serious adverse experience. (CDISC glossary)
Completed	To possess every necessary or normal part or component or step; having come or been brought to a conclusion (NCI)
Death	The absence of life or state of being dead (NCI)
Disease relapse	The return of a disease after a period of remission
Failure to meet randomization criteria	An indication that the subject has been unable to fulfill/satisfy the criteria required for assignment into a randomized group
Lack of efficacy	The lack of expected or desired effect related to a therapy (NCI)
Lost to follow-up	The loss or lack of continuation of a subject to follow-up
Noncompliance with study drug	An indication that a subject has not agreed with or followed the instructions related to the study medication (NCI)
Other	Different than the one(s) previously specified or mentioned (NCI)
Physician decision	A position, opinion or judgment reached after consideration by a physician with reference to subject (NCI)
Pregnancy	Pregnancy is the state or condition of having a developing embryo or fetus in the body (uterus), after union of an ovum and spermatozoon, during the period from conception to birth. (NCI)
Progressive disease	A disease process that is increasing in extent or severity (NCI)

[redacted]

CDISC Submission Value	CDISC Definition
Protocol deviation	An event or decision that stands in contrast to the guidelines set out by the protocol (NCI)
Recovery	A healing process and/or an outcome implying relative health. The term is typically used in the context of direct and indirect effects of sickness or injury. (NCI)
Screen failure	The potential subject who does not meet one or more criteria required for participation in a trial
Site terminated by sponsor	An indication that a clinical study was stopped at a particular site by its sponsor (NCI)
Study terminated by sponsor	An indication that a clinical study was stopped by its sponsor (NCI)
Technical problems	A problem with some technical aspect of a clinical study, usually related to an instrument (NCI)
Withdrawal by parent/guardian	An indication that a study participant has been removed from the study by the parent or legal guardian
Withdrawal by subject	An indication that a study participant has removed itself from the study (NCI)

10.6. Appendix 6: Study Tabular Summary

Parameter Group	Parameter	Value
Trial information	Trial Title	A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study to Evaluate the Safety and Efficacy of MT10109L (NivobotulinumtoxinA) for the Treatment of Lateral Canthal Lines With or Without Concurrent Treatment of Glabellar Lines
	[redacted]	[redacted]
	Trial Phase Classification	Phase 3
	Trial Indication	Lateral Canthal Lines
	Trial Indication Type	Treatment
	Trial Type	Efficacy Safety
	[redacted]	[redacted]
	Planned Country of Investigational Sites	United States, Canada, European Union
	Planned Number of Participants	375
	FDA-Regulated Device Study	No
	FDA-Regulated Drug Study	Yes
	Pediatric Study	No
Participant information	Diagnosis Group	Moderate to severe lateral canthal lines at maximum smile and moderate to severe glabellar lines at maximum frown
	Healthy Participant Indicator	No
	Planned Minimum Age of Participants	18
	Planned Maximum Age of Participants	Not applicable
	Sex of Participants	Both
	Stable Disease Minimum Duration	Not applicable

[redacted]

Parameter Group	Parameter	Value
Treatments	Investigational Therapy or Treatment	MT10109L (nivobotulinumtoxinA)
	Intervention Type	Drug
	Pharmacological Class of Invest. Therapy	NivobotulinumtoxinA
	Dose per Administration	24 U administered into 6 sites (0.1 mL per injection) in the bilateral LCL areas or 44 U administered as 11 (0.1 mL) injections into 6 sites in the bilateral LCL areas and 5 sites in the glabellar complex.
	[redacted]	[redacted]
	[redacted]	[redacted]
	Route of Administration	Intramuscular
	Current Therapy or Treatment	Not applicable
	Added on to Existing Treatments	No
	Control Type	Placebo
	Comparative Treatment Name	Not applicable
Trial design	Study Type	Interventional
	Intervention Model	Parallel
	Planned Number of Arms	3
	Trial is Randomized	Yes
	Randomization Quotient	2:2:1
	Trial Blinding Schema	Double-blind
	Stratification Factor	By baseline LCL severity at maximum smile assessed by the clinician (investigator or subinvestigator) using the FWS
	Adaptive Design	No
	Study Stop Rules	Not applicable

10.7. Appendix 7: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

Female Participants

In Germany, female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 10-2.

In other countries, female participants of childbearing potential are eligible to participate if they agree to use a highly effective or acceptable method of contraception consistently and correctly as described in Table 10-2 and Table 10-3.

Table 10-2 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of < 1% per year when used consistently and correctly*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • Oral • Intravaginal • Transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent[a]
Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • IUD • IUS • Etonogestrel implant (ie, Nexplanon®) Bilateral tubal occlusion Intrauterine copper contraceptive (ie, ParaGard®)
Vasectomized Partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual Abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

Table 10-3 Acceptable Contraceptive Methods

Acceptable Methods *Acceptable birth control methods that result in a failure of more than 1% per year include:* • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action • Male or female condom with or without spermicide • Cap, diaphragm, or sponge with spermicide • Nonhormonal intrauterine device • A combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods.

Pregnancy Testing:

- Pregnancy testing, with a sensitivity of 25 mIU/mL, will be performed according to instructions provided in the pregnancy test kit.
- WOCBP should only be included after a confirmed menstrual period and a negative urine pregnancy test at Day 1 and, if a participant meets retreatment criteria, a negative urine pregnancy test prior to retreatment.
- Additional pregnancy testing is not required during the study intervention period but can be performed at the investigator's discretion.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

Collection of Pregnancy Information:

Female Participants Who Become Pregnant

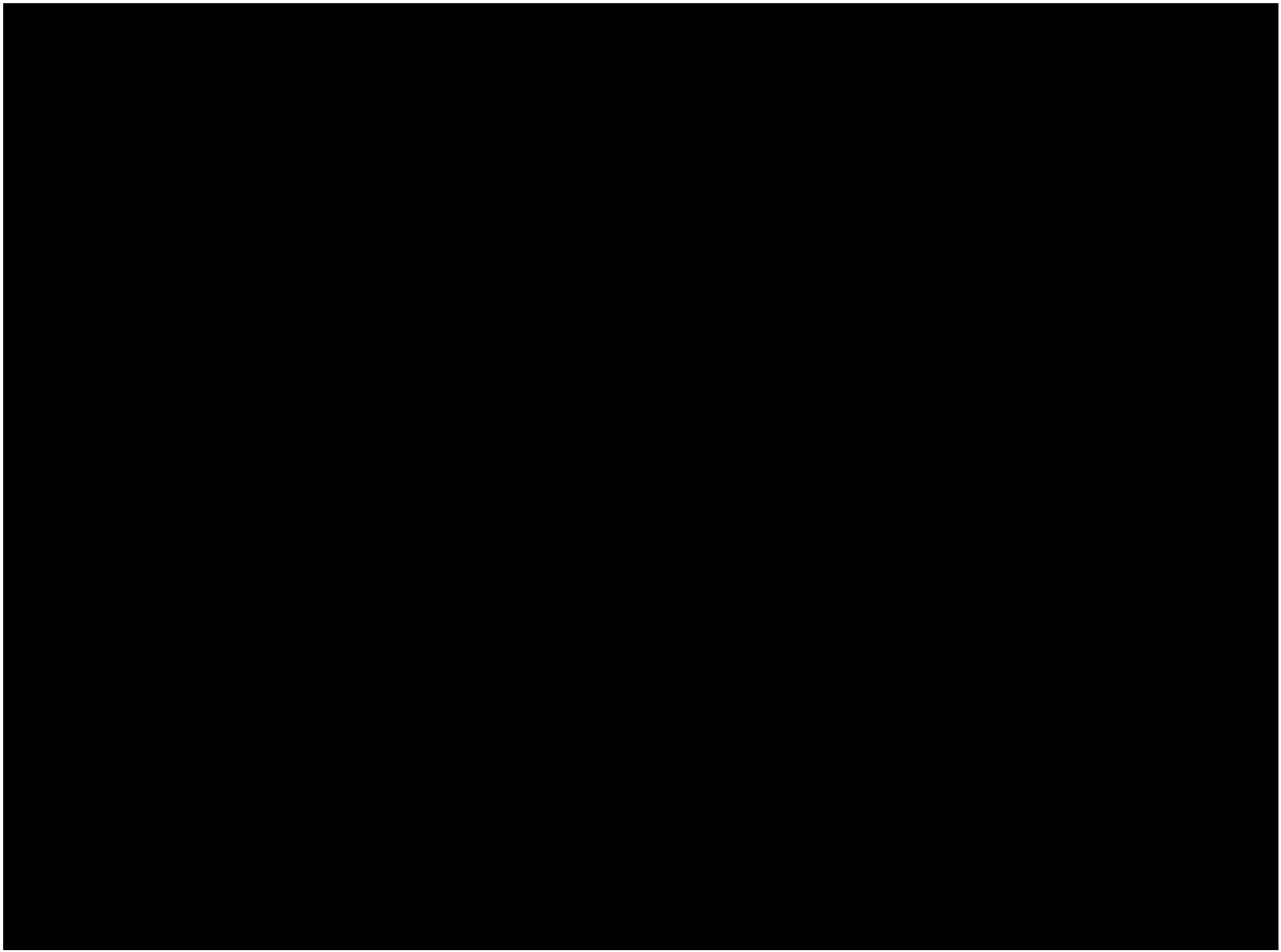
- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication will be reported as an AE or SAE. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) or genetic abnormalities (whether leading to an elective abortion or not) are always considered to be SAEs and will be reported as such. Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention and be withdrawn from the study.

