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

Protocol Number: MT10109L-002

Amendment Number: Amendment 4

Product: MT10109L (NivobotulinumtoxinA)

Brief Protocol Title: MT10109L in the Treatment of Lateral Canthal Lines

Development Phase: 3

[redacted]

Regulatory Agency Identifying Numbers: IND Number 121473;
EudraCT Number 2014-005279-10

[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	February 2019
Amendment 2	November 2018
Amendment 1	September 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
[redacted]	[redacted]	[redacted]
11 References	Added references	References added to Section 9.4.1.2

Table of Contents

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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

Protocol Number: MT10109L-002

Brief Title: MT10109L in the Treatment of Lateral Canthal 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) in participants with moderate to severe LCL [redacted]

Objectives and Endpoints:

Objectives	Endpoints
Primary • To compare the efficacy between 24 U MT10109L and placebo for the treatment of LCL in participants with moderate to severe LCL	*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]

[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. [redacted]
- Participants are adults ≥ 18 years of age [redacted].
- 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 the results must be available to the investigator prior to randomization on Day 1.
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Participants who complete the study will have an exit visit at Day 360.
- [redacted]

Number of Participants:

Approximately 225 participants will be enrolle[redacted]

[redacted]

MT10109L

Number of Sites:

Approximately 16 global sites

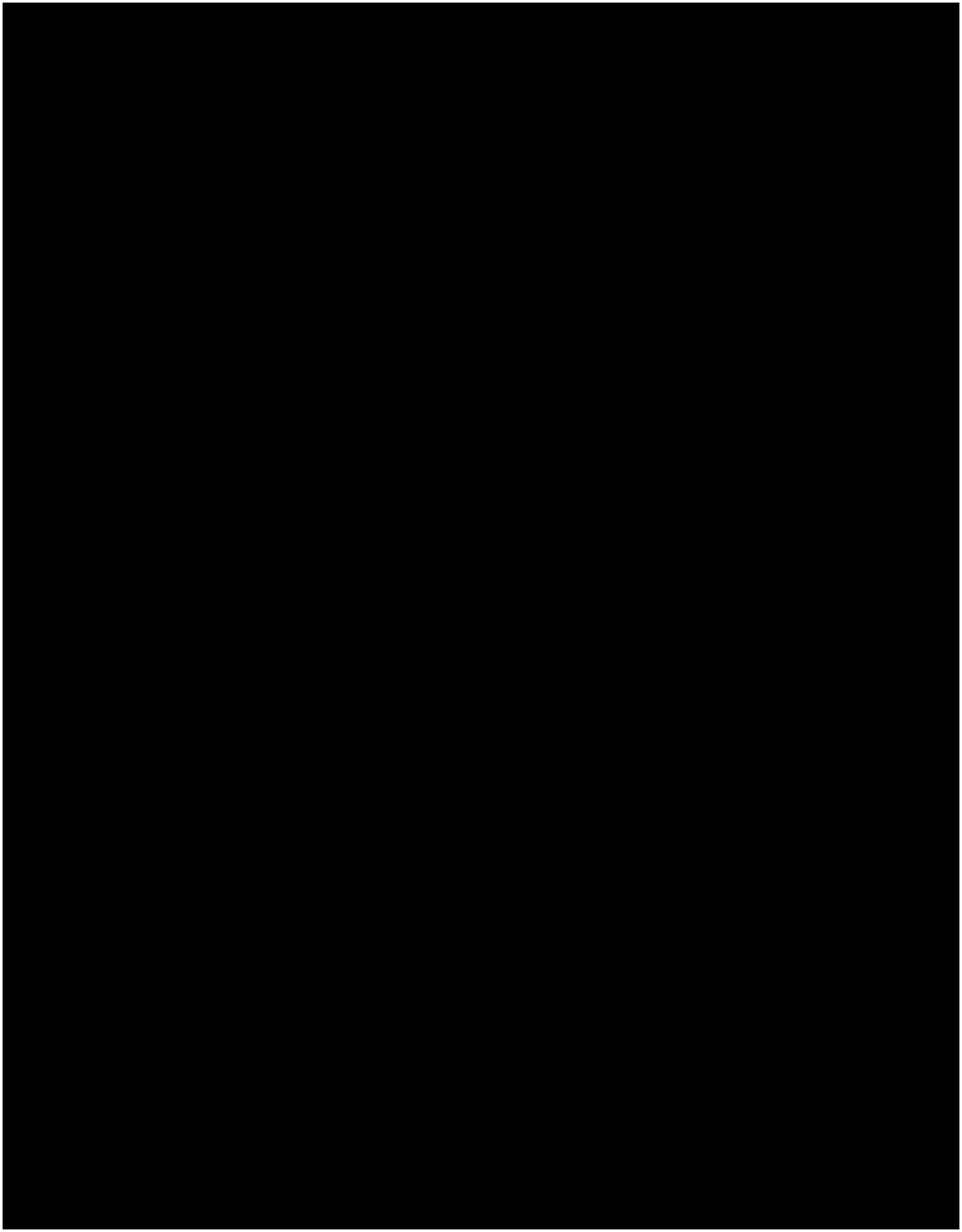
Intervention Groups and Study Duration:

- 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 or placebo.
- [redacted]

Data Monitoring Committee: No

[redacted]

[redacted]



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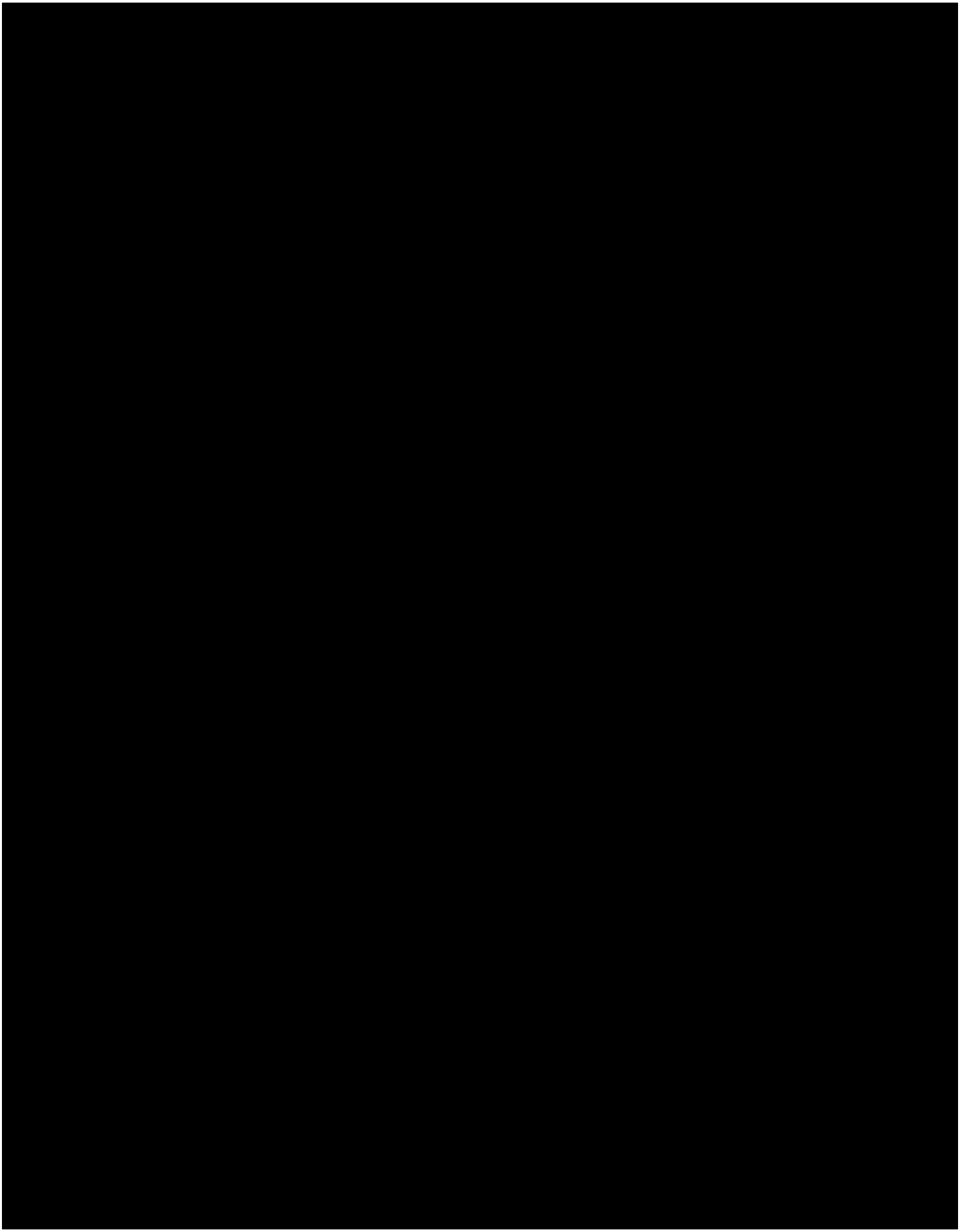

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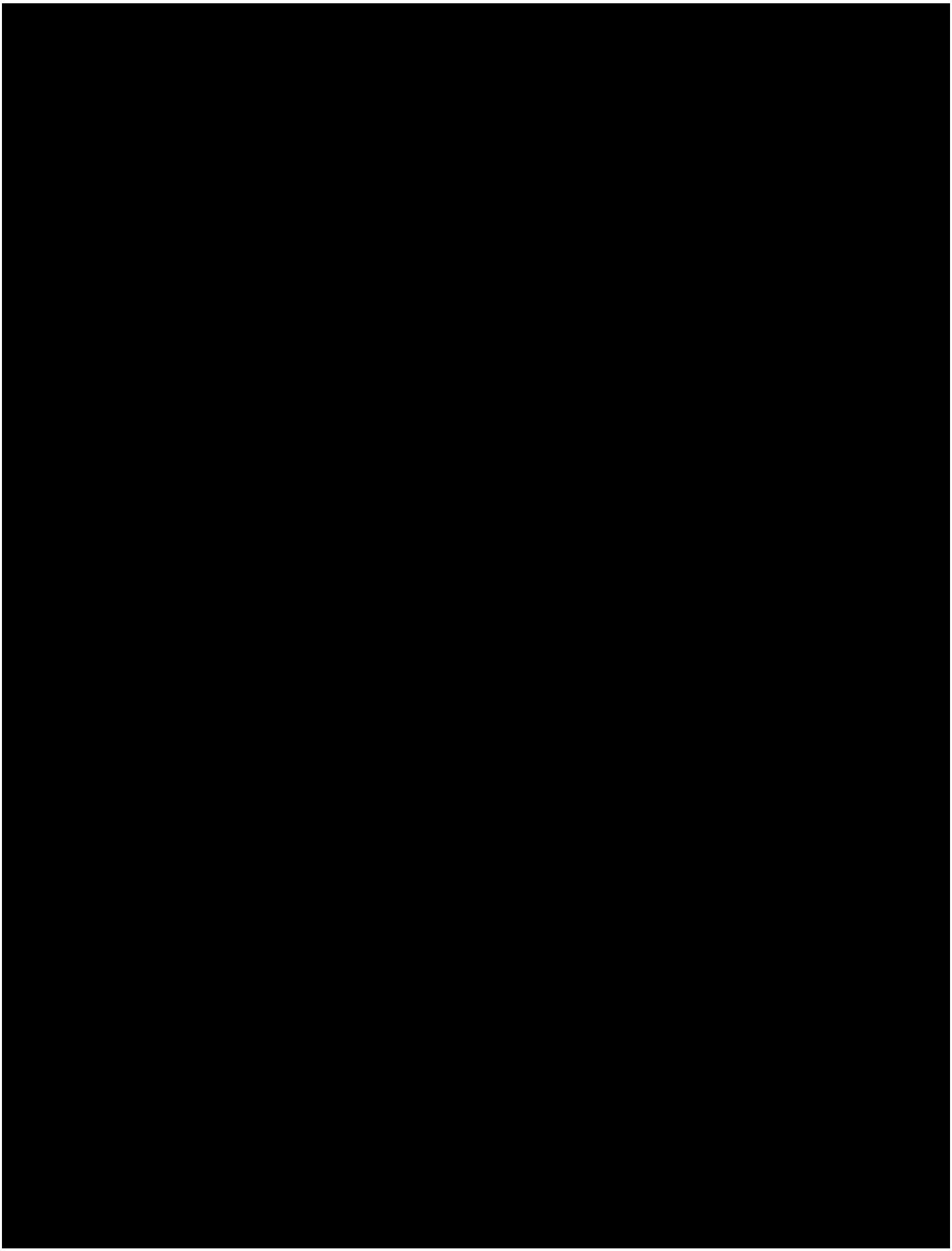

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2. Introduction

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 in participants with moderate to severe LCL [redacted]

2.2. Background

[redacted]

Lateral Canthal Lines (or CFL) are horizontal *smile lines* by the sides of the eyes, and GL 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).

