Title Page

Protocol Title: A Multicenter, Long-term, Open-label Study to Evaluate the Safety of MT10109L (NivobotulinumtoxinA) for the Treatment of Glabellar Lines and Lateral Canthal Lines

Protocol Number: MT10109L-004

Amendment Number: Amendment 5

Product: MT10109L (NivobotulinumtoxinA)

Brief Protocol Title: MT10109L in the Long-term, Open-label Treatment of Glabellar Lines and Lateral Canthal Lines

Development Phase: 3

Sponsor Name and Legal Registered Address:
Medytox Inc.
[redacted]

Regulatory Agency Identifying Numbers: IND Number 121473;
EudraCT Number 2014-005303-24

Emergency Telephone Number: Refer to the study contacts page

SAE Reporting Fax Number/Email:
[redacted]

Sponsor Signatory:

[redacted]

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

Protocol Amendment Summary of Changes Table

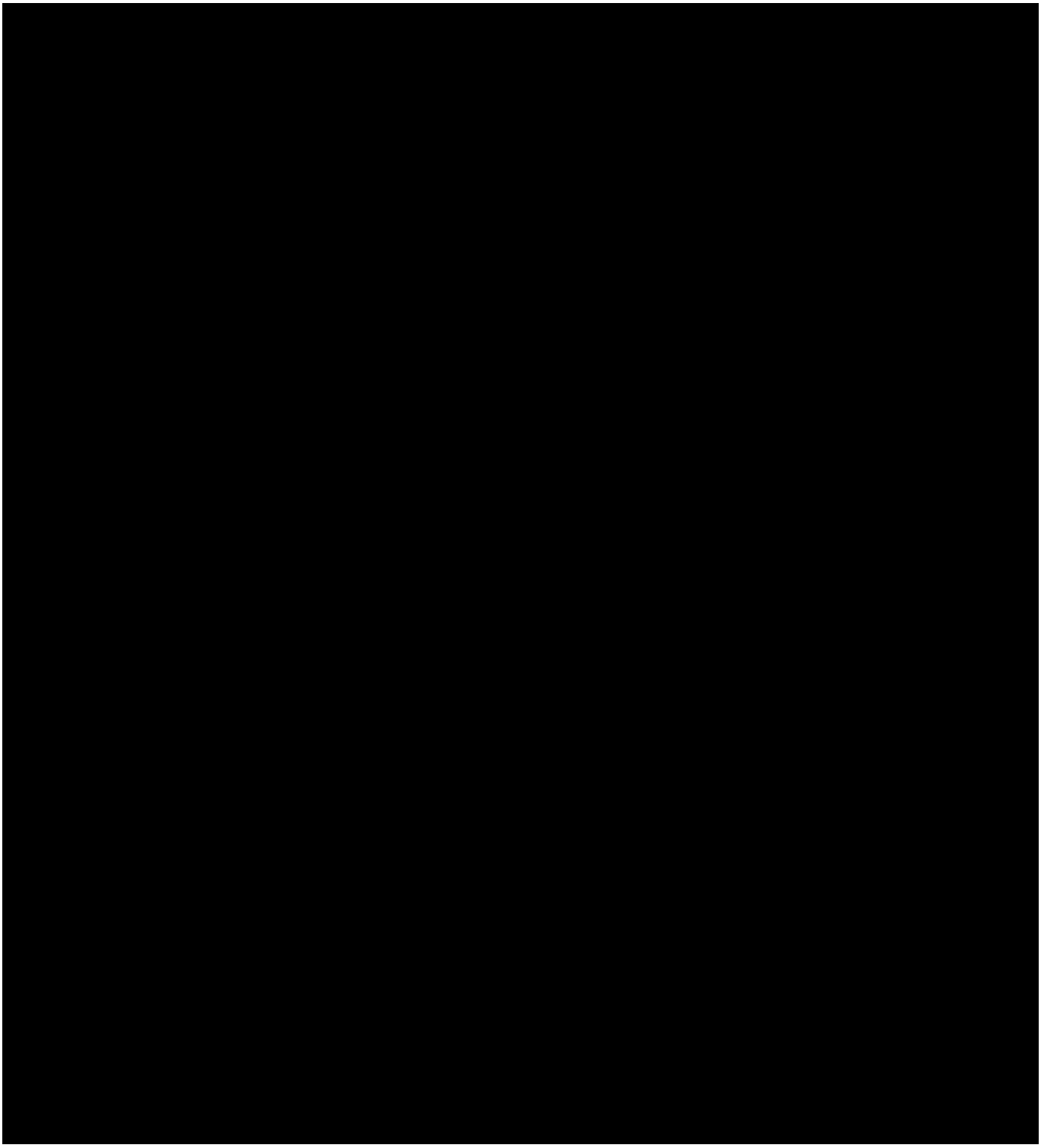
DOCUMENT HISTORY	
Document	**Date**
Amendment 5	June 2022
Amendment 4	October 2019
Amendment 3	June 2019
Amendment 2	November 2018
Amendment 1	September 2018
Original Protocol	July 2018

Amendment 5 (June 2022)

This amendment is considered to be not 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 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 for the changes implemented in this open-label, extension study was to reflect the new study sponsor and safety reporting information,



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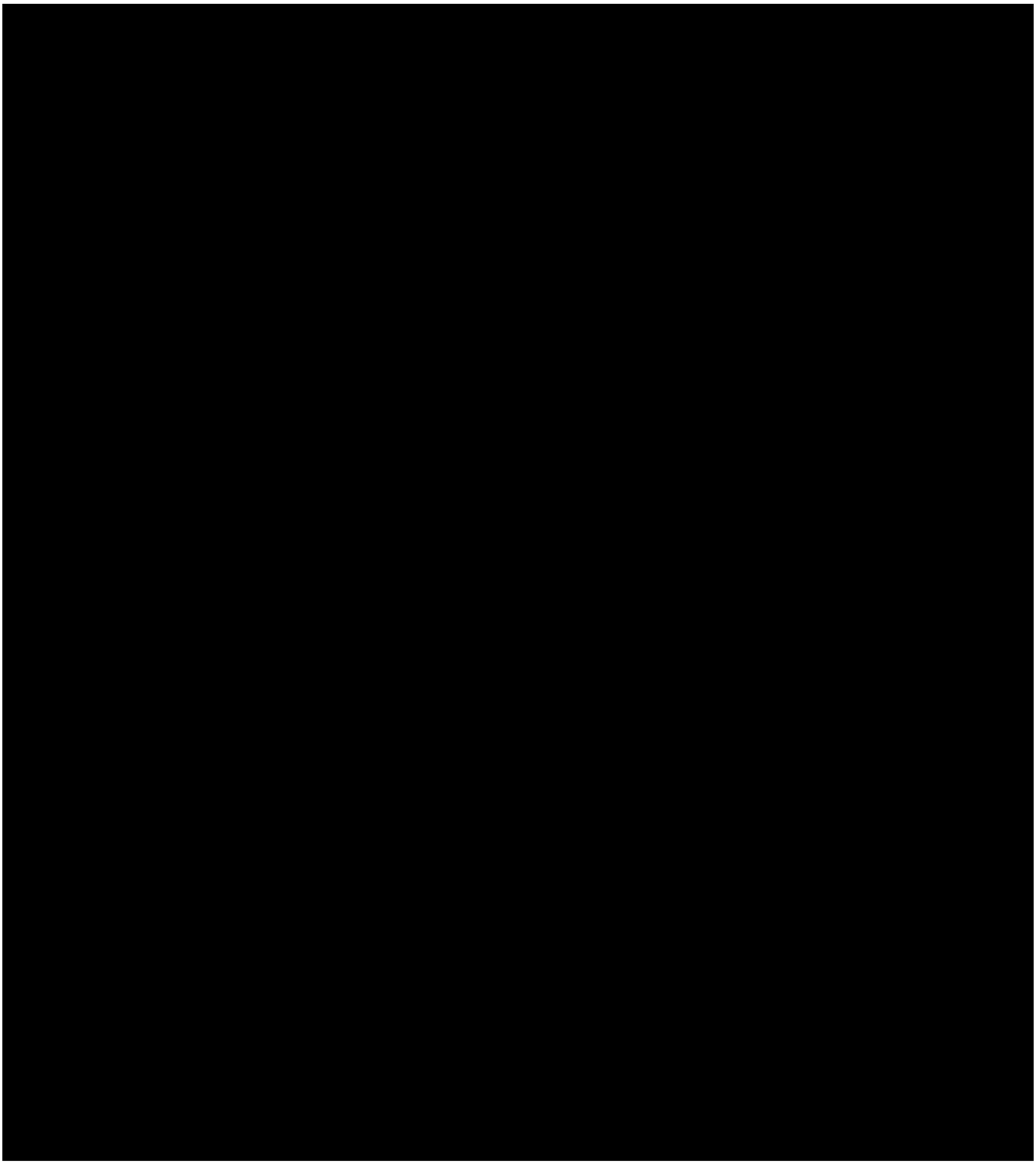