[redacted]

[redacted]

[redacted]

[redacted]



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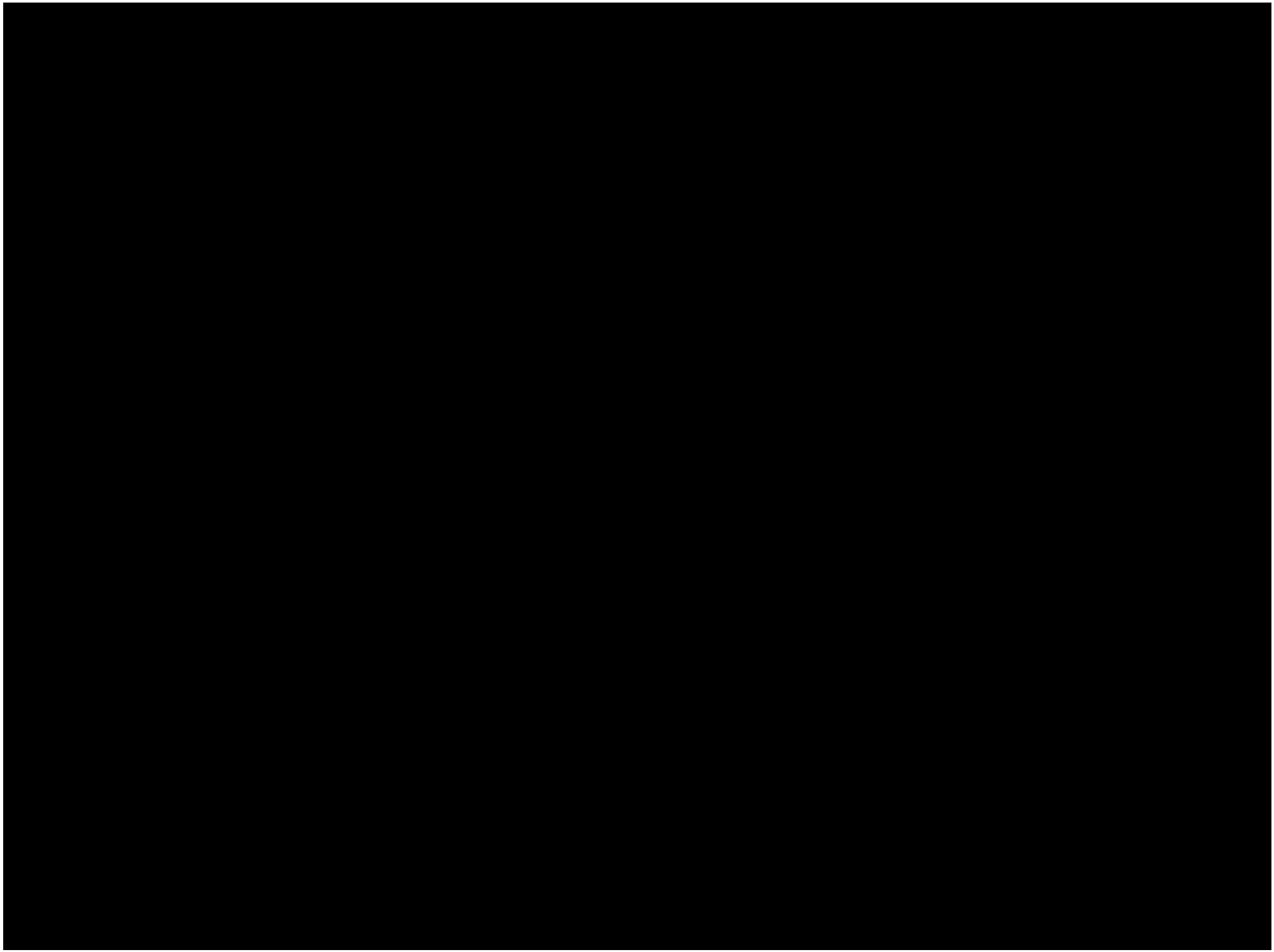