[redacted]

[redacted]

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 in participants with moderate to severe LCL	*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]

[redacted]

[redacted]

[redacted]

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. [redacted]
- Participants are adults ≥ 18 years of age [redacted]
- The primary efficacy measure is the investigators' and participants' assessments of LCL severity 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 the results must be available to the investigator prior to randomization on Day 1
- [redacted]
- Participants who complete the study will have an exit visit at Day 360.

[redacted]

- 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 225 participants will be enrolled at approximately 16 sites [redacted]
- [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 has an acceptable safety profile after single and repeat treatments.

[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, as specified in Section 5.1.

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:

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[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. [redacted]

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.

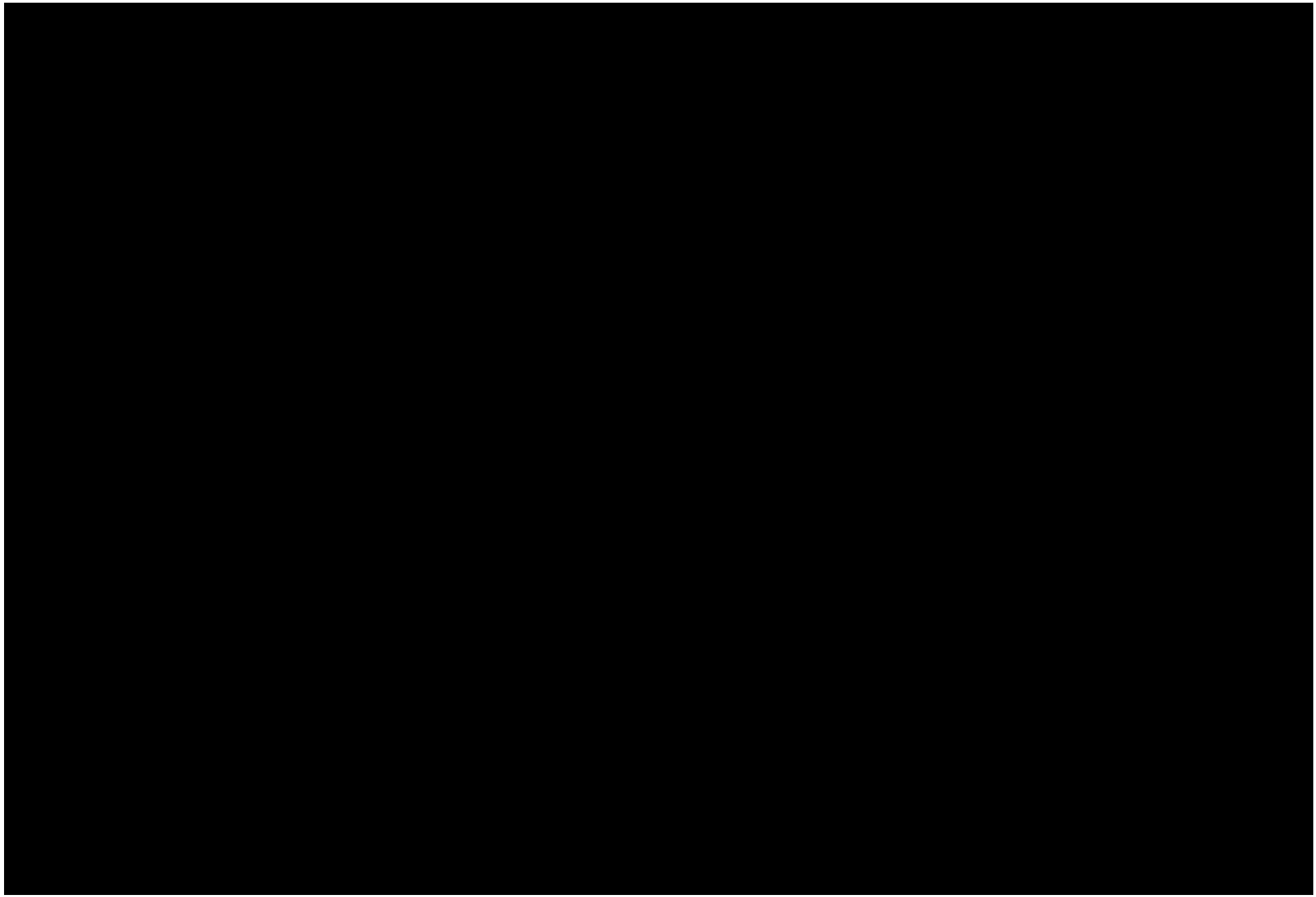
[redacted]

[redacted]

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. [redacted]

[redacted]



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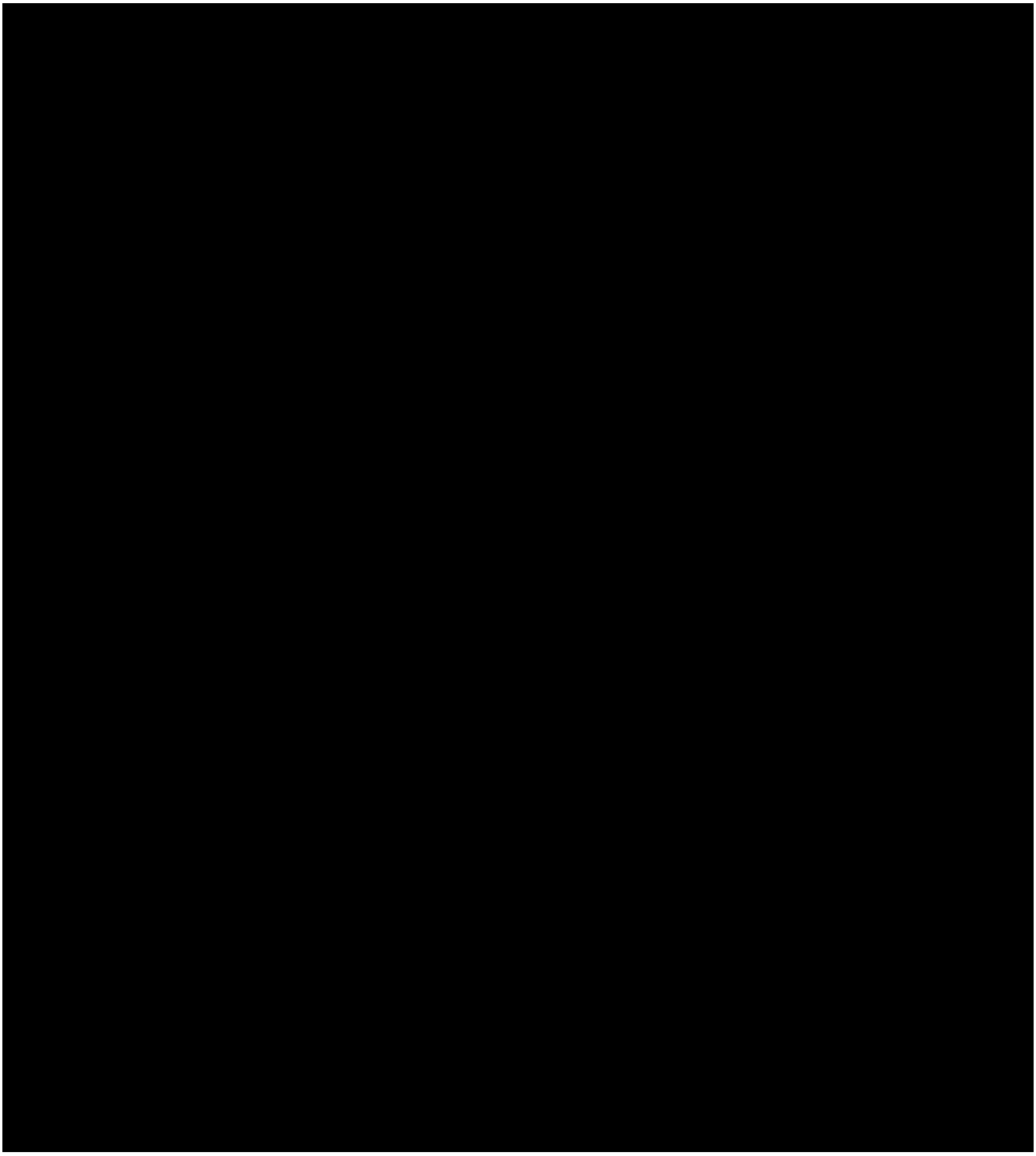

6.2. Preparation/Handling/Storage/Accountability

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.

[redacted]

[redacted]

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 the sponsor.

[redacted]

[redacted]

[redacted]

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]

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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.

[redacted]

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:

[redacted]

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.

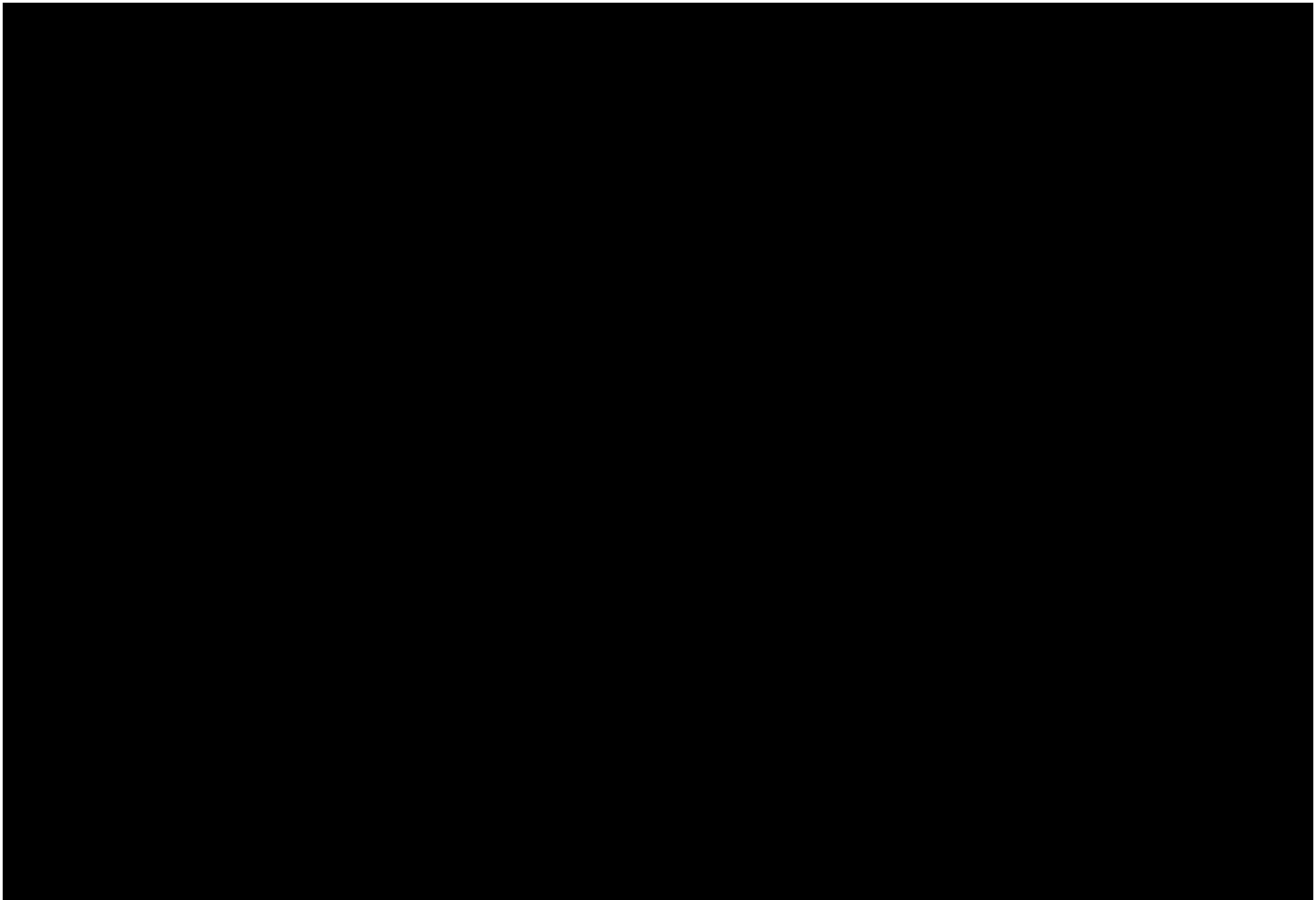
[redacted]

[redacted]

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.
- [redacted]
- [redacted]

[redacted]



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[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 [redacted]

[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.