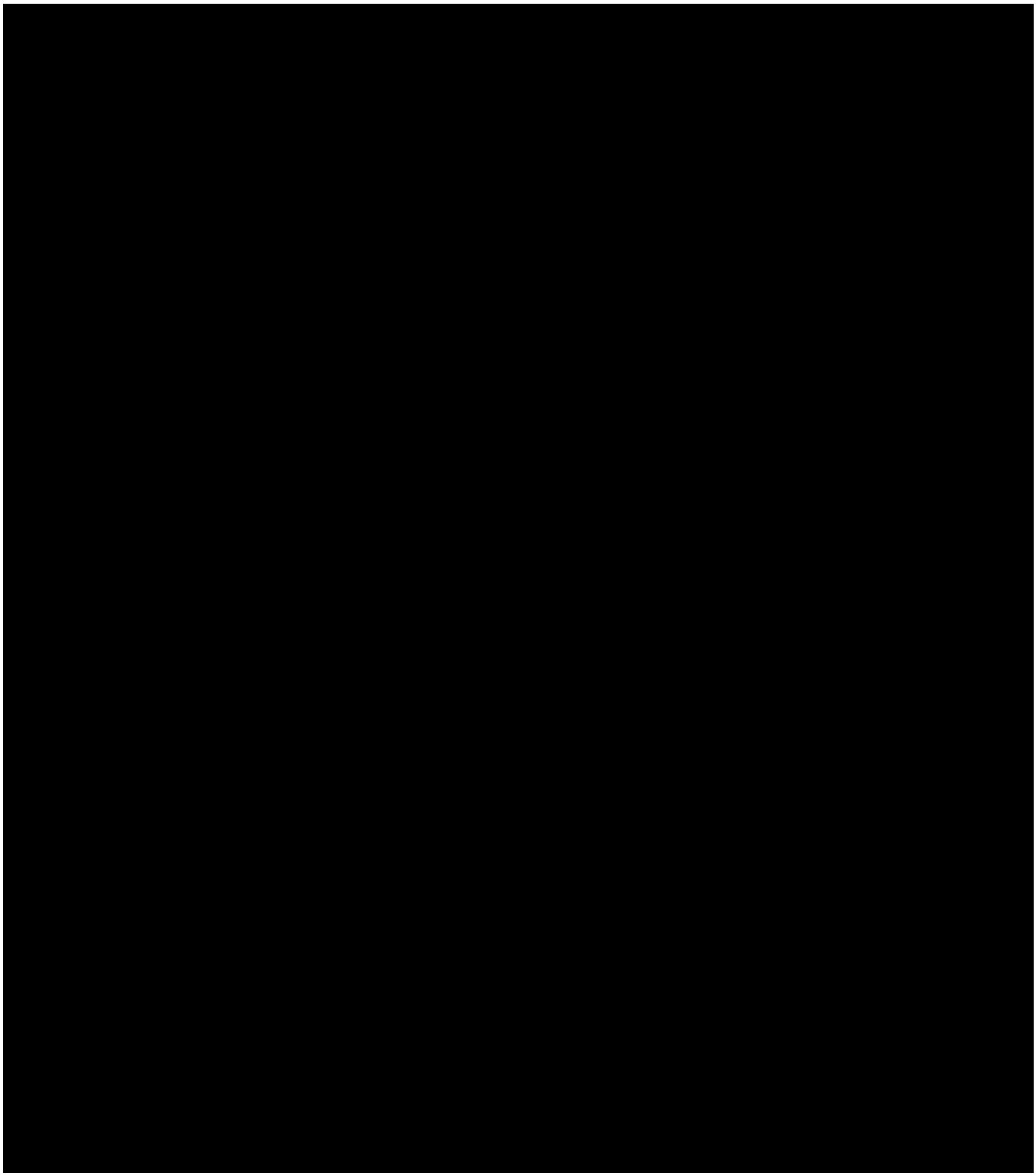

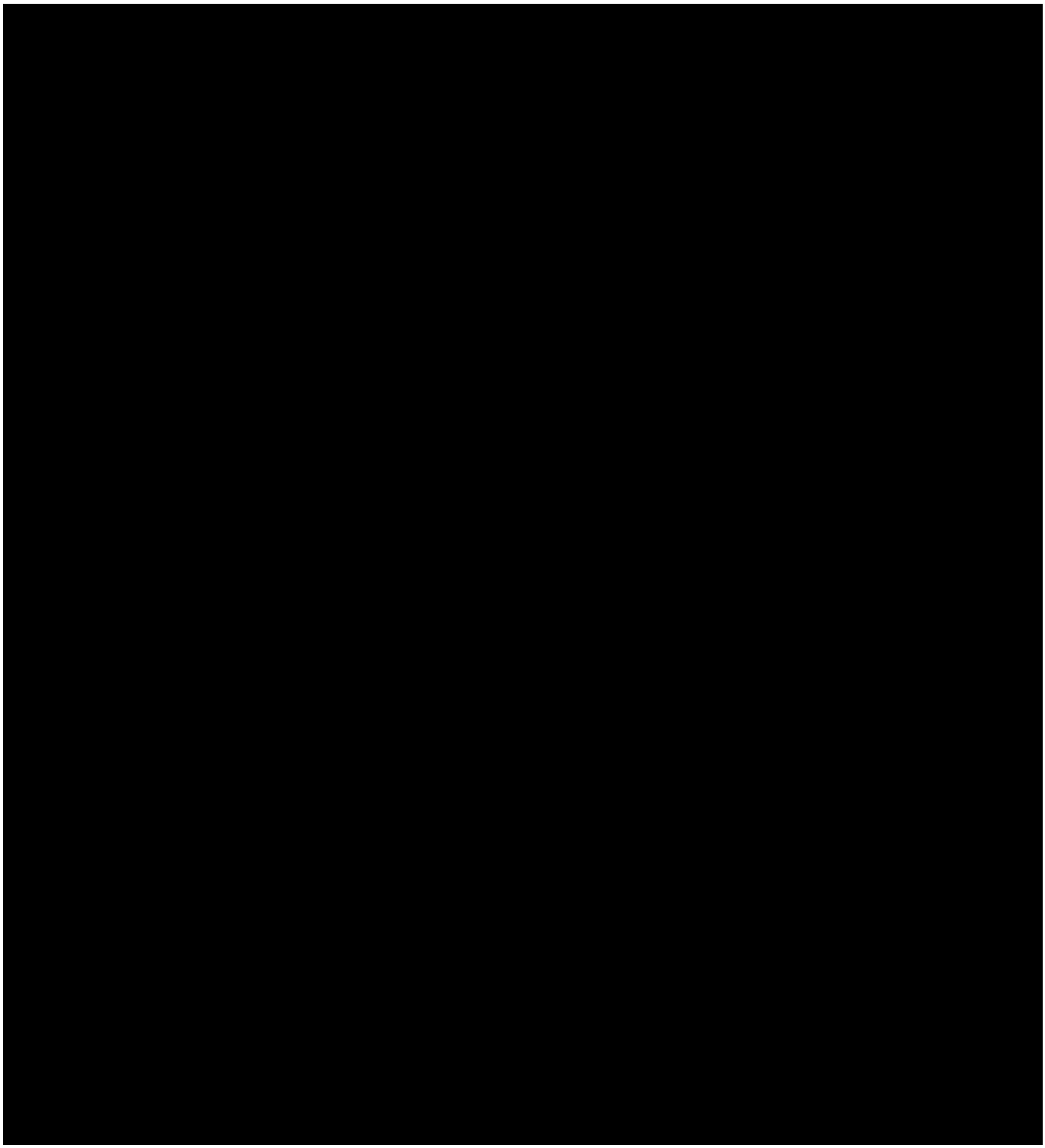

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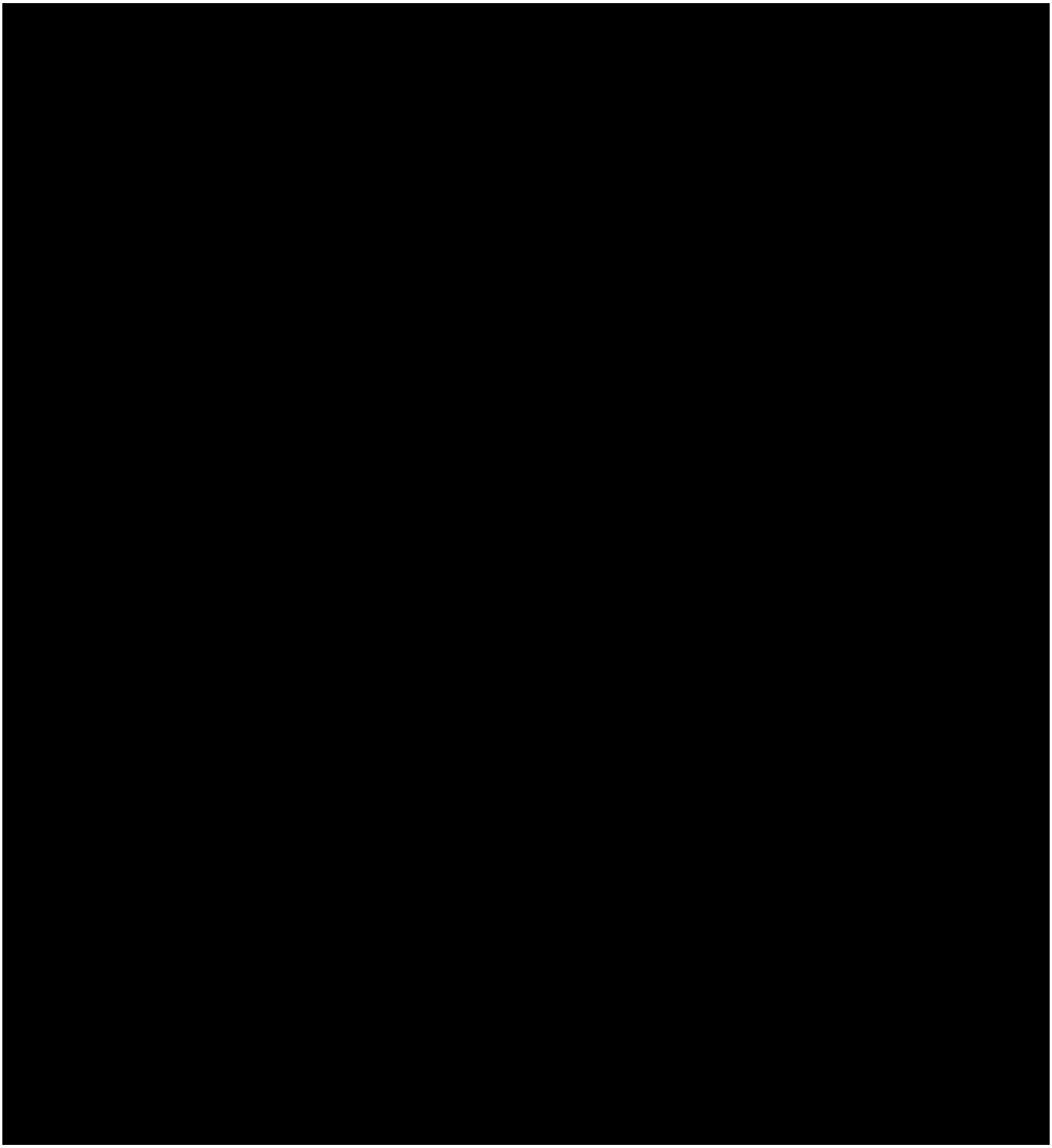

1. Protocol Summary

1.1. Synopsis

Protocol Title: A Multicenter, Long-term, Open-label Study to Evaluate the Safety of MT10109L (NivobotulinumtoxinA) for the Treatment of Glabellar Lines and Lateral Canthal Lines

Protocol Number: MT10109L-004

Brief Title: MT10109L in the Long-term Treatment of Glabellar Lines and Lateral Canthal Lines

Study Phase: 3

Study Rationale:

The purpose of this open-label, extension study is to evaluate the long-term safety of repeated MT10109L treatment of GL and/or LCL in participants with moderate to severe GL, LCL, or both (GL and LCL) who completed the lead-in pivotal Phase 3 studies (MT10109L-001, -002, -005, and -006) over an additional 24 months.