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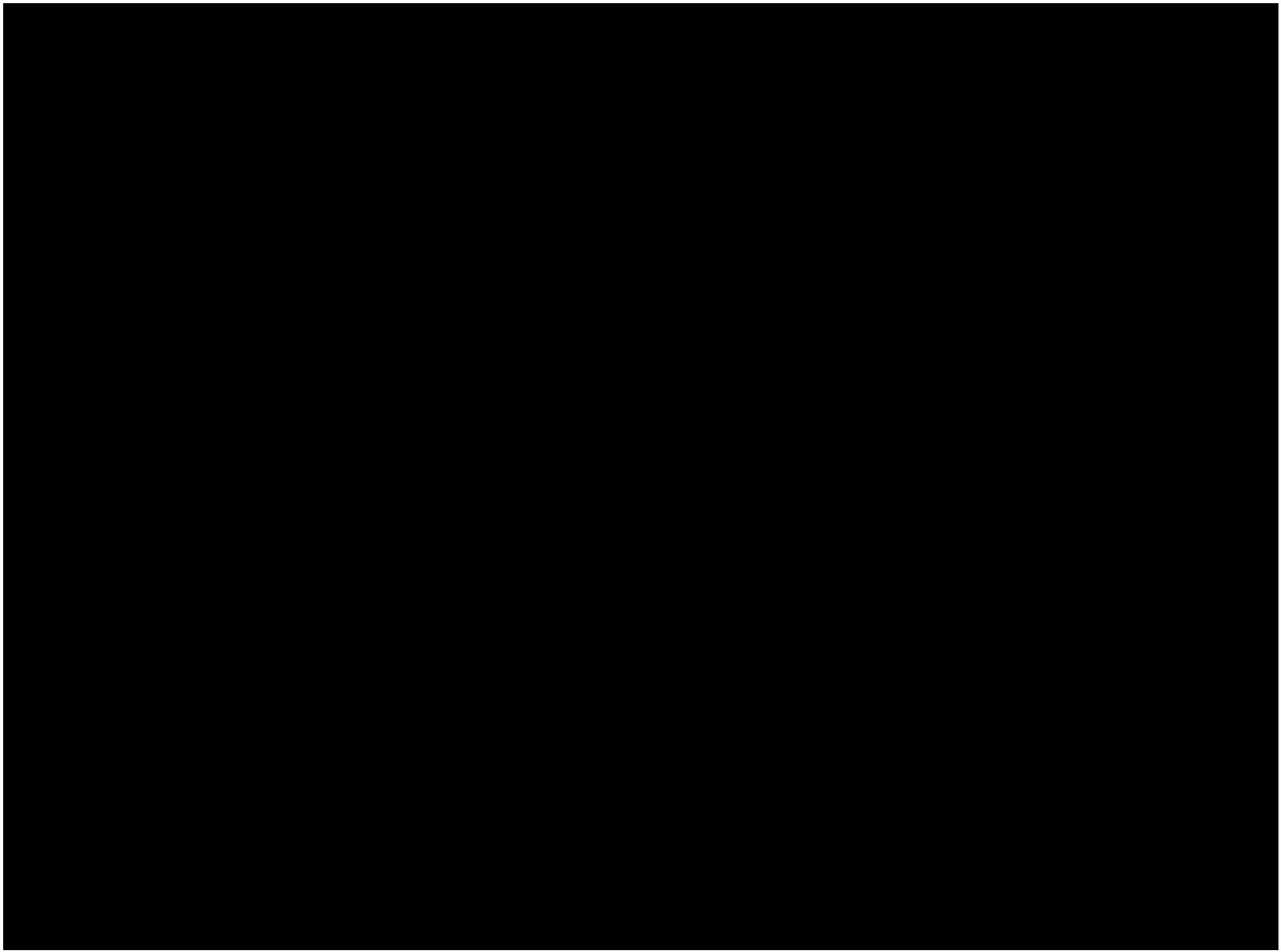

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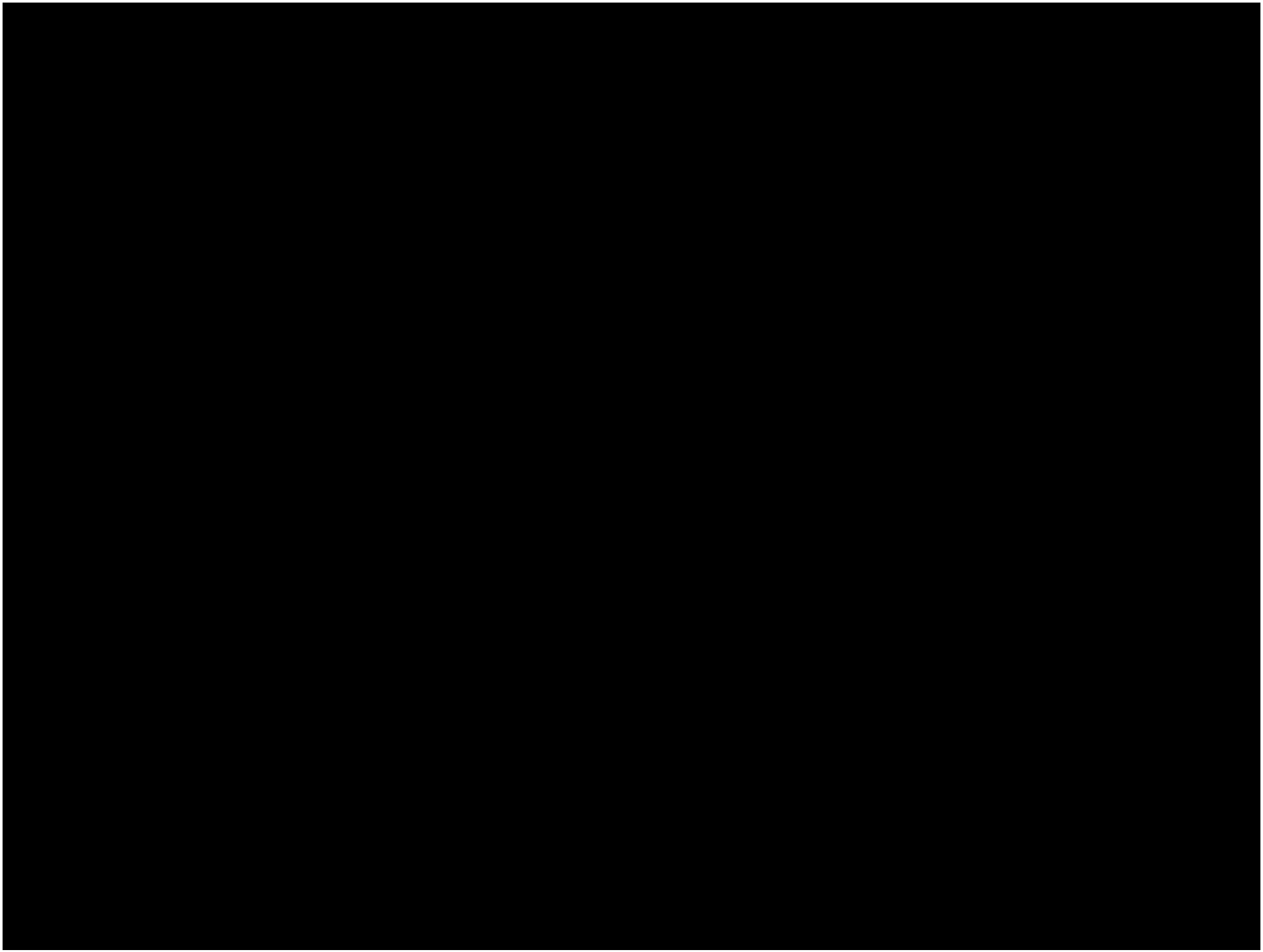