[redacted]

[redacted]

8.2.6. Hematology and Blood 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 [redacted]
- 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 Tests

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 (Table 8-1).

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]

The adverse drug reaction of eyelid oedema with BOTOX usually is mild in severity, reversible, and has a low incidence. Therefore, no treatment for this reaction is recommended. If moderate or severe eyelid oedema occurs, medical help should be sought as needed.

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

For participants who received study intervention, all adverse events from the signing of the ICF until 30 days after the last study visit will be collected at the timepoints specified in the SoA [redacted] and as observed or reported spontaneously by study participants. [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 [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 [redacted] 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

[redacted]

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.
- 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.

[redacted]

- 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 that is above the maximum recommended dose according to the 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 that is under the minimum recommended dose according to the 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

[redacted]

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.

[redacted]

[redacted]

[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 with 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 a ≥ 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 a ≥ 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 225 participants will be randomized into the study [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]

[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.

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. LCL severity is defined as the average of the left and right side of LCL for each participant at each timepoint.

9.4.1. Efficacy Analyses

9.4.1.1. Primary Efficacy Endpoints

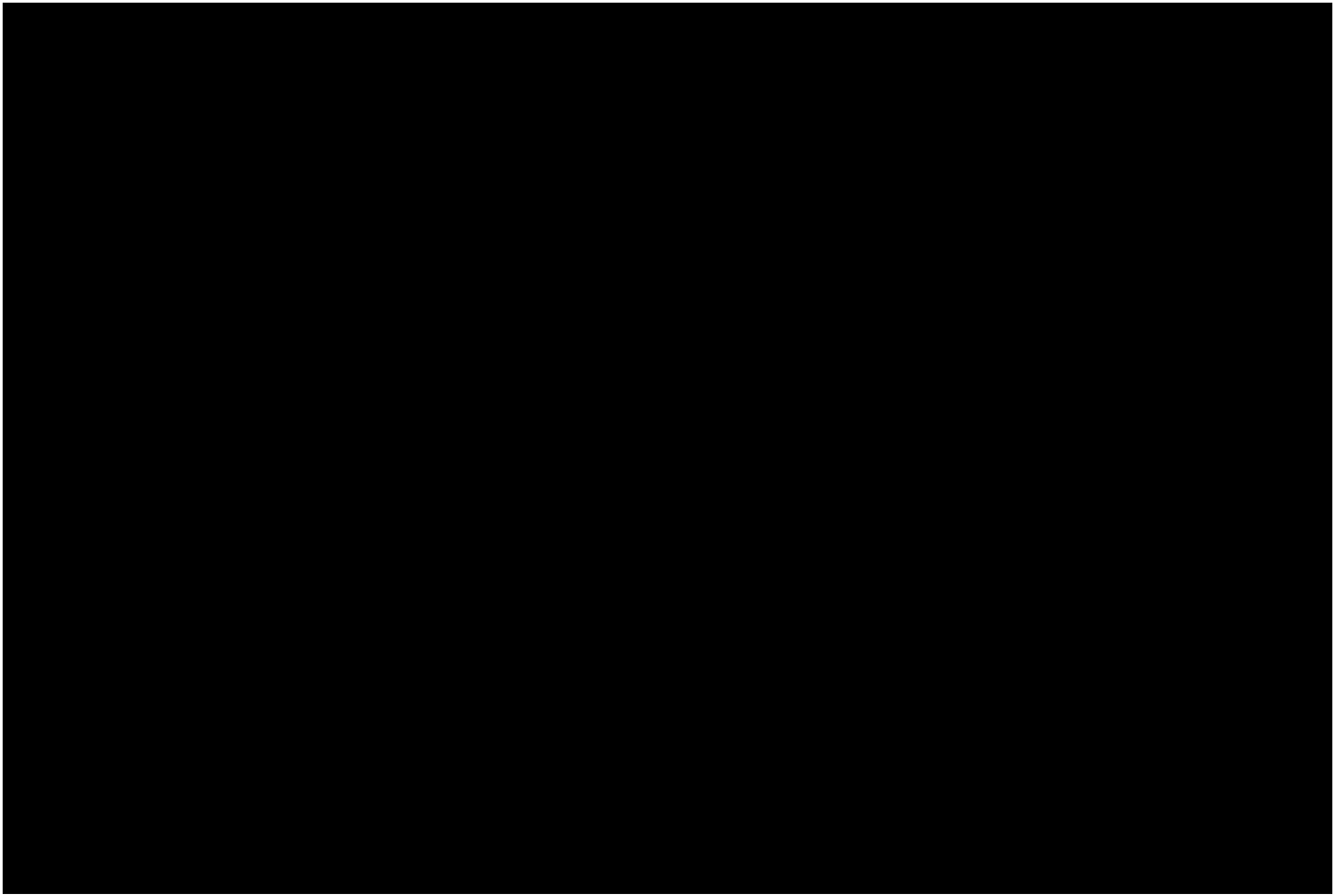
For the FDA, the composite efficacy endpoints are the proportion of participants with a ≥ 2-grade improvement from baseline on the FWS according to both investigator and participant assessments of LCL severity at maximum smile at Day 30 using the ITT population after a single IM injection of MT10109L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

[redacted]



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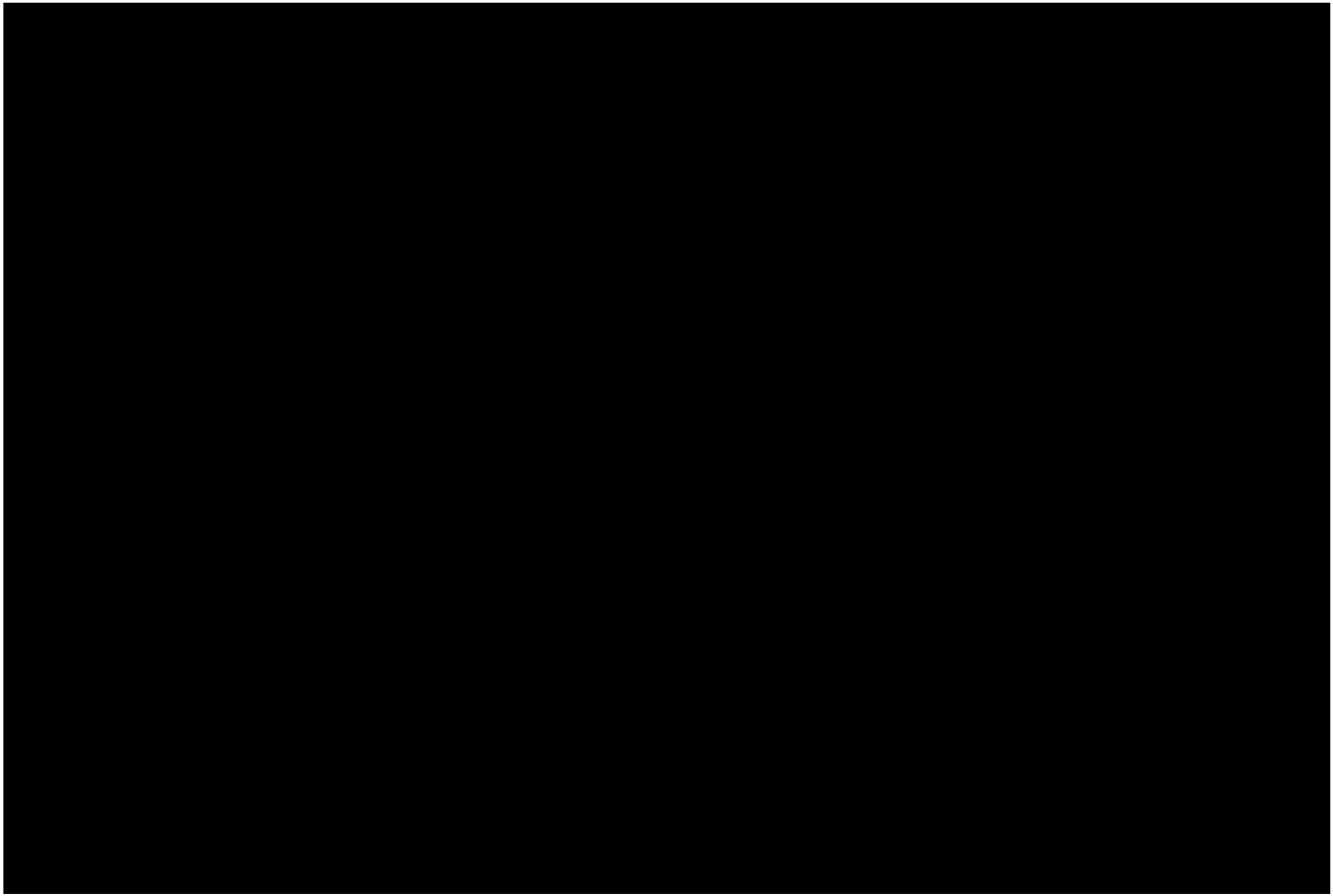

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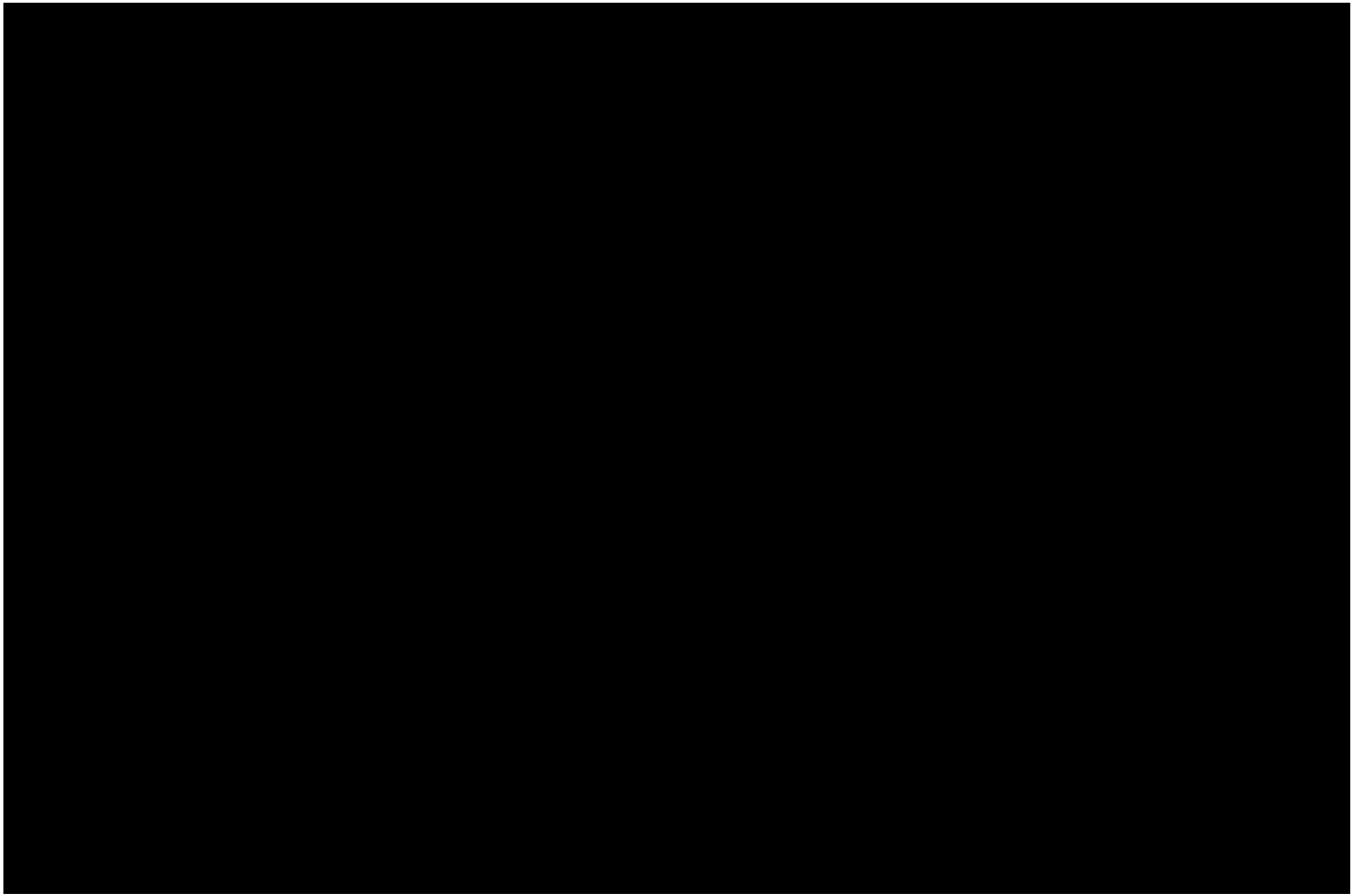