Objectives and Endpoints:

Objective	Endpoints
Primary	
• To evaluate the long-term safety of repeat treatments of MT10109L in participants with *moderate to severe* GL, LCL, or both (GL and LCL)	• Incidence of adverse events, change from baseline in vital sign parameters, and presence of binding and neutralizing antibodies

Overall Study Design:

- This is a multicenter, open-label, repeat treatment study to evaluate the long-term safety of MT10109L in treating GL, LCL, or both (GL and LCL). [redacted]

- All participants who complete studies MT10109L-001 (GL), MT10109L-002 (LCL), MT10109L-005 (GL with or without LCL), and MT10109L-006 (LCL with or without GL) will be eligible to enroll into this 24-month open-label extension study (Study MT10109L-004).
- [redacted]
- [redacted]
- Participants who complete this study will have an exit visit on Day 720.

Number of Participants:

All eligible participants who complete the lead-in pivotal Phase 3 studies (MT10109L-001, -002, -005, and -006) can enroll in the current study. [redacted]

Number of Sites:

All sites from the lead-in Phase 3 studies will participate (approximately 44 global sites).

Intervention Groups and Study Duration:

- The total duration of study participation for each participant is approximately 24 months (Day 1/study entry to Day 720/or early exit).
- [redacted]
  - [redacted]
  - [redacted]
    - [redacted]

- [redacted]
  - [redacted]
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  - [redacted]
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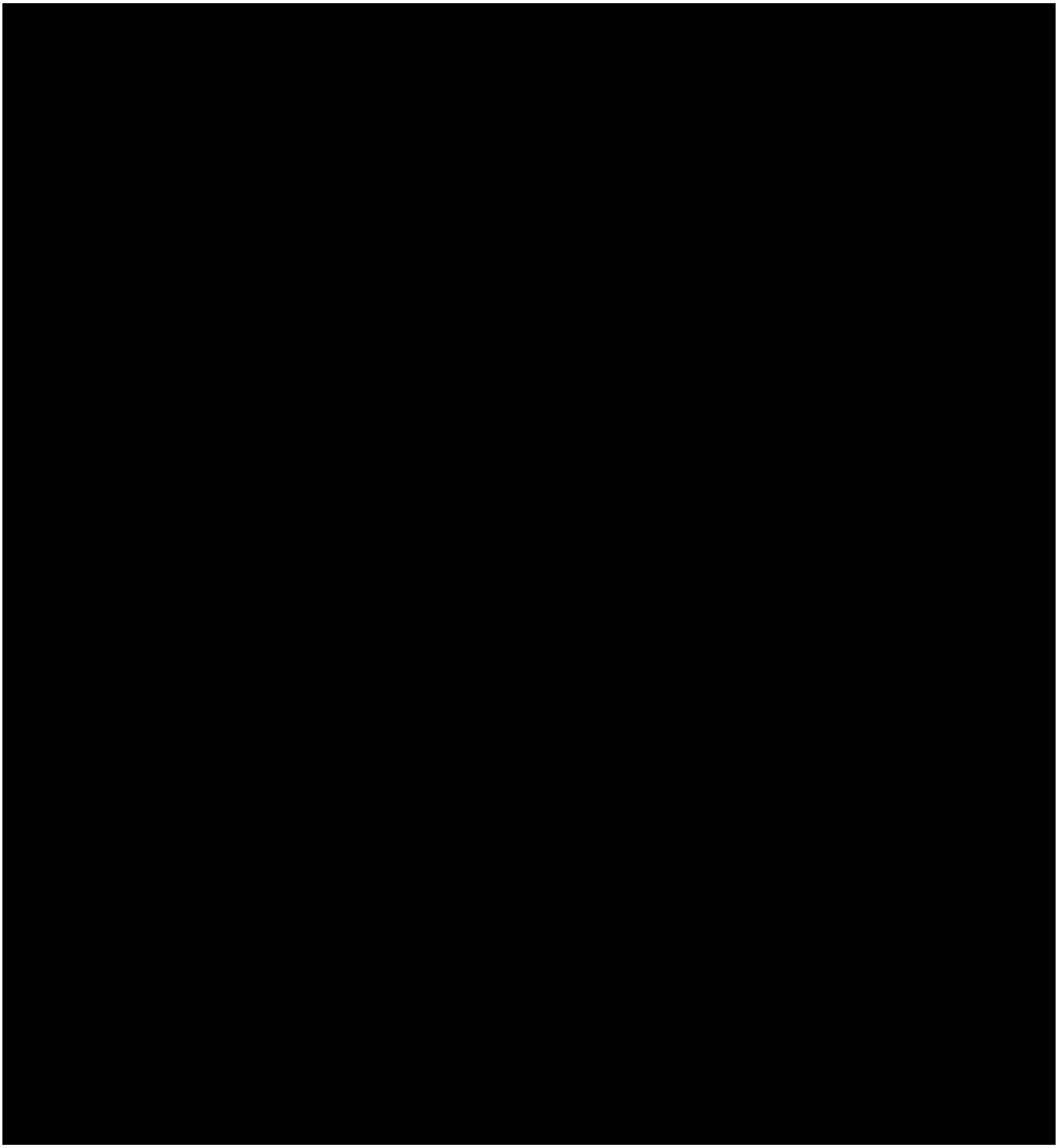
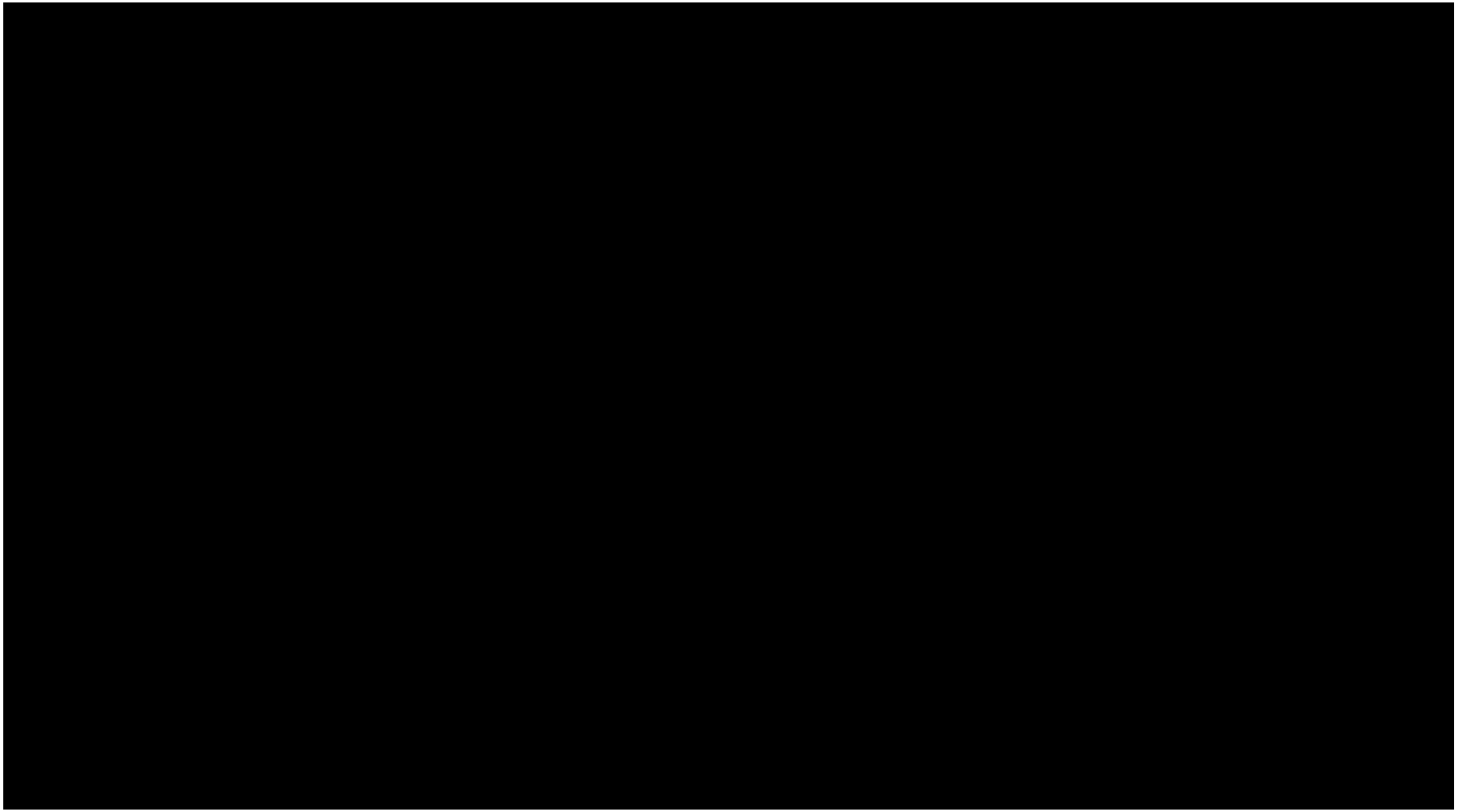
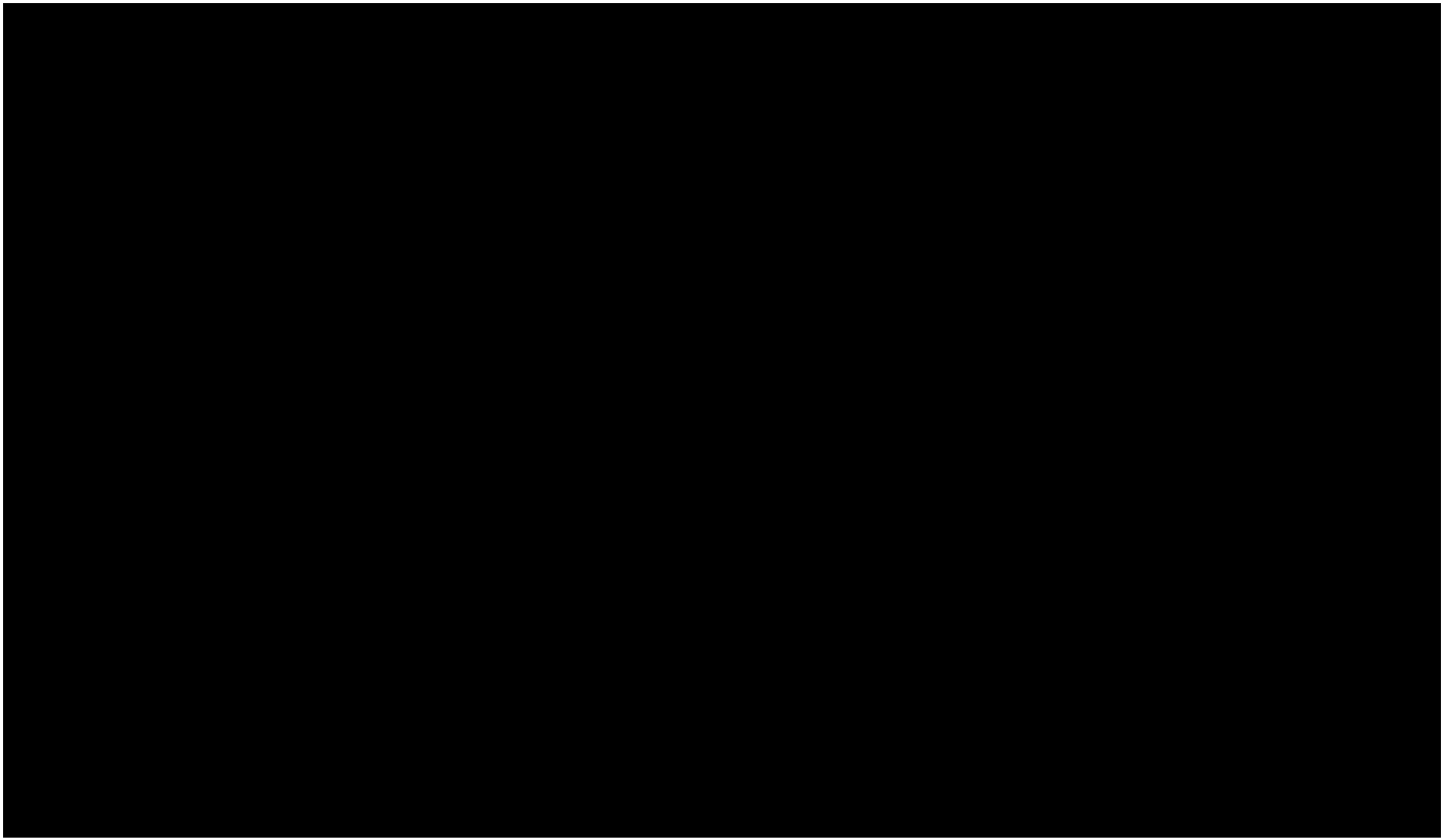
Data Monitoring Committee: No