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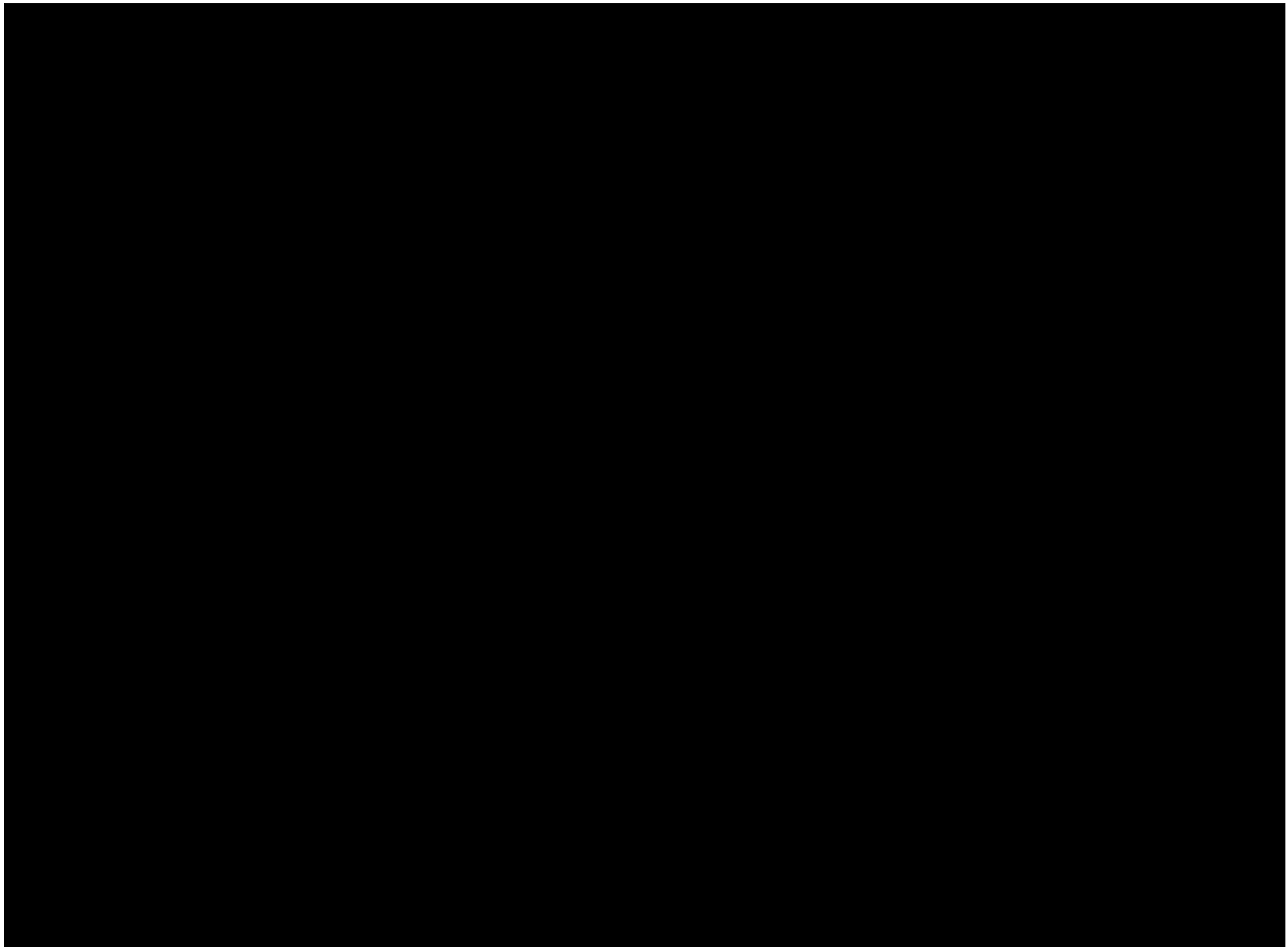

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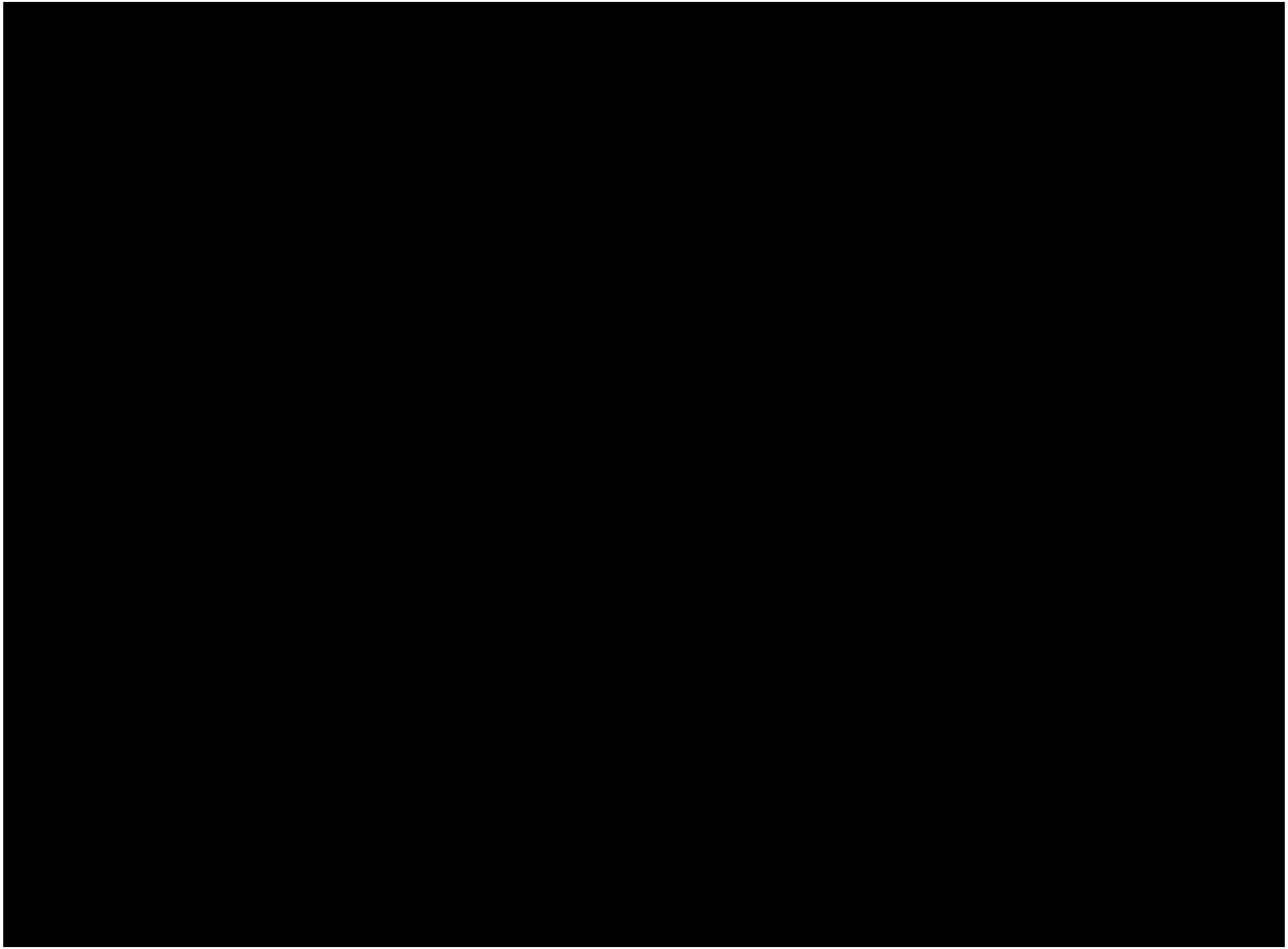