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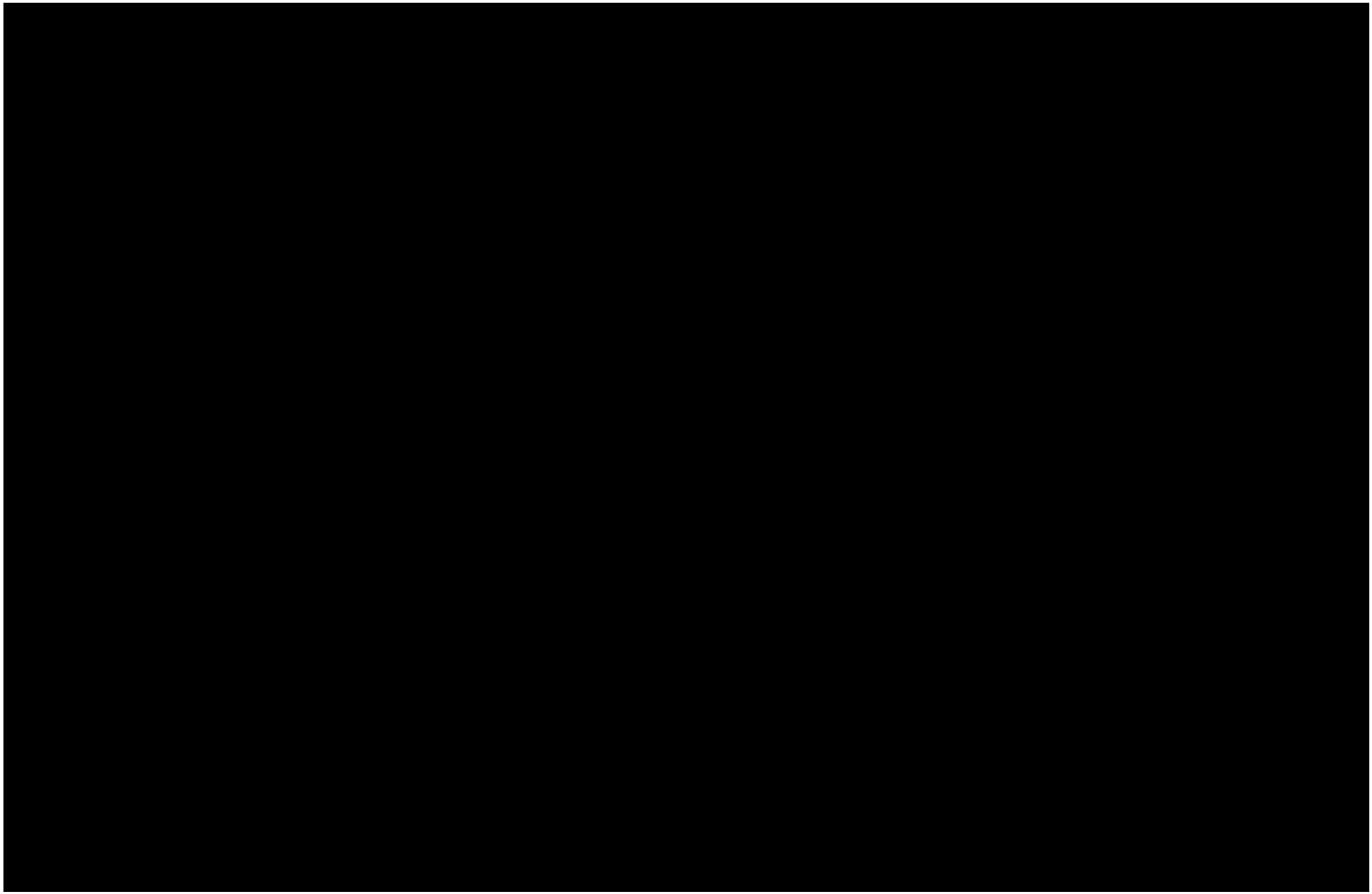

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9.4.2. Safety Analyses

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

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]

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.

[redacted]

[redacted]

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 [redacted] 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.

[redacted]

[redacted]

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 personnel 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.

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

[redacted]

- 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
- 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

[redacted]

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, 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]

10.4. Appendix 4: Abbreviations

Term/Abbreviation	Definition
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
CIOMS	Council for International Organizations of Medical Sciences
CMH	Cochran-Mantel-Haenszel
CONSORT	Consolidated Standards of Reporting Trials
CFR	Code of Federal Regulations
DVD	digital versatile disc
ECG	electrocardiogram
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
EU	European Union
FDA	Food and Drug Administration
FLO-11	11-item Facial Line Outcomes questionnaire
FLSQ	Facial Line Satisfaction Questionnaire
FWS	Facial Wrinkle Scale with Photonumeric Guide
GCP	Good Clinical Practices
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
ICH	International Conference on Harmonisation
IEC	Independent 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 cells
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
TEAE	treatment-emergent adverse events
U	Units
UFL	upper facial lines
ULN	upper limit of normal value provided by the laboratory
US	United States
WBC	white blood cells
WOCBP	woman of childbearing potential

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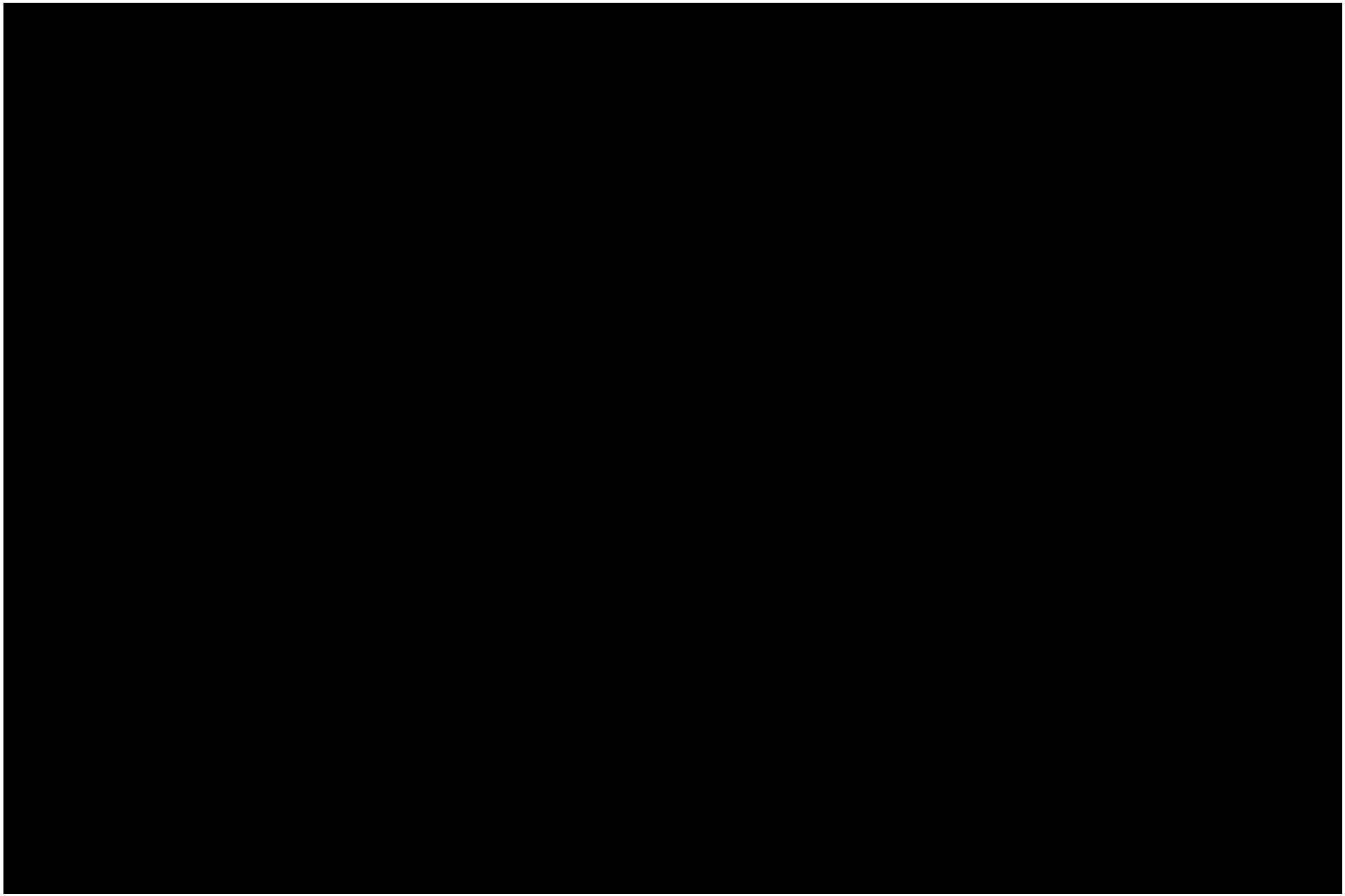