1.2. Schema







2. Introduction

2.1. Study Rationale

The purpose of this open-label, extension study is to evaluate the long-term safety of repeated MT10109L treatment of GL and/or LCL in participants with moderate to severe GL, LCL, or both (GL and LCL) who completed the lead-in pivotal Phase 3 studies (MT10109L-001, -002, - 005, and -006) over an additional 24 months.

The clinical development program for MT10109L in the treatment of GL and LCL includes 4 pivotal Phase 3 double-blind, randomized, parallel-group, placebo-controlled, multicenter clinical studies. Each of these studies will provide the primary safety and efficacy data for MT10109L treatment of GL (Studies MT10109L-001 and -005) and LCL (Studies MT10109L-002 and -006). Participants completing these studies will be eligible to enroll into the current 24-month open-label extension study (Study MT10109L-004) and continue their treatment of GL, LCL, or both GL and LCL.

2.2. Background

[redacted]

Glabellar lines are deep furrows or frown lines in the glabellar area of the face and LCL (or CFL) are horizontal smile lines by the sides of the eyes. 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 GL and LCL 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 GL and LCL) 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).

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]

The purpose of this open-label, extension study is to evaluate the long-term safety of repeated MT10109L treatment of GL and/or LCL in participants with moderate to severe GL, LCL, or both (GL and LCL) who completed the lead-in pivotal Phase 3 studies (MT10109L-001, -002, - 005, and -006) over an additional 24 months. This information will supplement the primary safety and efficacy data from the 4 pivotal lead-in Phase 3 studies. Together with their lead-in Phase 3 study participation, participants who complete this study will provide up to 3 years of continuous treatment exposure data.

2.3. Benefit/Risk Assessment

Generally, the popularity of BoNT/A cosmetic treatment of GL and LCL 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).

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]

3. Objectives and Endpoints

Objectives	Endpoints
Primary • To evaluate the long-term safety of repeat treatments of MT10109L in participants with *moderate to severe* GL, LCL, or both (GL and LCL)	• Incidence of adverse events, change from baseline in vital signs, and presence of binding and neutralizing antibodies
Other[a]	[redacted]

[a] There are no objectives associated with the efficacy endpoints in this study.

[b] *Baseline* is from the lead-in studies for all efficacy endpoints in this study.

4. Study Design

4.1. Overall Design

- [redacted]

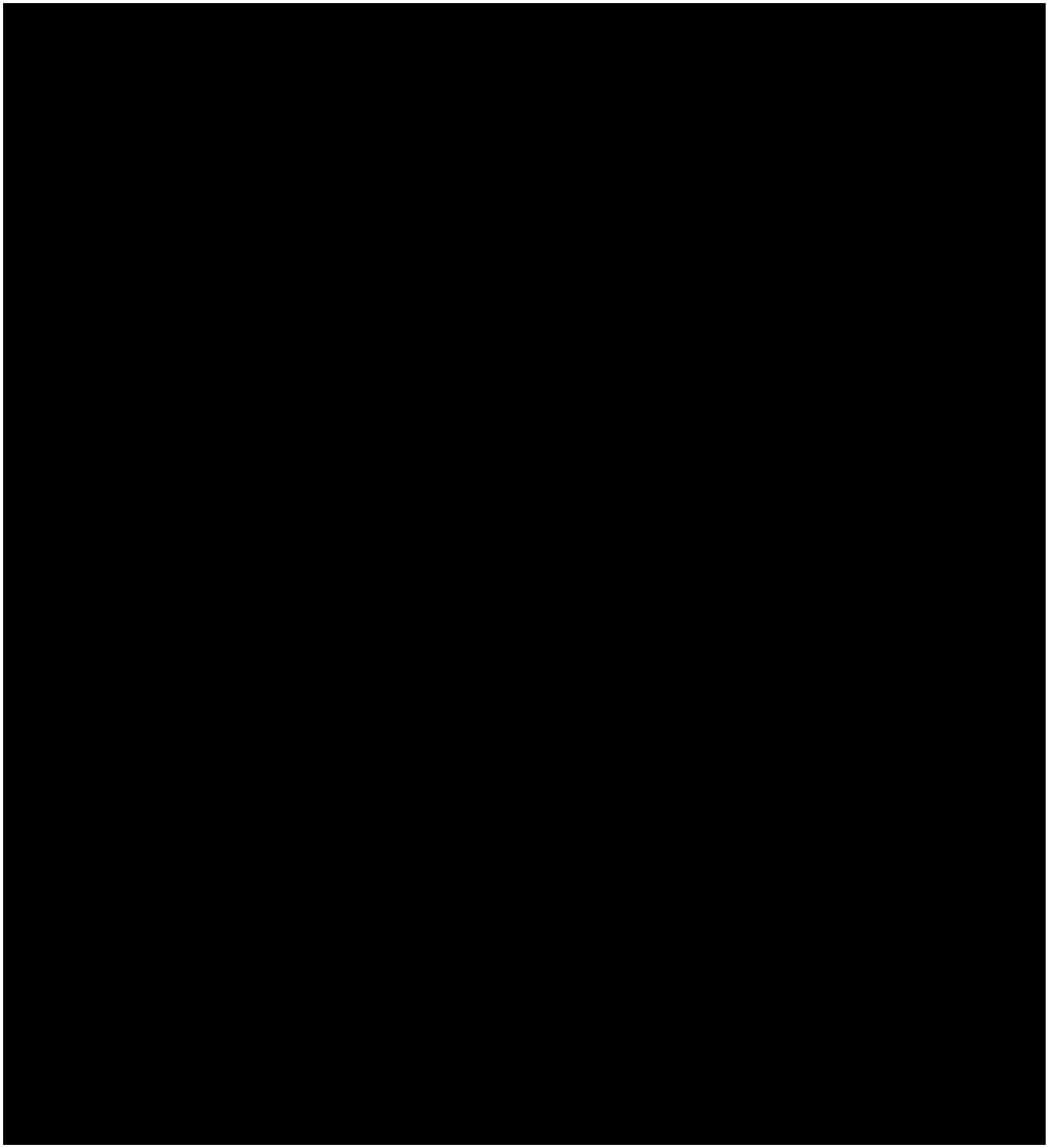
[redacted]

- All participants who complete studies MT10109L-001 (GL), MT10109L-002 (LCL), MT10109L-005 (GL with or without LCL), and MT10109L-006 (LCL with or without GL) will be eligible to enroll into this 24-month open-label extension study (Study MT10109L-004).
- Approximately 800 participants will be enrolled at approximately 44 global sites [redacted].
- [redacted]

[redacted]

  - [redacted]
  - [redacted]
  - [redacted]

- Participants who complete this study will have an exit visit on Day 720.