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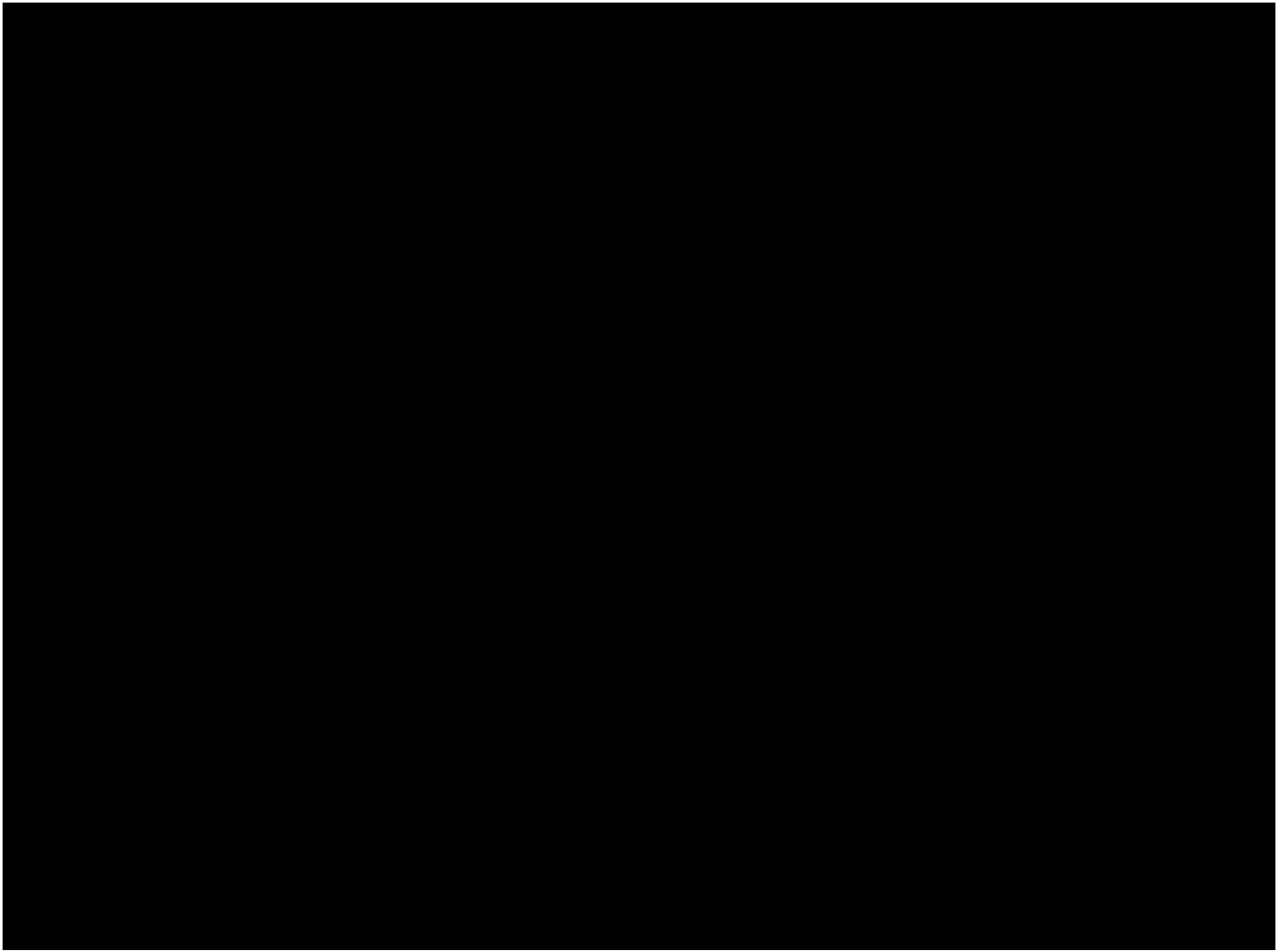

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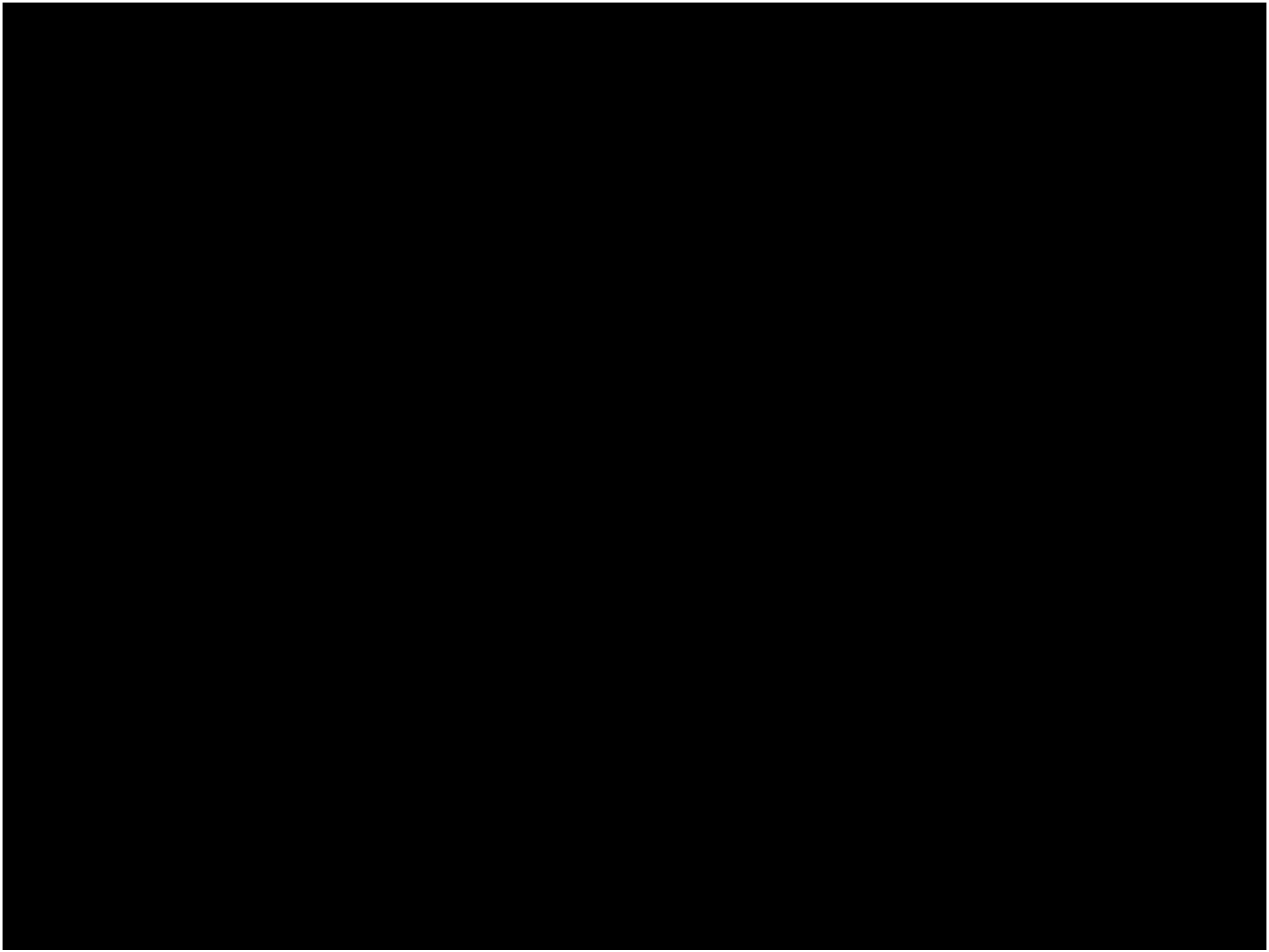