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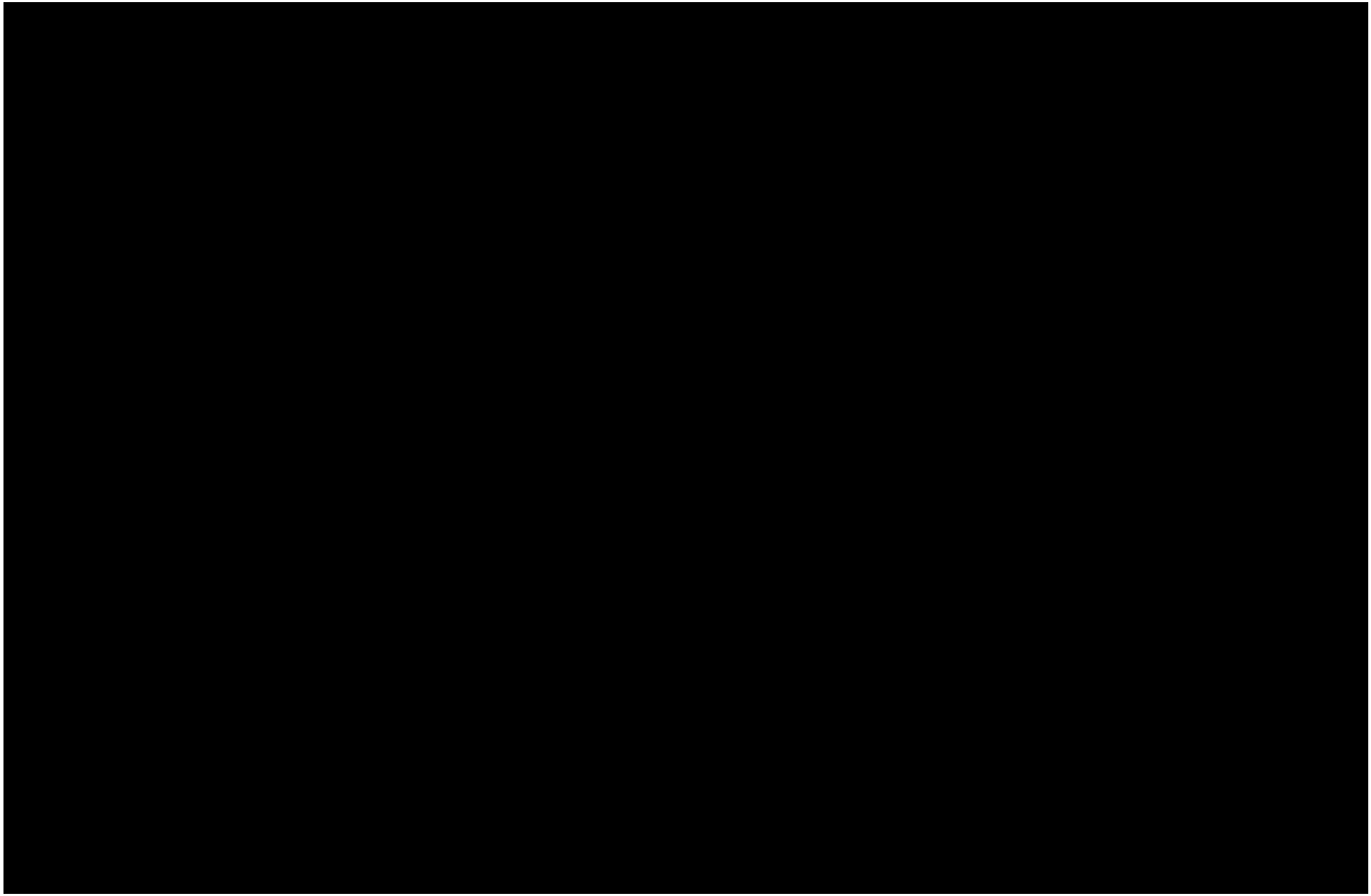

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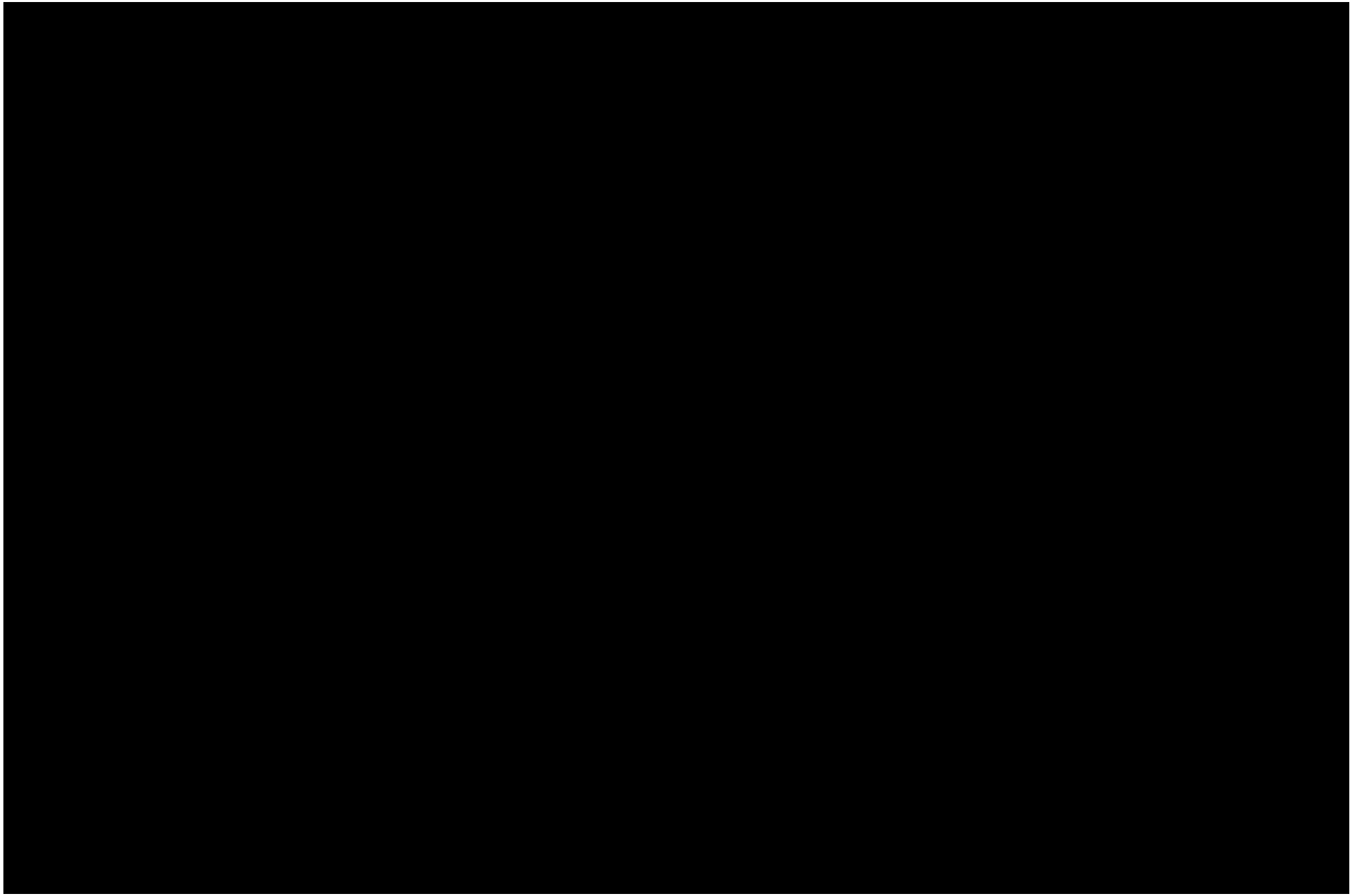

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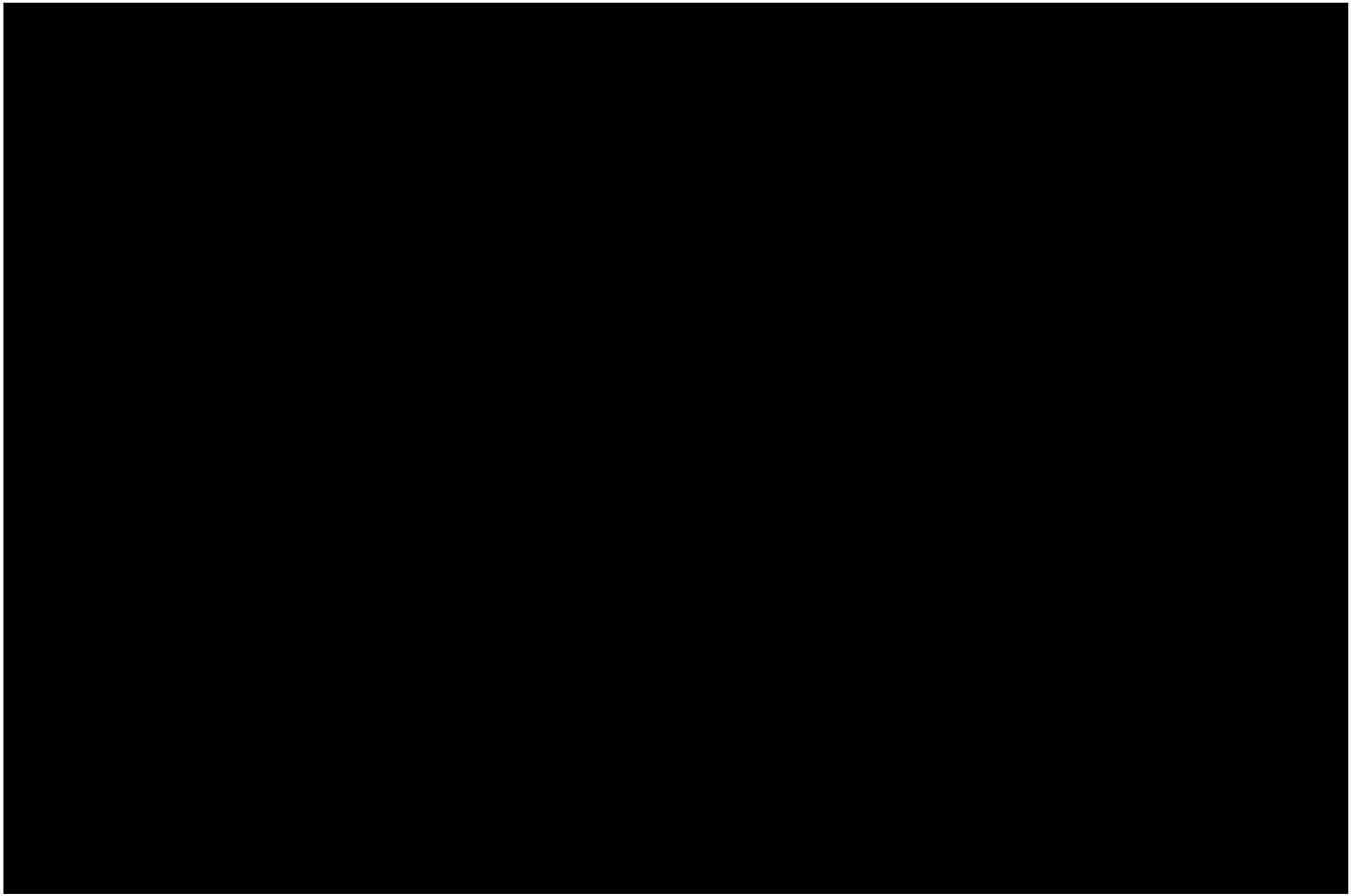

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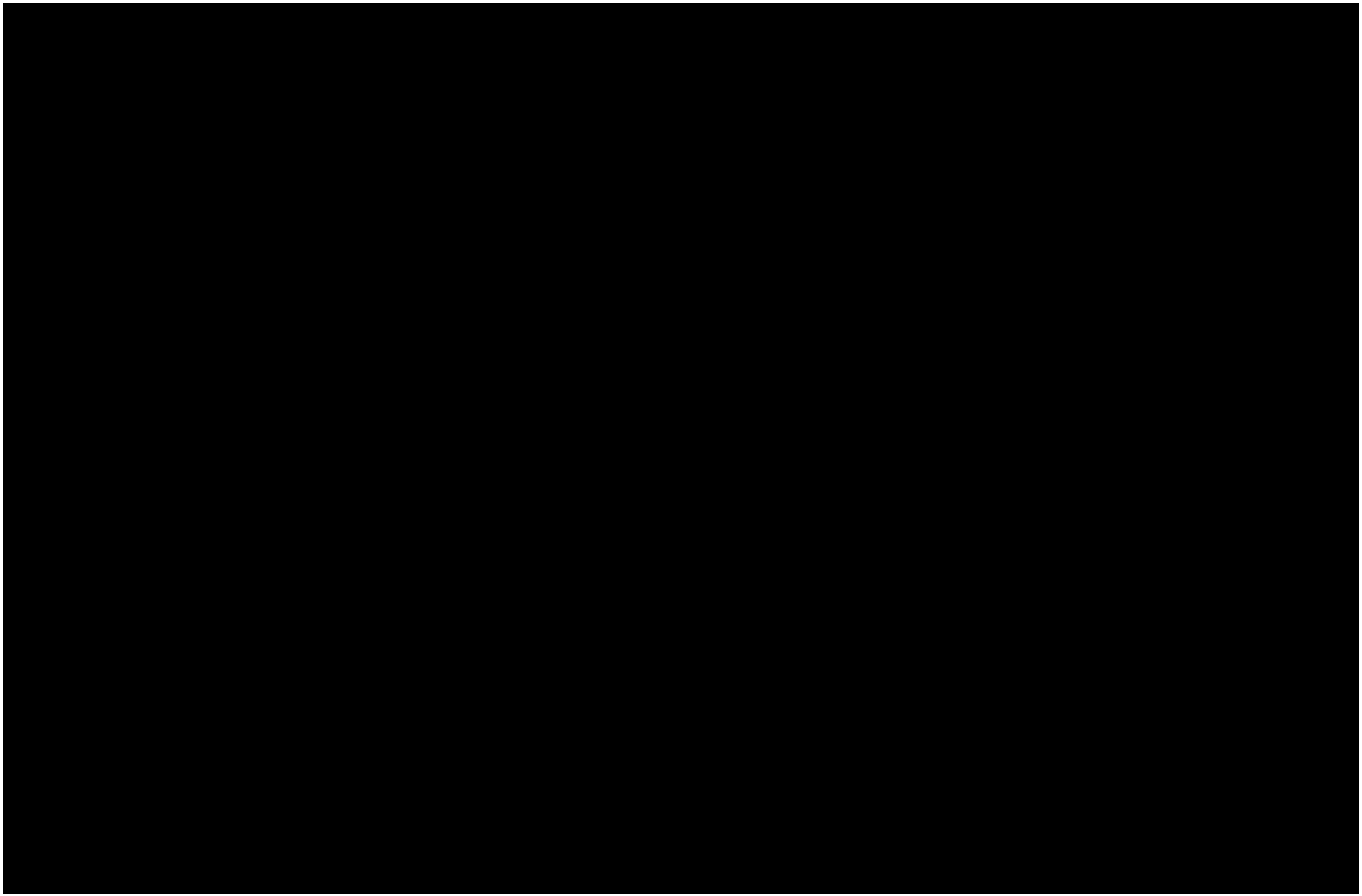