4.2. Scientific Rationale for Study Design

MT10109L is a BoNT/A product being developed for IM injection in the treatment of GL and LCL. These indications are currently treated with other BoNT/A products. [redacted] This study is designed to assess the long-term safety of repeat treatments of MT10109L in the treatment of GL, LCL, or both (GL and LCL). Efficacy after repeated treatments will also be explored.

4.3. Justification for Dose

[redacted]

4.4. End of Study Definition

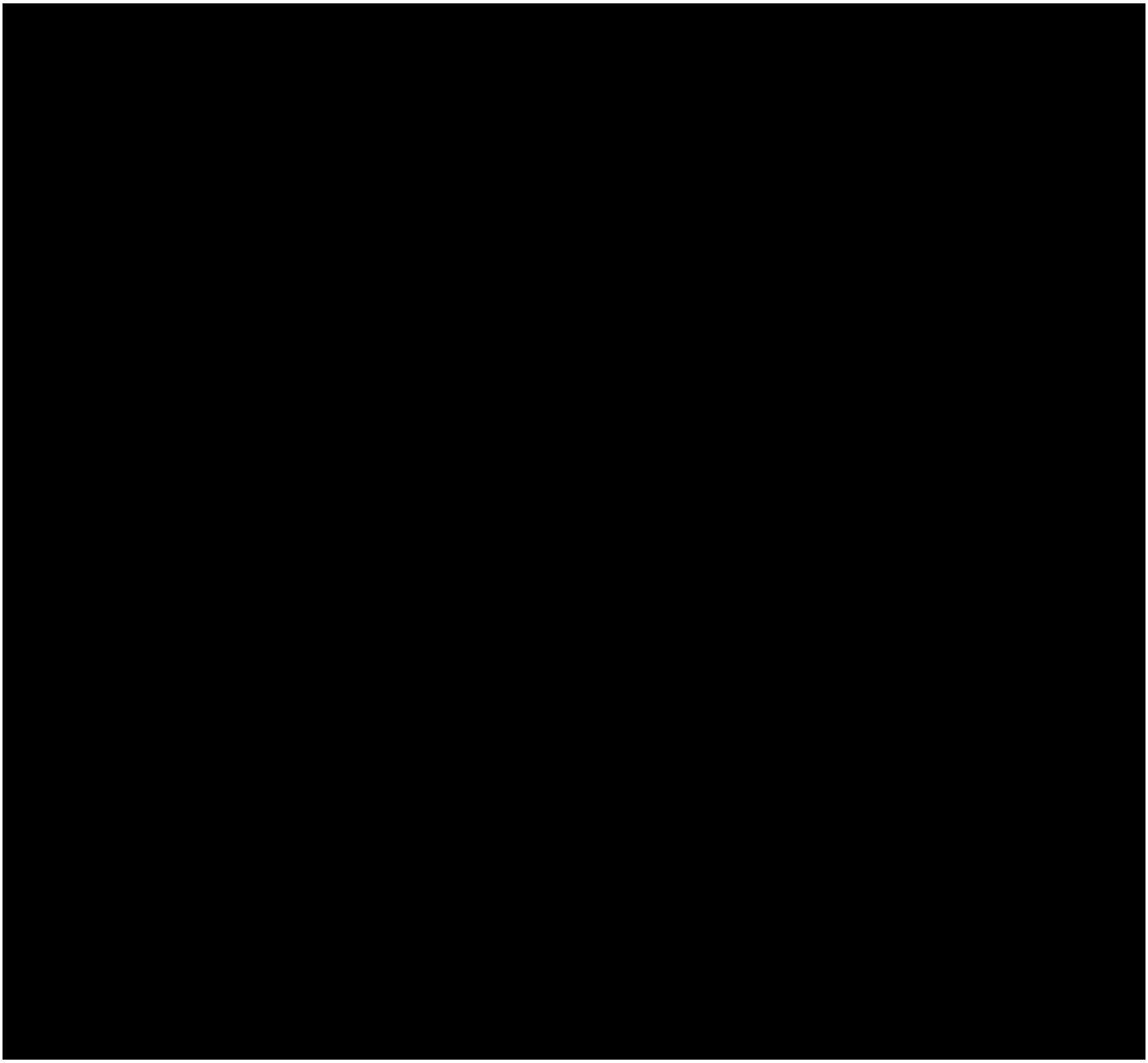
The end of the study is defined as the date of the last scheduled procedure shown in the SoA for the last participant in the study globally.

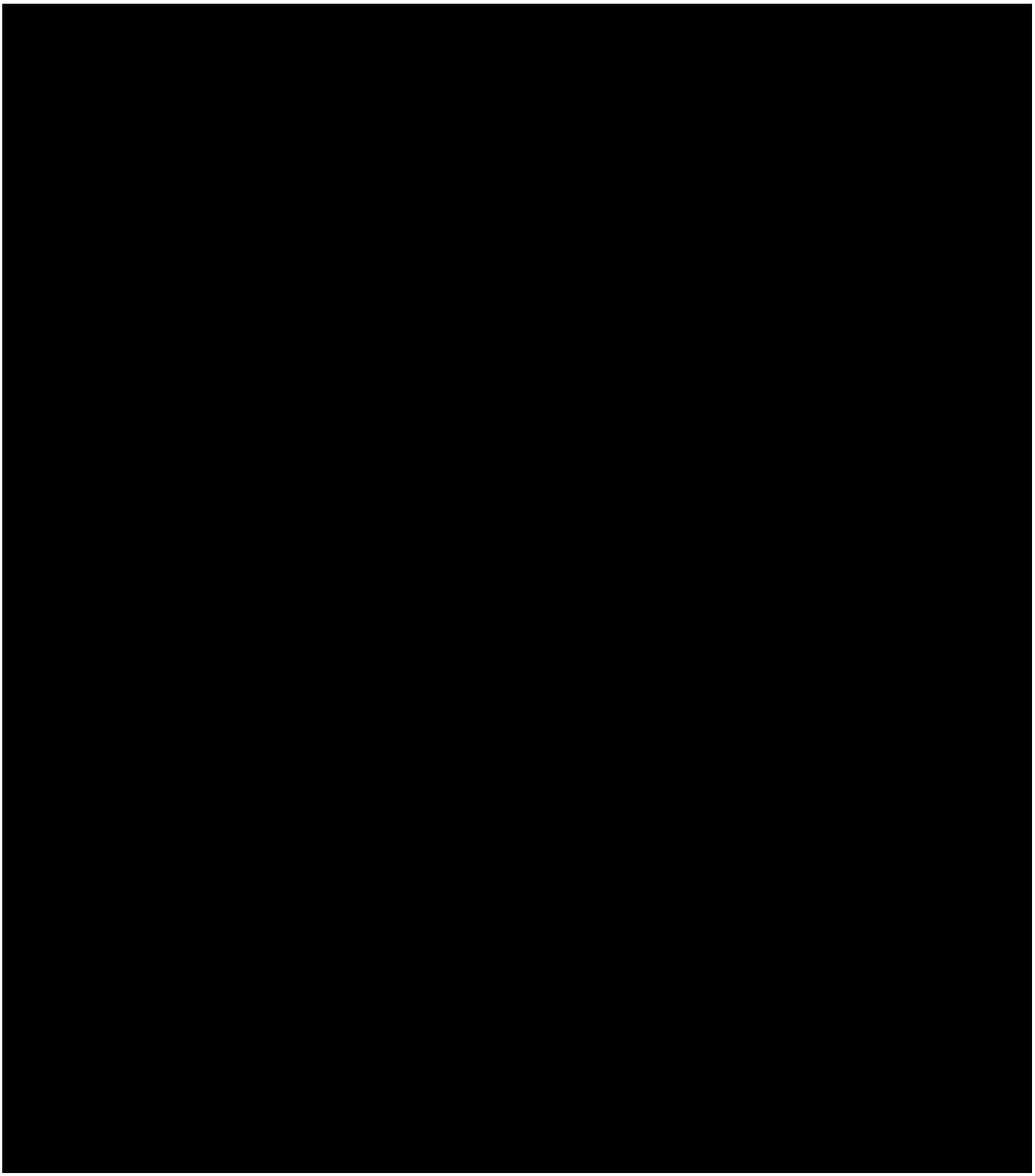
A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the SoA.

5. Study Population

Participants who complete Studies MT10109L-001 (GL), MT10109L-002 (LCL), MT10109L-005 (GL with or without LCL), and MT10109L-006 (LCL with or without GL) will be eligible to enroll into this 24-month open-label extension study.

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





[redacted]

5.3. Lifestyle Considerations

No restrictions are required.