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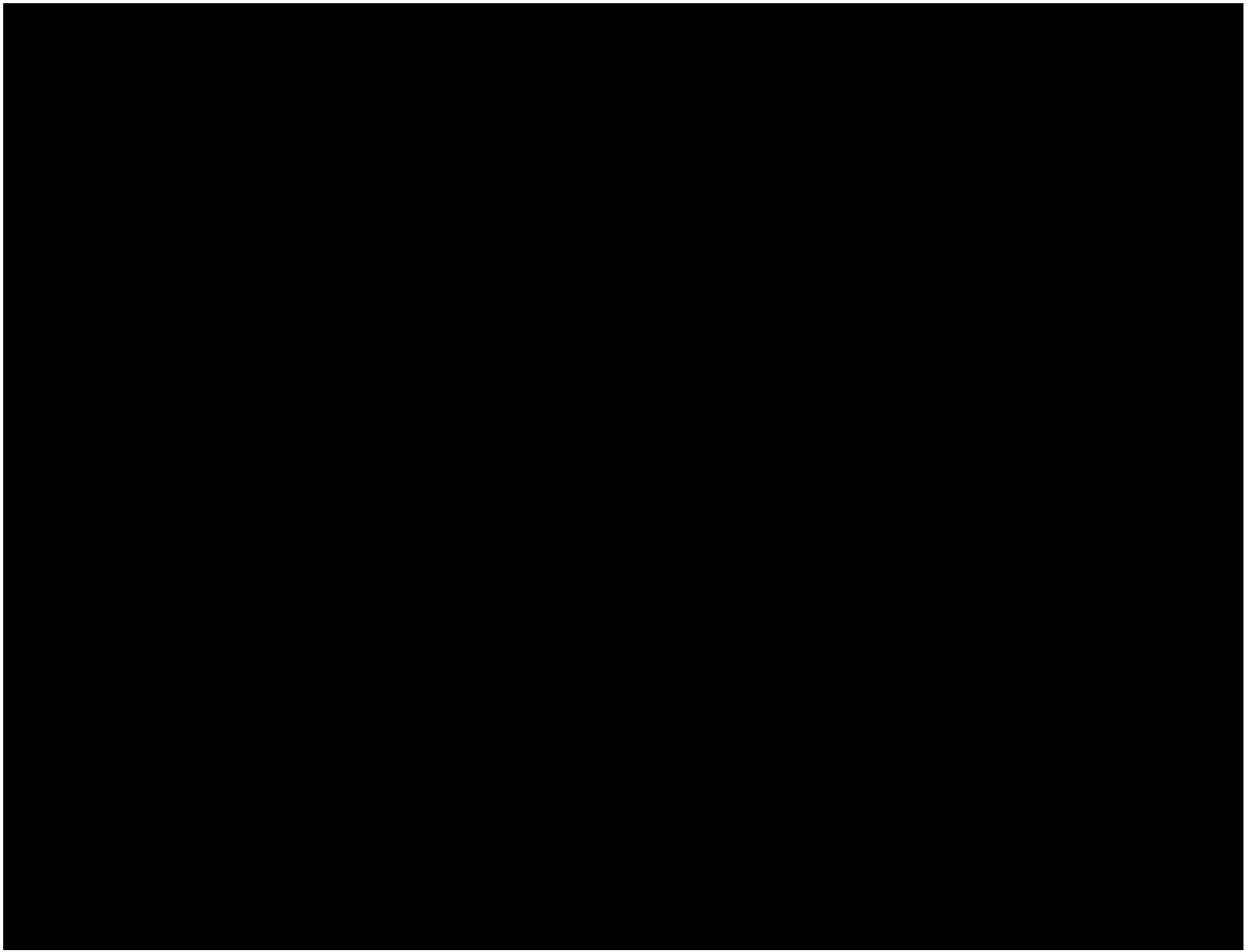

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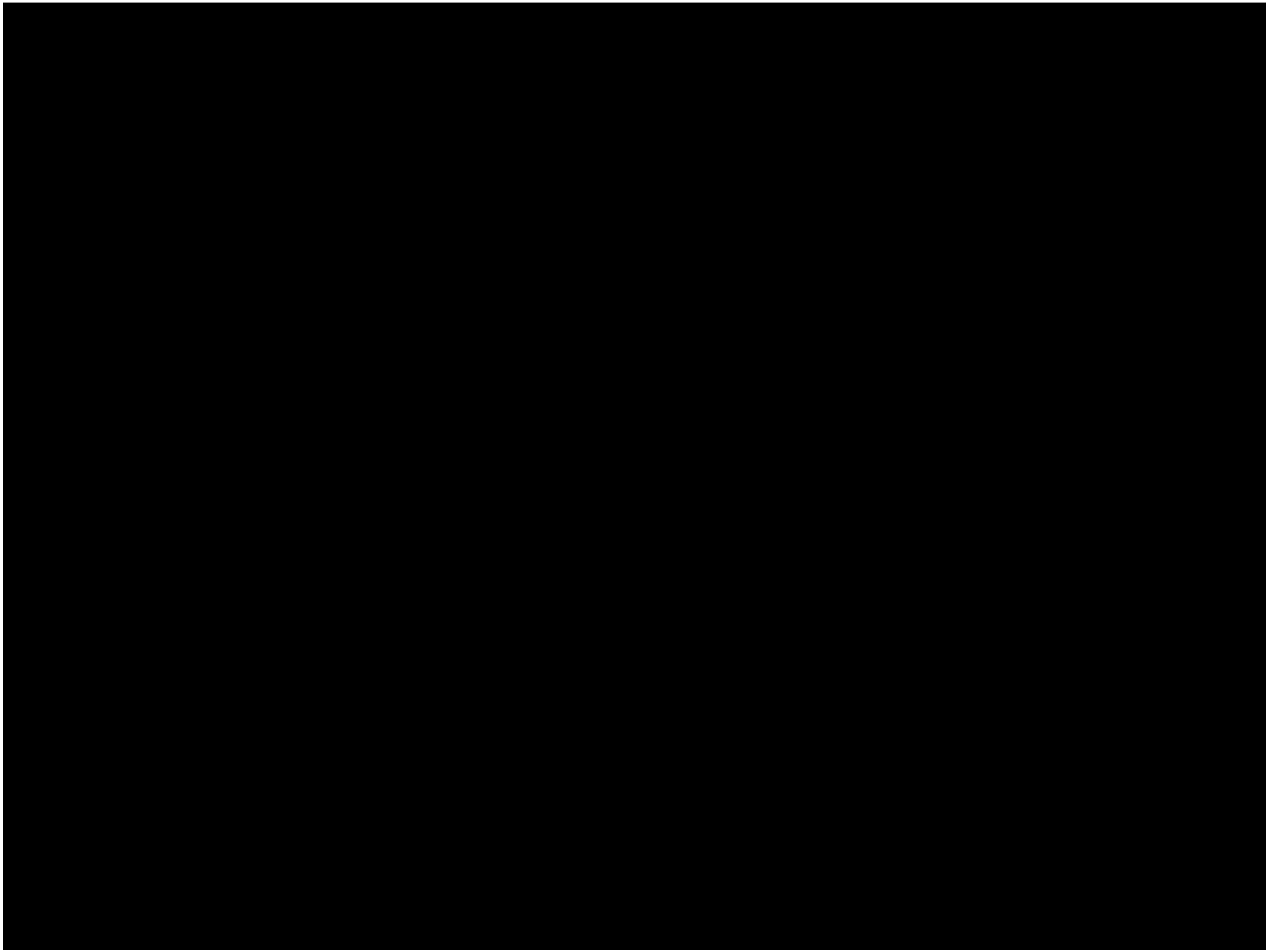