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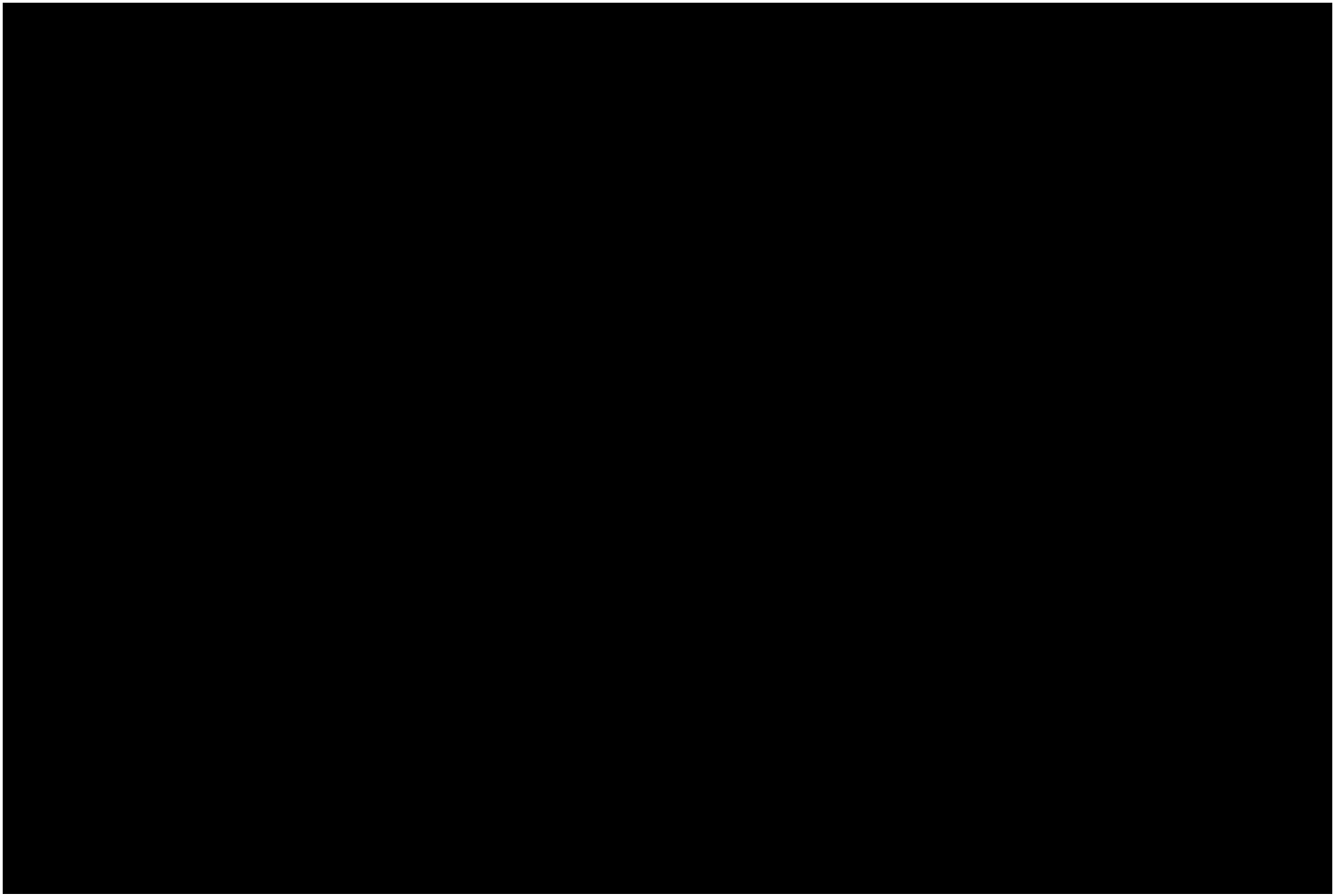

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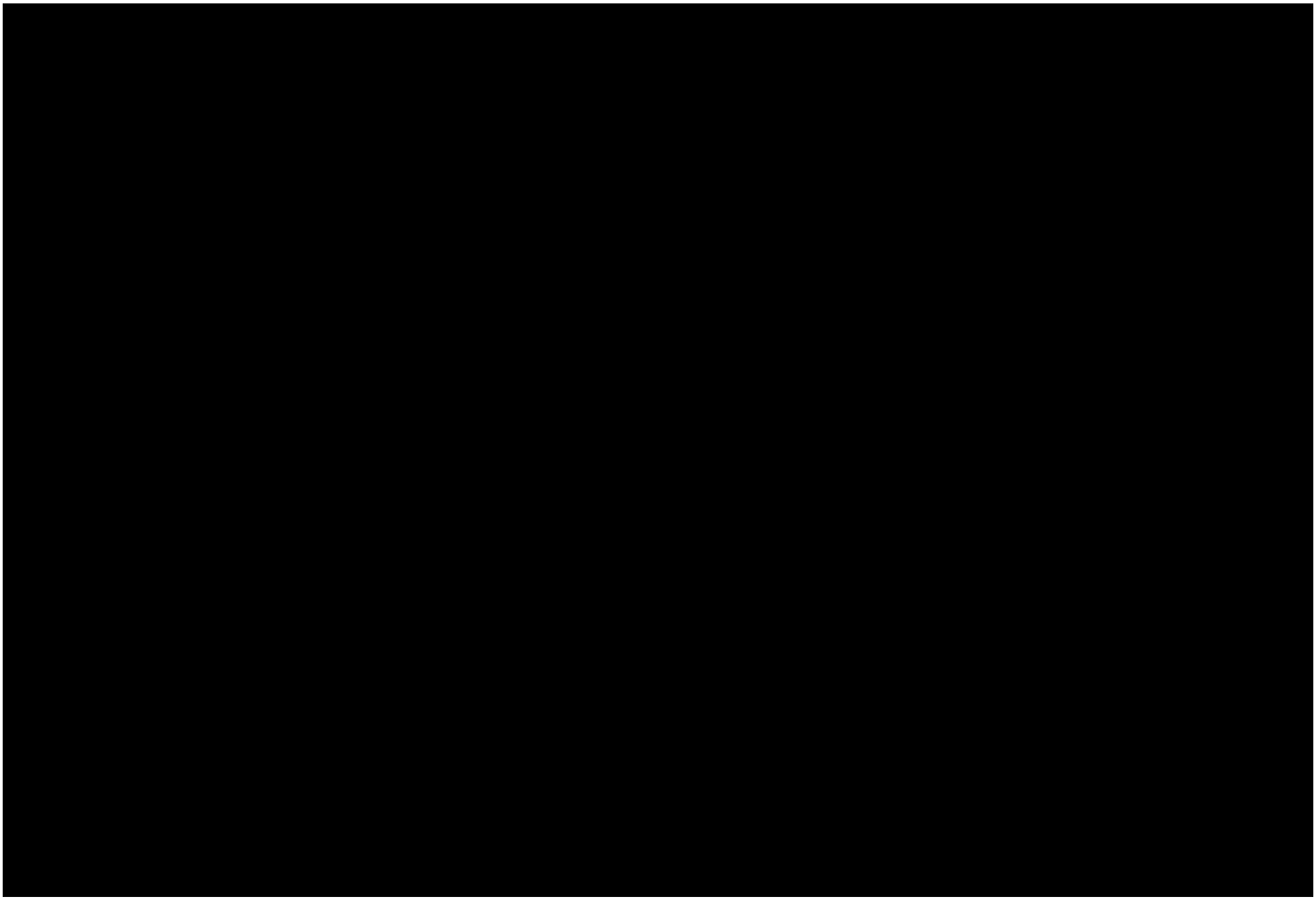

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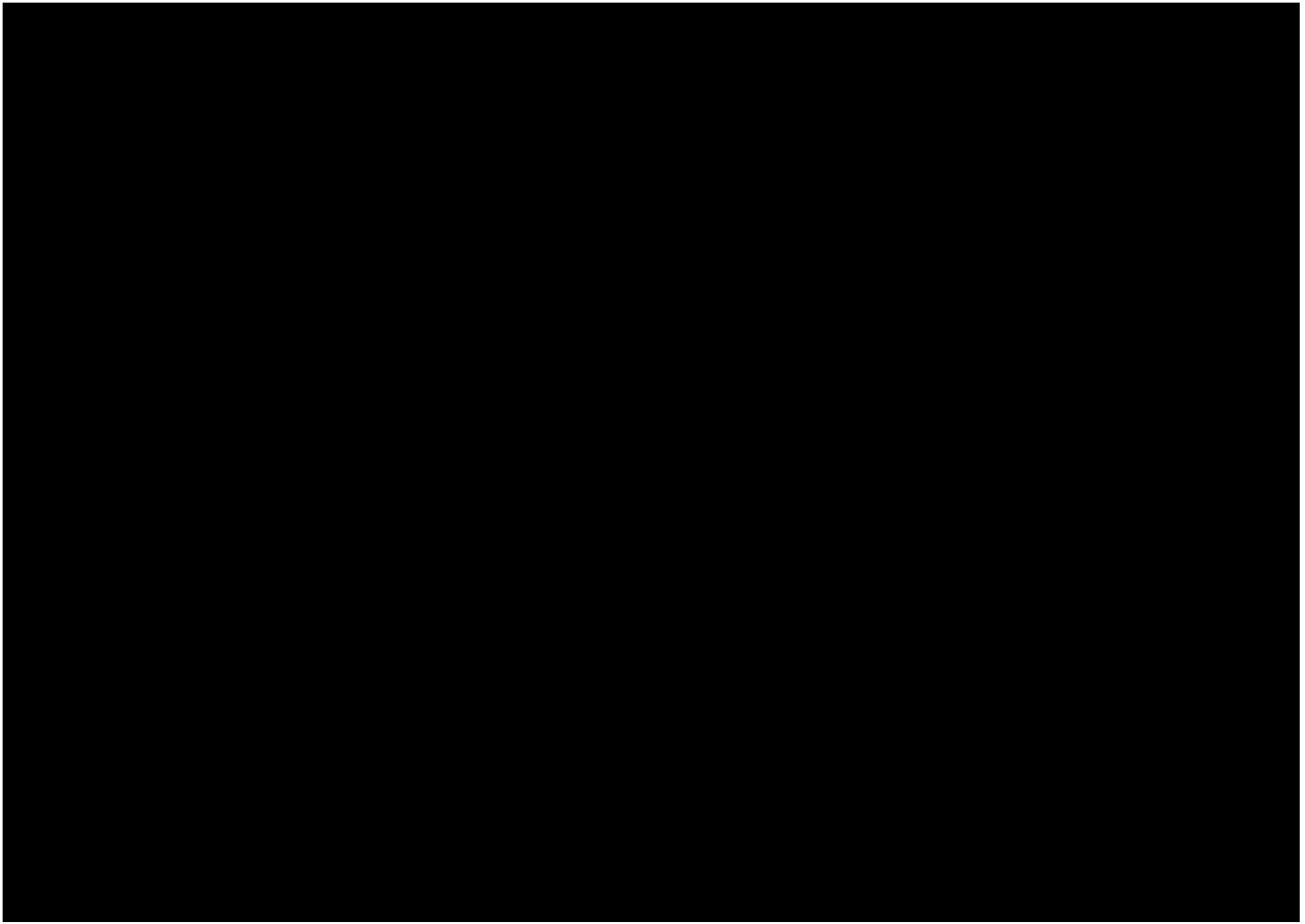