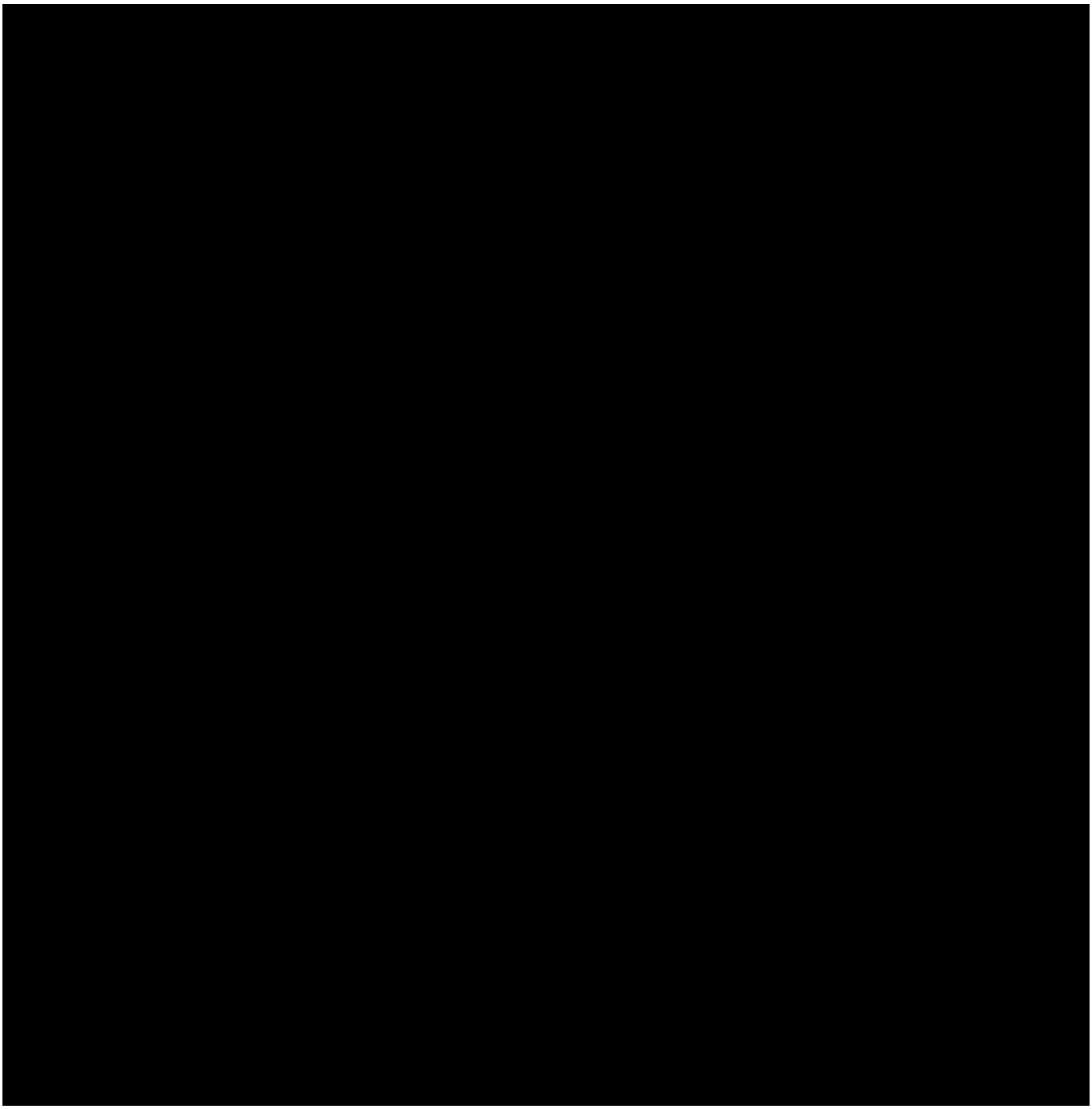
5.4. Screen Failures

[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]

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]

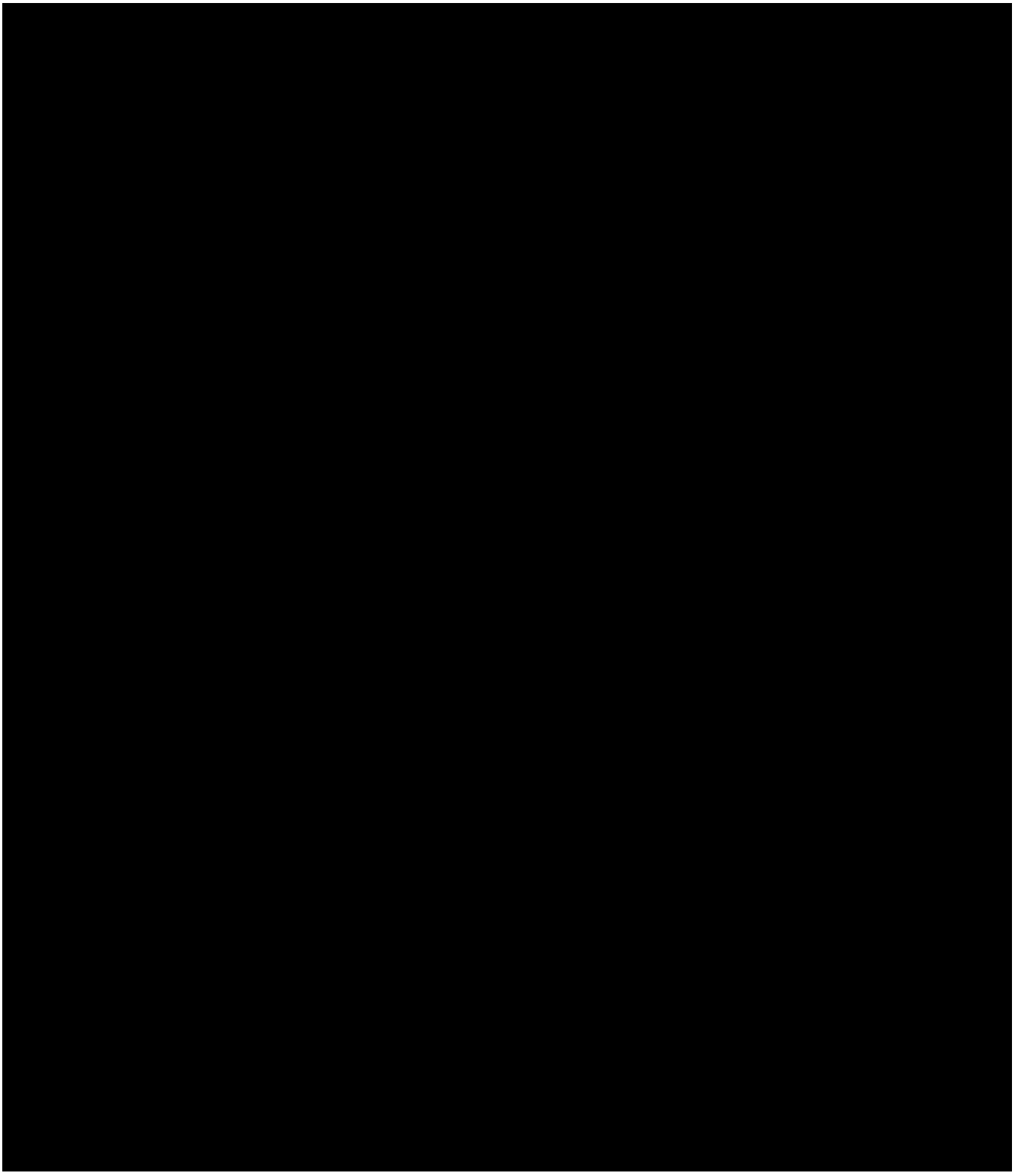
[redacted]

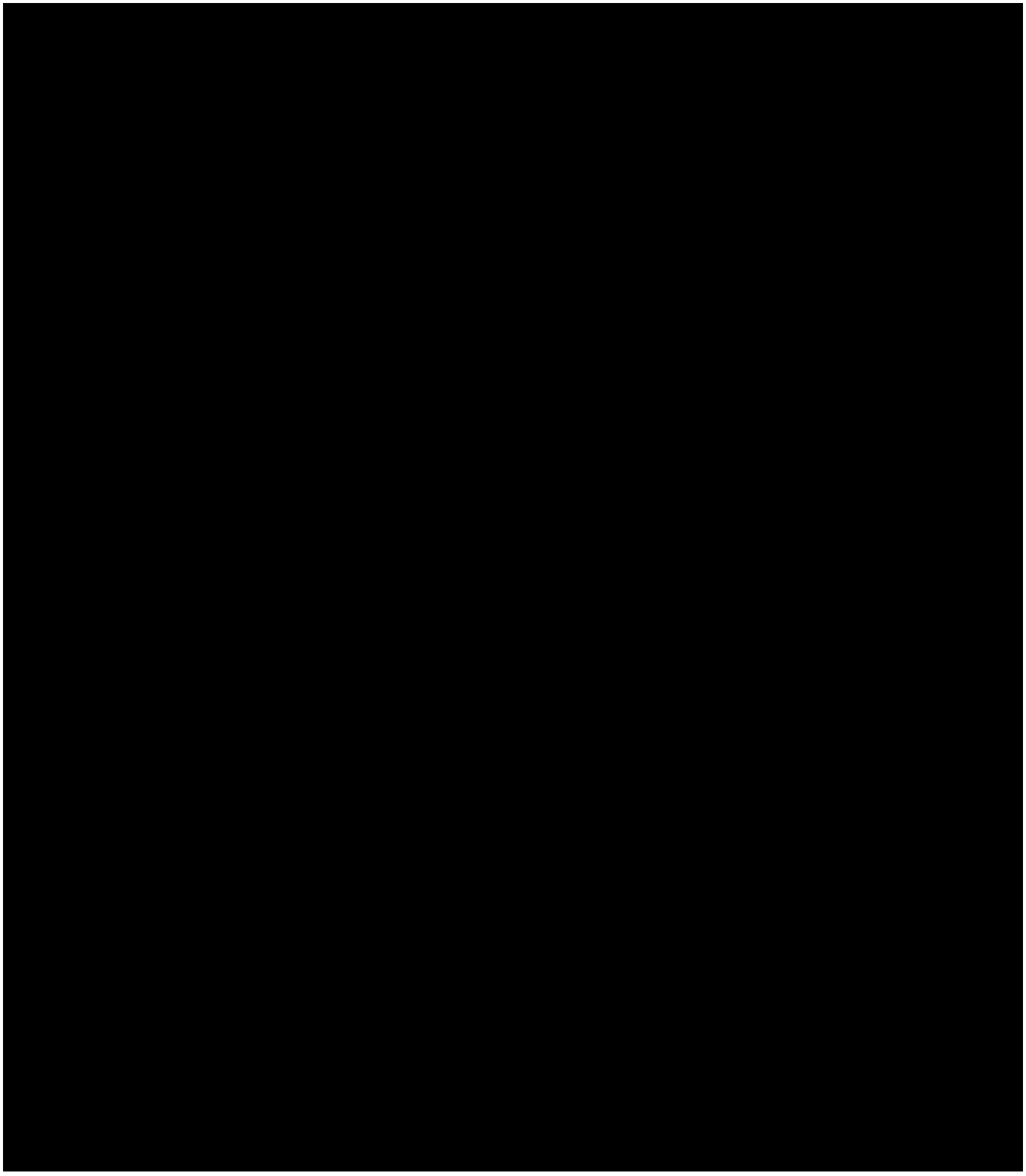
The GL study interventions will be administered as IM injections at 5 injection sites in the glabellar complex, 2 in each corrugator muscle and 1 in the procerus (Figure 6-1 A). The LCL study interventions will be administered as bilaterally symmetrical IM injections at 3 injection sites in the lateral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