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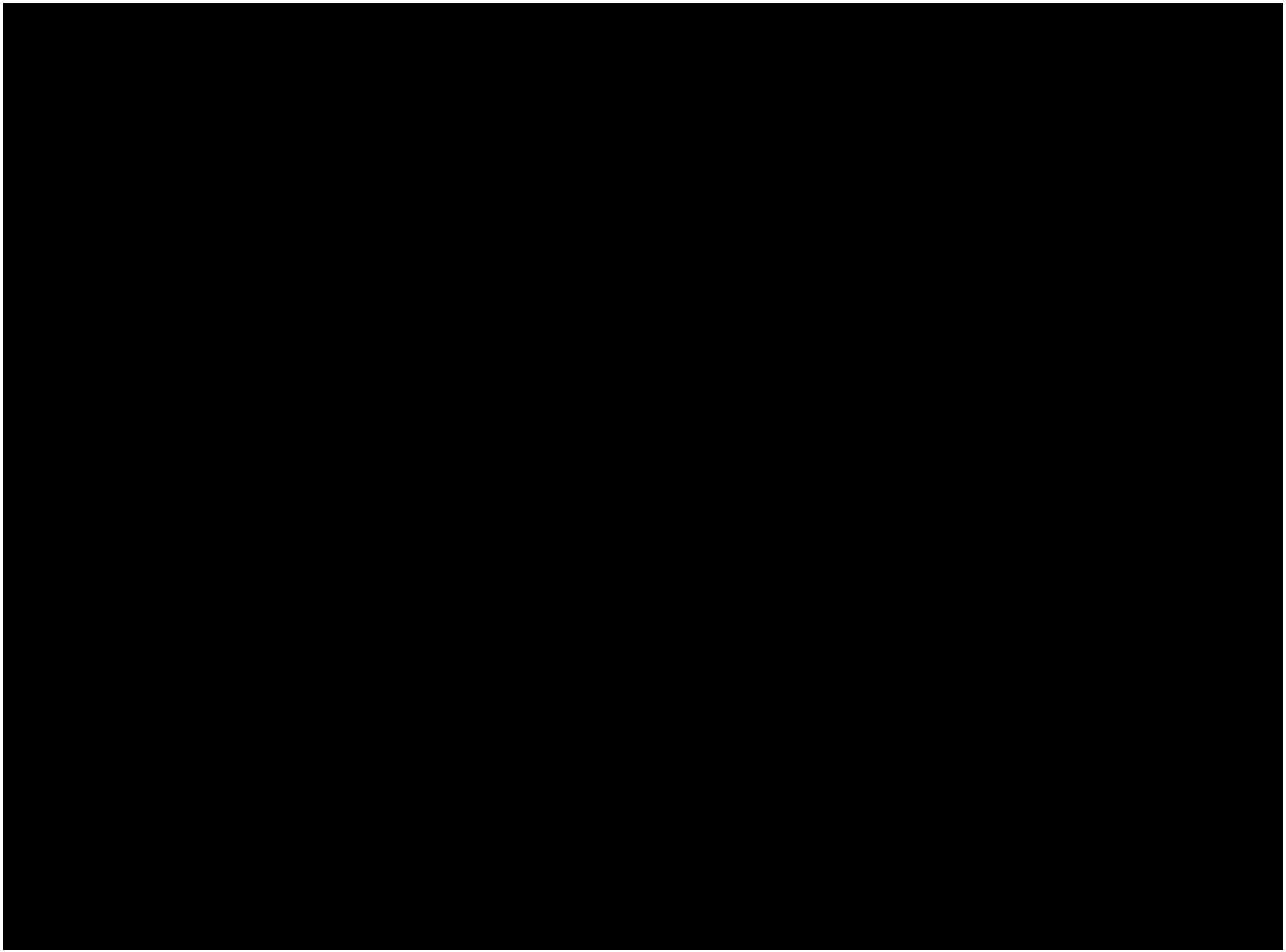

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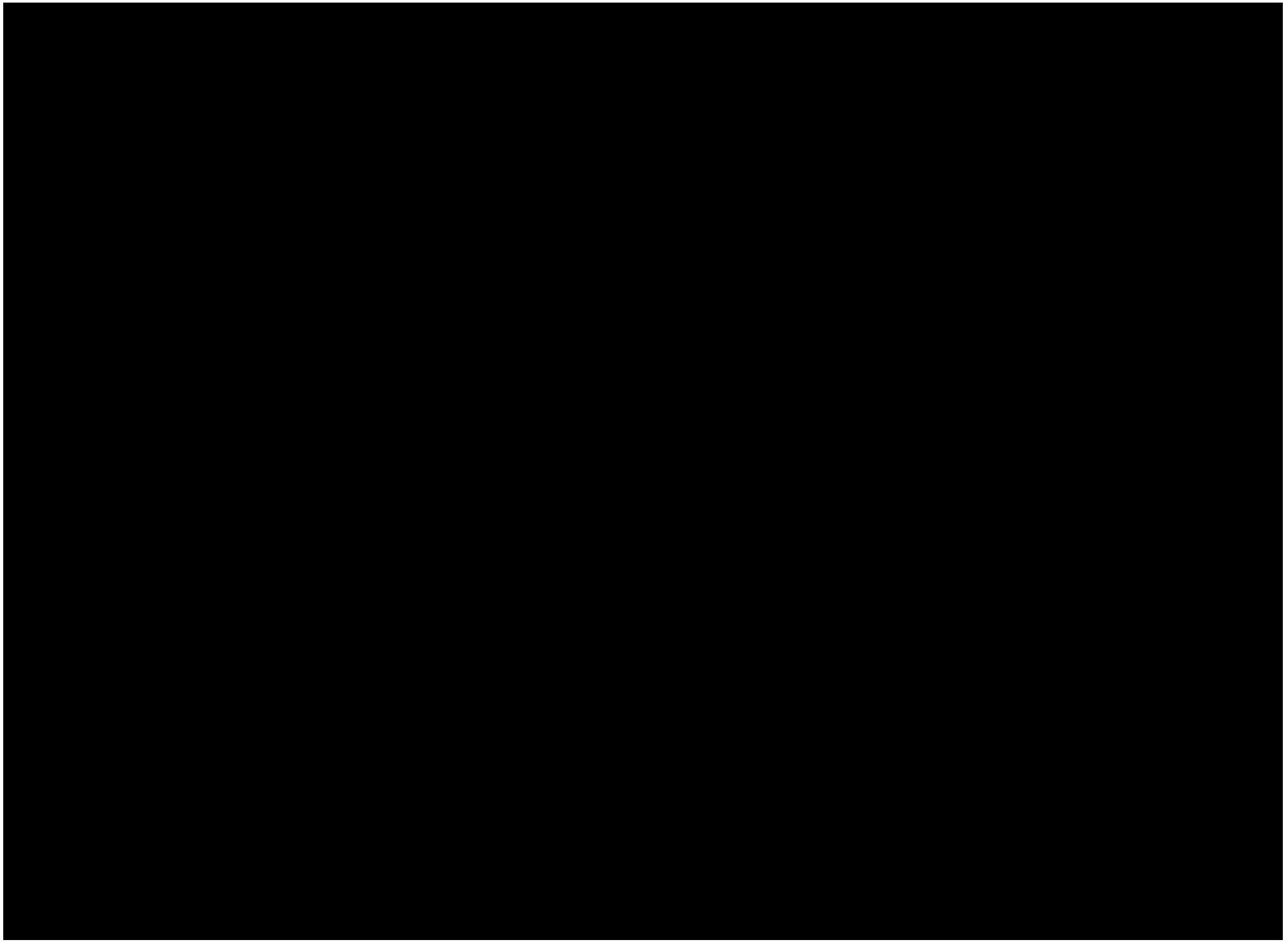