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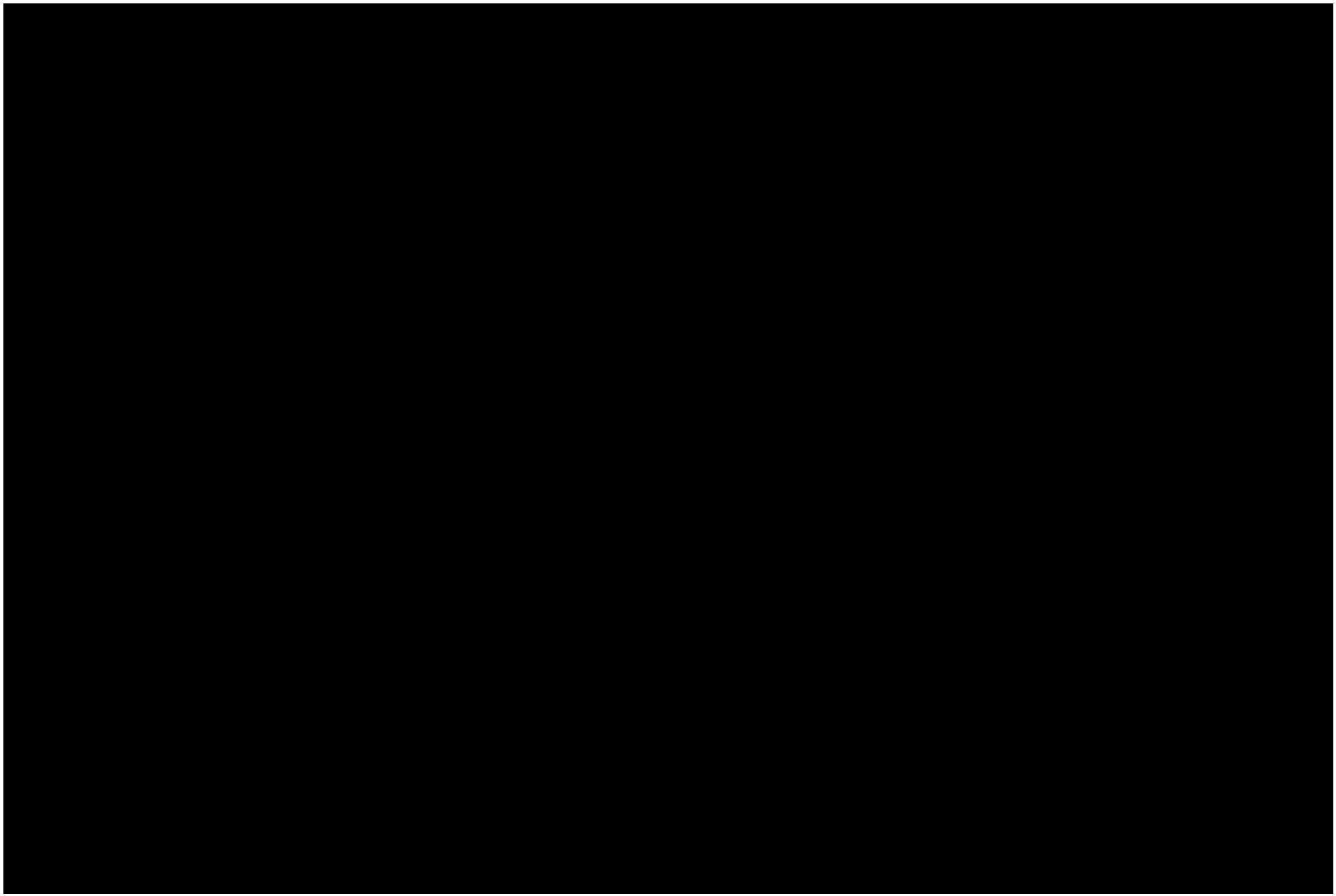

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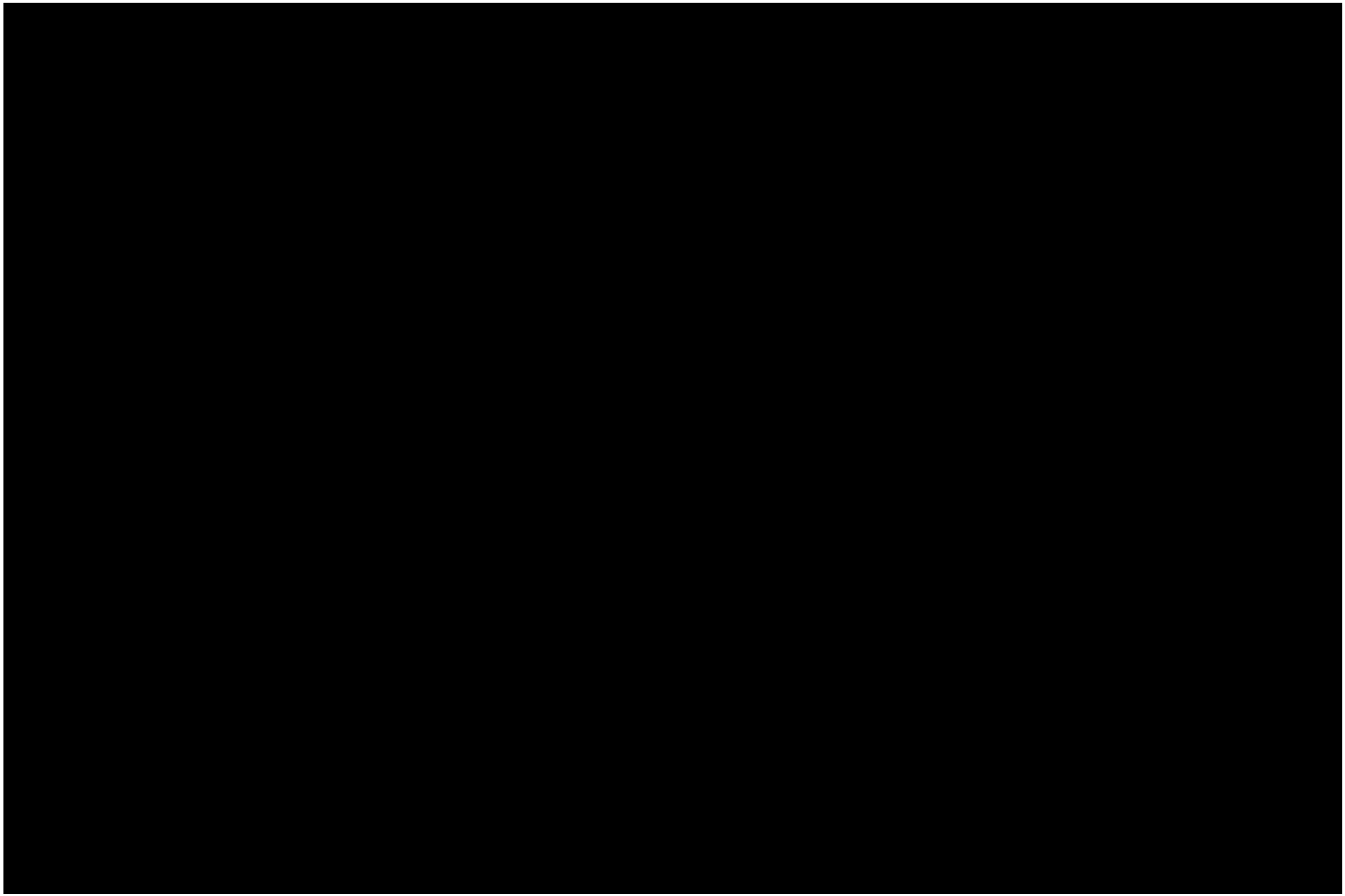

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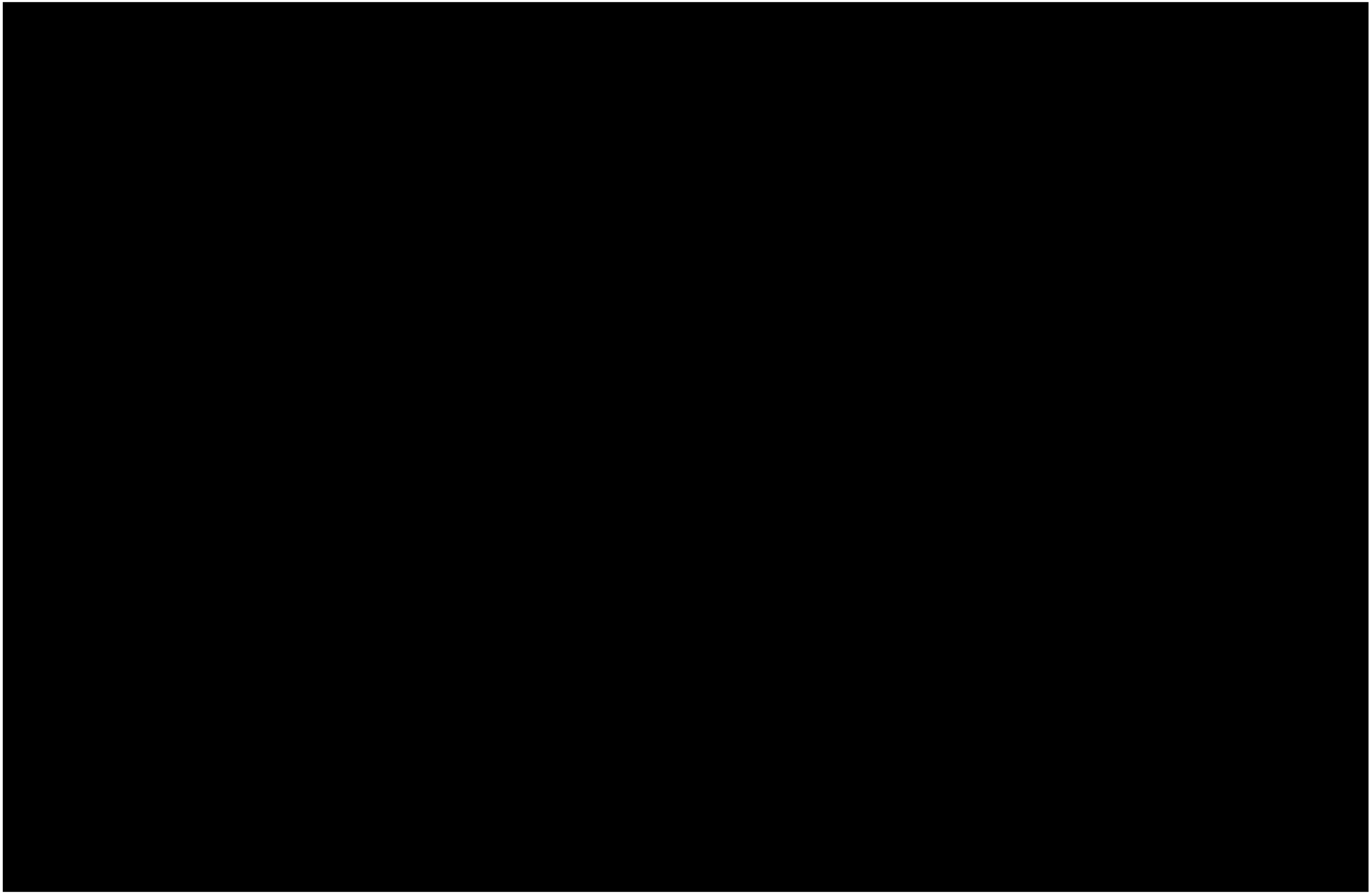