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

Glabellar Line Injection Technique

[redacted]





GL and LCL Participants

GL and LCL will be treated together, following the appropriate injection technique for each area, as described above.

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

This is an open-label study.

The participant's identification number from the lead-in Phase 3 study will be used in this extension study. This will serve as the participant identification number on all study documents.

[redacted].

6.4. Study Intervention Compliance

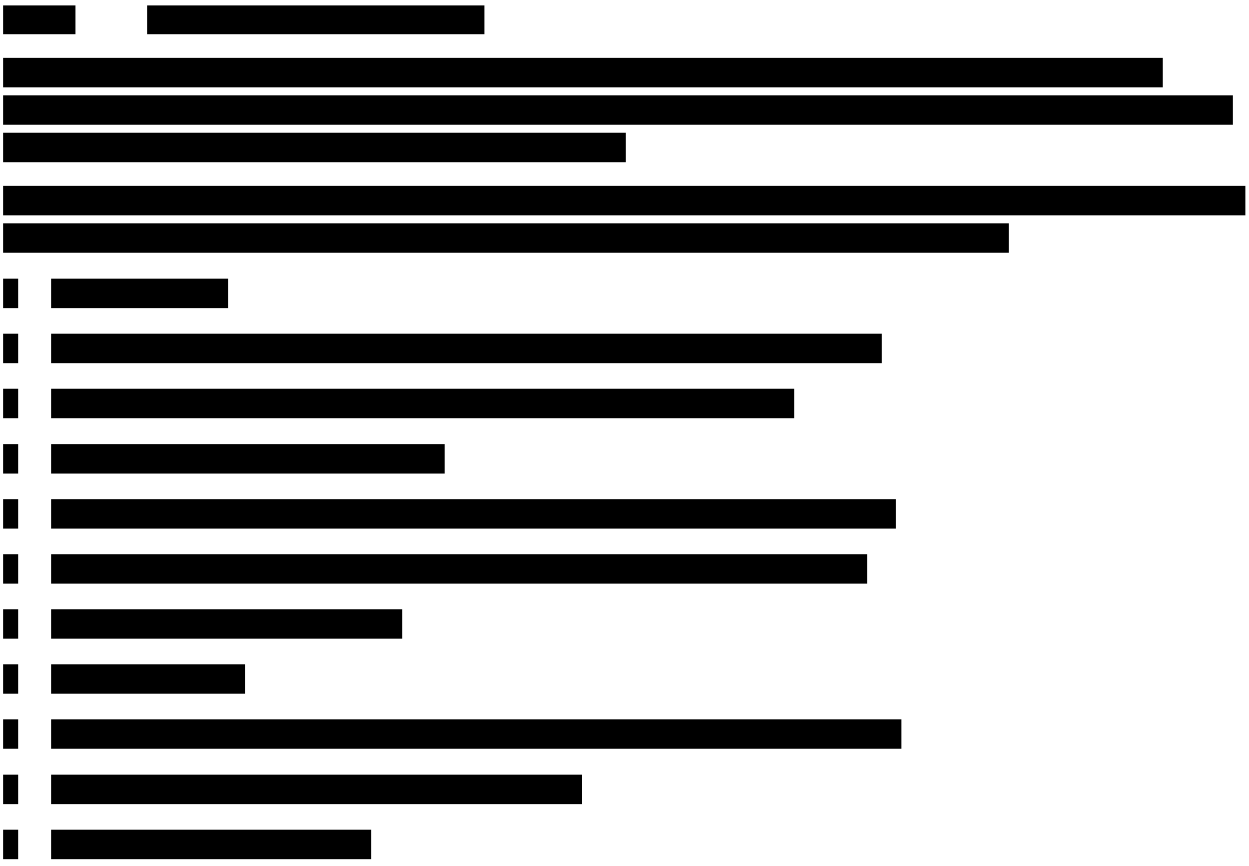
Participants will receive all doses under the direct supervision of study site personnel. Study intervention compliance will not be calculated.

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 each study visit, 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.



[redacted]

[redacted]

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.

[redacted]

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.

Participants entering from the lead-in Phase 3 studies will receive open-label study intervention based on meeting retreatment criteria.

[redacted]

[redacted]

[redacted]

6.7. Intervention After the End of the Study

There is no further intervention following the end of the study.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

A premature discontinuation will occur if a participant who signs the ICF 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 must be discontinued for the following reasons:

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

Women who test positive for urine pregnancy test will NOT receive further interventions and will be discontinued from the study. They must 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.

7.2. Participant Discontinuation/Withdrawal From the Study

- A participant may withdraw from the study at any time at his/her own requestor 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:

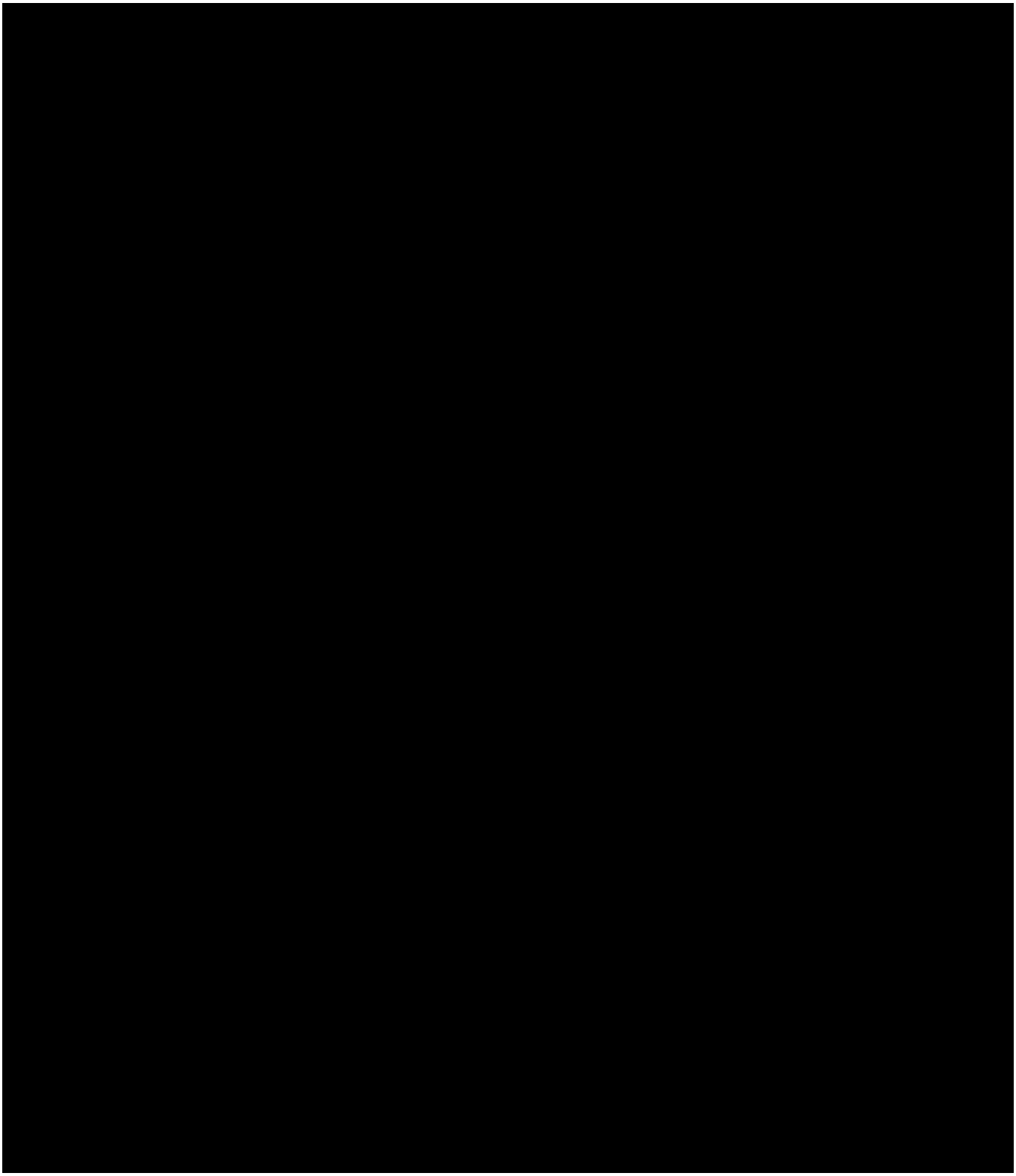
- The study site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a 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 must 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.
- [redacted]
- All assessments must be completed after the participant removes their make-up (if wearing any) and before administration of study intervention.