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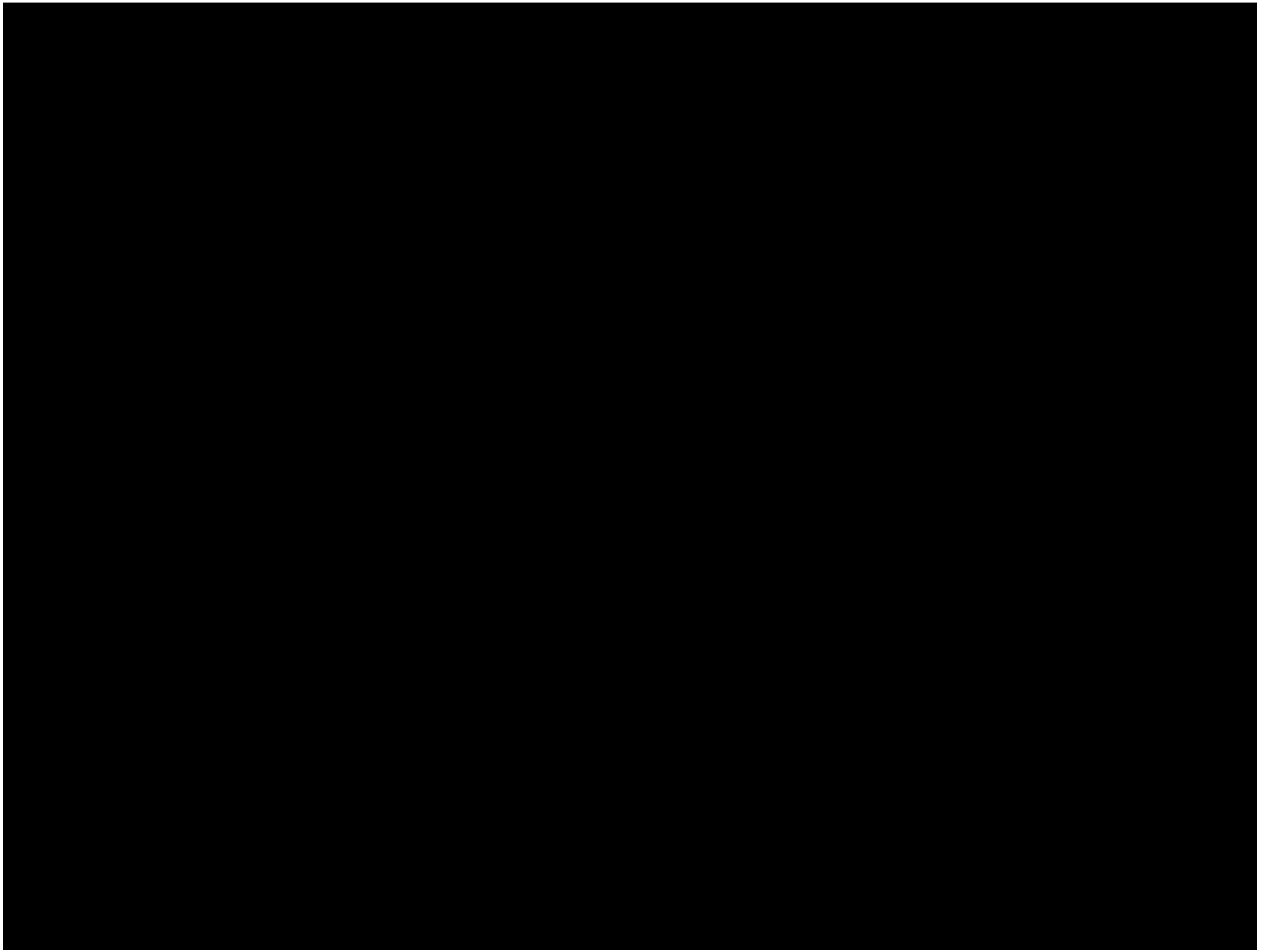

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10.10. Appendix 10: Protocol Amendment History

The protocol amendment summary of changes table for the current amendment is located directly before the table of contents.

Amendment 1 (August 2018)

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study. The editorial nature of this amendment is intended to provide clarity of information throughout the document.

Overall Rationale for the Amendment:

The overall rationale for the changes implemented in the protocol amendment were administrative in nature.

Section Number and Name	Description of Change	Brief Rationale
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
2.3/Benefit/ Risk Assessment	Separated "hypersensitivity" from other events	Hypersensitivity was associated with the treatment of masseter muscle hypertrophy, not glabellar lines
Throughout	Minor editorial revisions	Minor, therefore have not been summarized

Amendment 2 (November 2018)

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

[redacted]

Overall Rationale for the Amendment:

The overall rationale for the change implemented in the protocol was administrative in nature.

Section No. and Name	Description of Change	Brief Rationale
[redacted]	[redacted]	Administrative
8.8 Biomarkers and Other Assessments	Changed BOTOX to MT10109L	Editorial

Amendment 3 (March 2019)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The primary purpose of this protocol amendment was to integrate feedback and recommendations from health authorities and improve clarity of study processes as summarized below.

Section No. and Name	Description of Change	Brief Rationale
1.1 (Synopsis), 3 (Objectives and Endpoints), 9.4.1.1 (Primary Efficacy Endpoints), and 9.4.2 (Safety Analyses)	Clarified the primary objective and endpoint, added secondary objectives, and secondary safety endpoints	Updated per health authority feedback
1.1 (Synopsis), 3 (Objectives and Endpoints), and 9.4.1.3 (Secondary Efficacy Endpoints)	Added new secondary efficacy endpoints	New addition
[redacted]	[redacted]	[redacted]
1.1 (Synopsis) and 4.1 (Overall Design)	Added statement that there will be individual variability in time to meet retreatment criteria	Improve clarity
[redacted]	[redacted]	[redacted]

[redacted]

Section No. and Name	Description of Change	Brief Rationale
[redacted]	[redacted]	[redacted]
3 (Objectives and Endpoints)	Added statement to provide additional detail on exploratory endpoints	Updated per recommendation by health authority
4.1 (Overall Design)	Deleted statement about minimum requirement for the number of study participants at each study site	Consistent with the new protocol template
5 (Study Population)	Added information on the participant recruitment process	Updated per recommendation by health authority
5.4 (Screen Failures)	Rescreening criteria were clarified	Improve clarity
6.1.2 (Instructions for Use and Administration)	Added text to clarify required qualification and training of physicians	Updated per recommendation by health authority
8 (Study Assessments and Procedures)	Updated the amount of blood collected during the study for each participant	Update
8 (Study Assessments and Procedures)	Added information on storage periods and point of time of destruction of biological samples	Updated per recommendation by health authority
8.3.1 (Time Period and Frequency for Collecting	Added text to clarify that collection of adverse events at follow-up visits only	Improve clarity

Section No. and Name	Description of Change	Brief Rationale
Adverse Event and Serious Adverse Event Information) and 8.3.3 (Follow-up of Adverse Events and Serious Adverse Events)	applies to participants who received study intervention	
[redacted]	[redacted]	[redacted]
8.3.5 (Pregnancy) and Appendix 7 (subsection *Collection of Pregnancy Information*)	Revised the description of which pregnancy outcomes are considered serious adverse events (SAEs)	Consistent with the new protocol template
8.8 (Biomarkers and Other Assessments)	Added statement to clarify the schedule for collecting blood samples for immunogenicity testing	Improve clarity
[redacted]	[redacted]	[redacted]
9.4.1.2 (Primary Analyses)	Added text to describe the methods of sensitivity analyses	Clarification of process

[redacted]

Section No. and Name	Description of Change	Brief Rationale
9.4.1.4 (Secondary Analyses)	Provided details on the ranking order for hierarchical testing of MT10109L 24 U and MT10109L 44 U versus placebo	Clarification of process
9.4.1.5 (Exploratory Efficacy Endpoints)	Reclassified some of the secondary efficacy endpoints as exploratory efficacy endpoints	Update
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
9.4.2.1 (Adverse Events)	Revised the duration after which an adverse event will not be counted as a treatment-emergent adverse event (TEAE)	Correction
[redacted]	[redacted]	[redacted]
9.4.2.2 (Vital Signs), 9.4.2.3 (Electrocardiograms), and 9.4.2.4 (Hematology/Chemistry Laboratory Testing)	Modified the description of analyses for clarity	Improve clarity
Appendix 1 (subsection of *Compliance with Protocol*)	Added text to clarify compliance with GCP regulations and procedures, and training of investigators on study requirements	Updated per recommendation by health authority
Appendix 3 (subsection of AE of Special Interest)	Revised the timeframe for which to report nonserious AESIs	Correction
[redacted]	[redacted]	[redacted]

[redacted]

Section No. and Name	Description of Change	Brief Rationale
Appendix 7 (Table 10-3)	Added text to include as one of the acceptable birth control methods the option of male or female condoms without spermicide (in addition to male or female condoms with spermicide)	Correction
Throughout	Minor editorial revisions	Minor, therefore have not been summarized

11. References

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Electronic Signatures

User	Date	Justification
[redacted]	[redacted]	[redacted]