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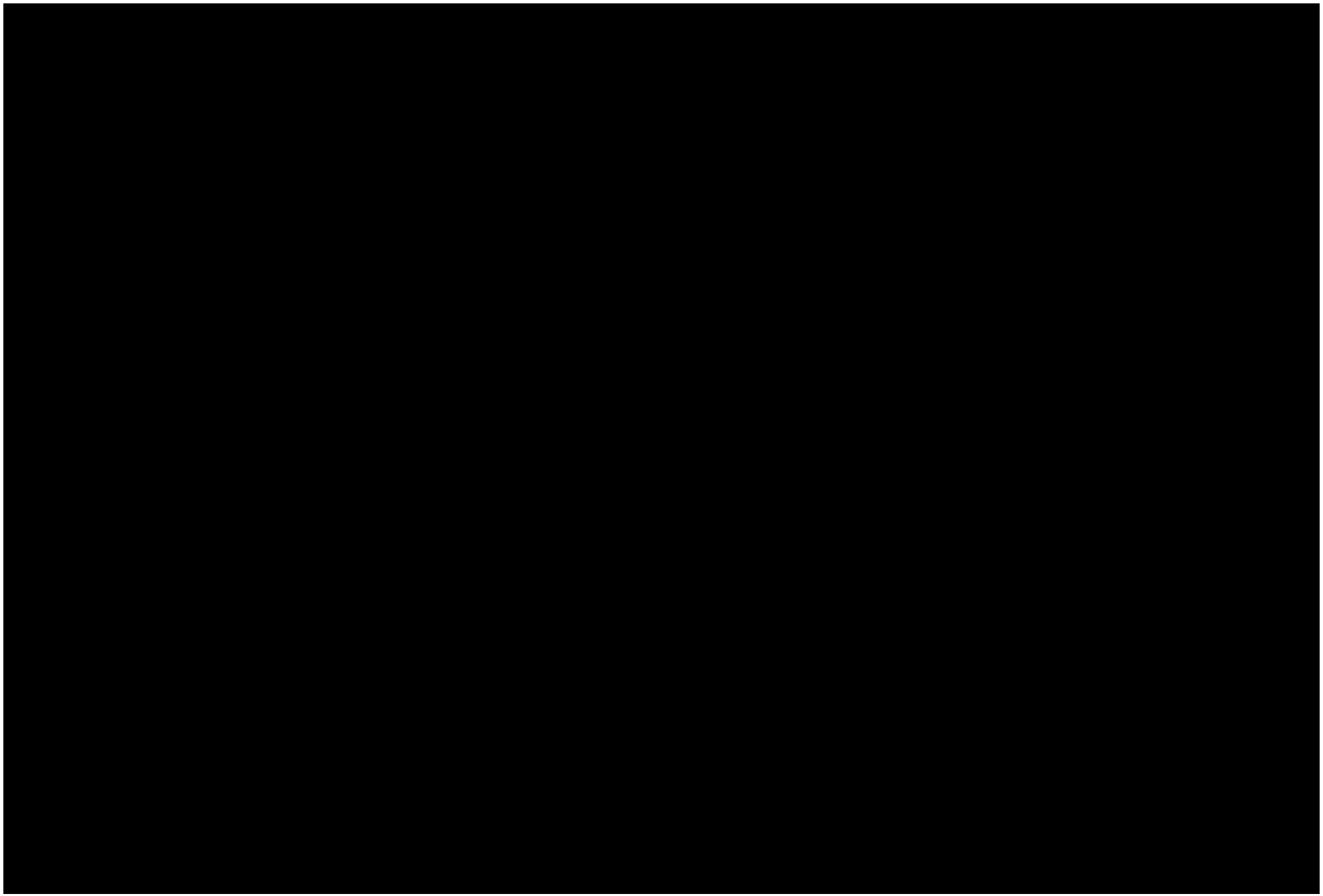

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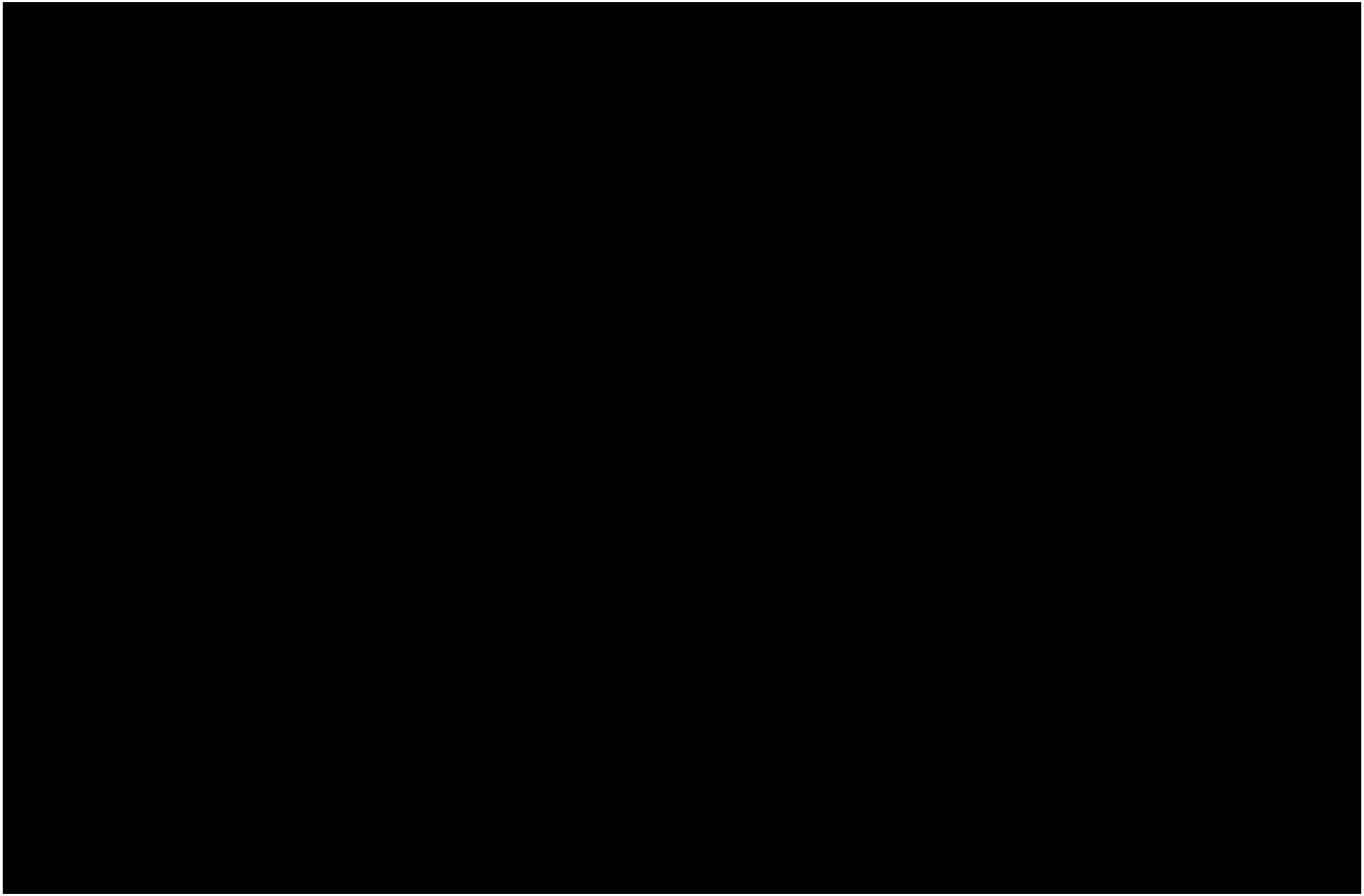

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10.10. Appendix 10: Protocol Amendment History

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

[redacted]

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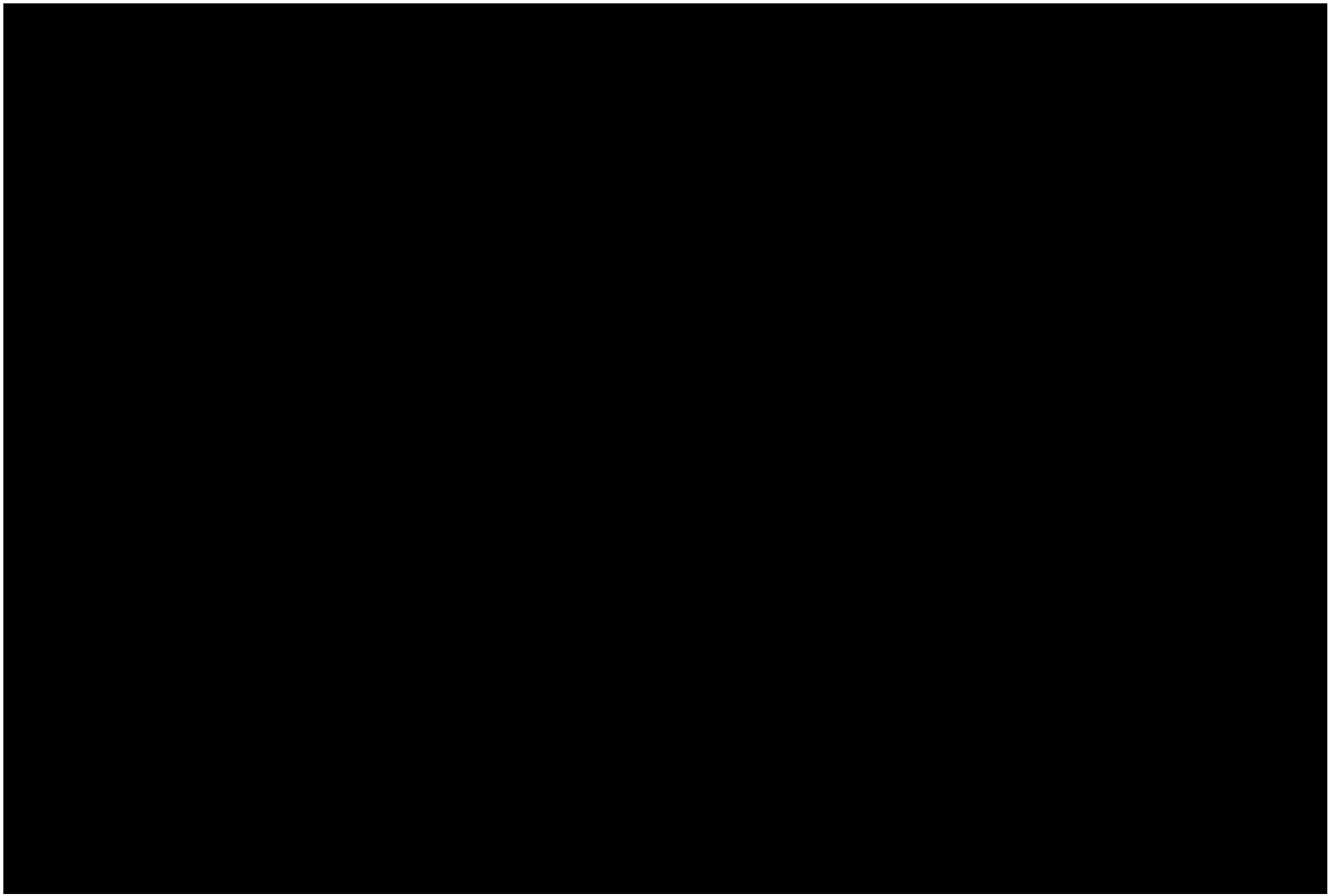
[redacted]



Approval Date: 30-Sep-2020 22:56:17 (GMT)

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Electronic Signatures

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