[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. 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.

8.2.3. 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.

8.2.4. 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).

[redacted]

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

Table 8-1 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)

Table 8-2 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)

The adverse drug reactions of eyelid edema, eyelid ptosis, facial pain, facial paresis, and muscular weakness with BOTOX are usually 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]

All adverse events will be collected from the signing of the ICF at the timepoints specified in the SoA (Section 1.3), and as observed or reported spontaneously by study participants until 30 days after the participant's last study visit.

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 will be collected from the signing of the ICF study at the timepoints specified in the SoA (Section 1.3), and as observed or reported spontaneously by study participants, until at least 12 weeks after the participant's last administration of MT10109L intervention.

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.

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 at subsequent visits/contacts. All TEAEs including SAEs, AESIs (Section 8.3.6), and TEAEs that lead to study discontinuation 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** and **Belgium**, only highly effective contraception methods are allowed for this study.
- Women who test positive for urine pregnancy test will NOT receive further intervention and will be discontinued from the study.

- Women who test positive for urine pregnancy test must 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 reference safety information or protocol for the study intervention or comparator as applicable. See Section 8.4 for information on the 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 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 likely not 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, eyelid ptosis, diplopia, and 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 MSP 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.

[redacted]

[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. In Stage 2, only samples that are confirmed positive in the ELISA will be tested for neutralizing antibodies to MT10109L.

8.9. Medical Resource Utilization and Health Economics

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

9. Statistical Considerations

9.1. Statistical Hypotheses

Not applicable.

9.2. Sample Size Determination

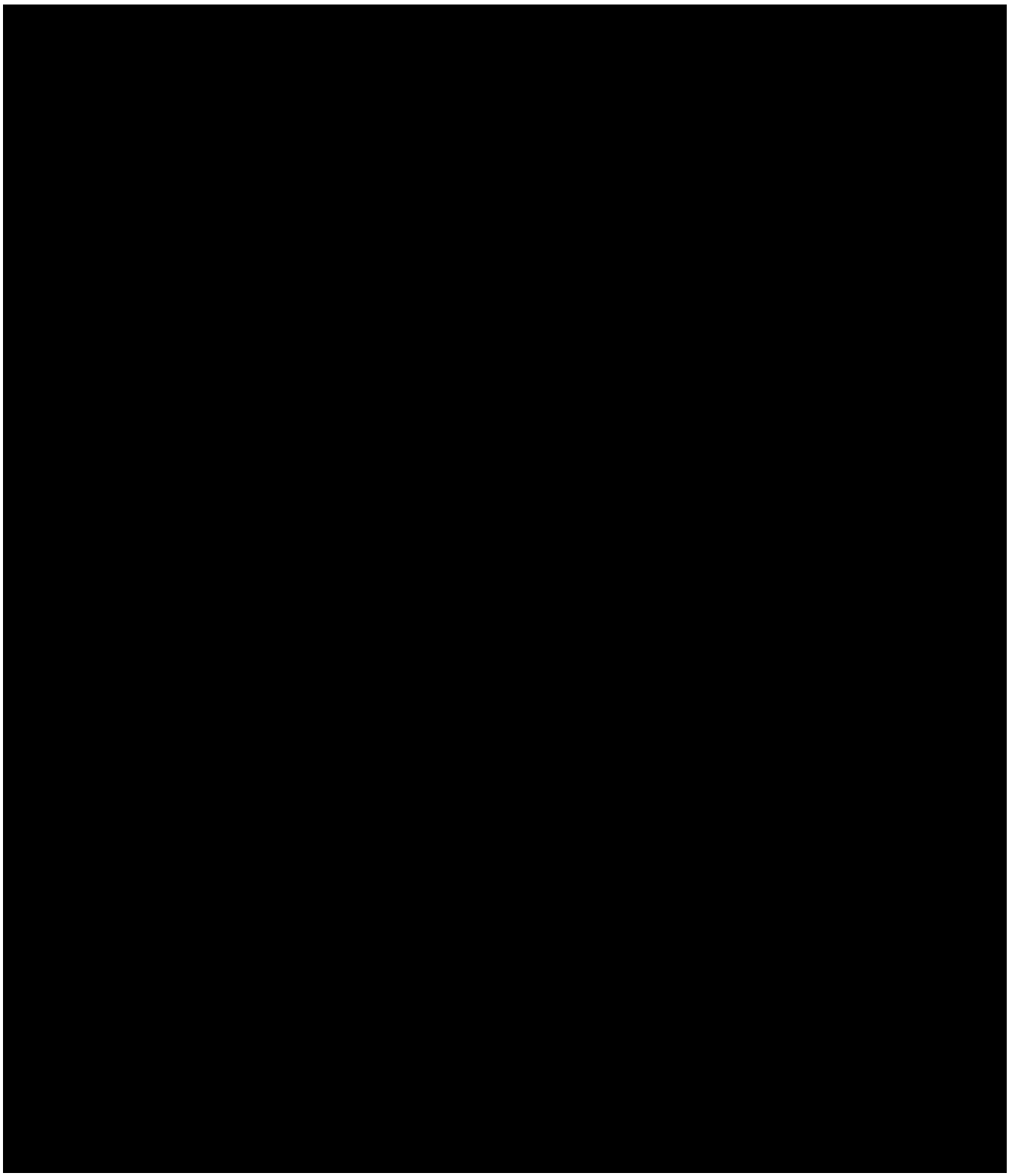
For this long-term follow-up study, no formal statistical power/sample size calculation was used. Approximately 800 participants are anticipated to be enrolled into this study. [redacted]

9.3. Populations for Analyses

[redacted]

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock 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 efficacy endpoints.



[redacted]

9.4.2. Safety Analyses

The safety parameters will include:

- Adverse events
- Vital signs
- Immunogenicity analyses

9.4.2.1. Adverse Events

[redacted]

An adverse event that occurs more than 30 days after study exit will not be counted as a TEAE.

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 [redacted].

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 by MT10109L cycle.

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 MT10109L intervention.

[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 for each 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

[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 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 or their legally authorized representatives 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.

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 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.

10.2. Appendix 2: Clinical Laboratory Tests

Not applicable.

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

10.3.1. Definition of Adverse Event (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 safety assessments (eg, 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
- 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

10.3.2. 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.

10.3.3. 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.

Follow-up of AEs and SAEs
• See Section 8.3.3

10.3.4. Reporting of SAEs

SAE Reporting

- [redacted]
- [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

AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
BoNT/A	botulinum toxin type A
CFL	crow's feet lines
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
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
[redacted]	[redacted]
[redacted]	[redacted]
FSH	follicle-stimulating hormone
[redacted]	[redacted]
GCP	Good Clinical Practice
GL	glabellar lines
HIPAA	Health Insurance Portability and Accountability Act
HRT	hormonal replacement therapy
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	institutional ethics committee
IM	intramuscular
IND	investigational new drug application
IRB	institutional review board

ISO	International Organization for Standardization
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
[redacted]	[redacted]
MSP	medical safety physician
[redacted]	[redacted]
PRO	patient-reported outcome
SAE	serious adverse event
SAP	statistical analysis plan
SoA	schedule of activities
SUSAR	suspected unexpected serious adverse reactions
TCA	trichloroacetic acid
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent SAE
U	unit
UFL	upper facial lines
US	United States
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 participant 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
Non-compliance 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)

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, Long-term, Open-label Study to Evaluate the Safety of MT10109L (NivobotulinumtoxinA) for the Treatment of Glabellar Lines and Lateral Canthal Lines
	Clinical Study Sponsor	Medytox, Inc.
	Trial Phase Classification	Phase 3
	Trial Indication	Glabellar Lines and Lateral Canthal Lines
	Trial Indication Type	Intervention
	Trial Type	Safety
	Trial Length	Approximately 24 months
	Planned Country of Investigational Sites	United States, Canada, European Union, and Russia
	Planned Number of Participants	Approximately 800 participants
	FDA-Regulated Device Study	No
	FDA-Regulated Drug Study	Yes
	Pediatric Study	No
Participant information	Diagnosis Group	Participants who completed lead-in Phase 3 studies MT10109L-001 (GL), MT10109L-002 (LCL), MT10109L-005 (GL with or without LCL), and MT10109L-006 (LCL with or without GL)
	Healthy Participant Indicator	No
	Planned Minimum Age of Participants	19
	Planned Maximum Age of Participants	Not applicable (66 years of age for studies in Russia)
	Sex of Participants	Both
	Stable Disease Minimum Duration	Not applicable

Parameter Group	Parameter	Value
Interventions	Investigational Therapy or Intervention	MT10109L (NivobotulinumtoxinA)
	Intervention Type	Drug
	Pharmacological Class of Invest. Therapy	NivobotulinumtoxinA
	[redacted]	[redacted]
	Dose Units	4 U per 0.1 mL
	Dosing Frequency	Up to 9 interventions
	Route of Administration	Intramuscular
	Current Therapy or Intervention	Not applicable
	Added on to Existing Interventions	No
	Control Type	None
	Comparative Intervention Name	Not applicable
Trial design	Study Type	Interventional
	Intervention Model	Open-label
	Planned Number of Arms	3
	Trial is Randomized	No
	Randomization Quotient	Not applicable
	Trial Blinding Schema	Open-label
	Stratification Factor	Not applicable
	Adaptive Design	No
	Study Stop Rules	Not applicable

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

10.7.1. 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 continue to use one of the nonestrogen hormonal highly effective contraception methods from the lead-in study if they wish to continue their HRT during the current study.

10.7.2. Contraception Guidance

Female Participants

[redacted]

Table 10-1 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 10-2 Acceptable Contraceptive 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.

10.7.3. Pregnancy Testing

- Pregnancy testing, with a sensitivity of [redacted] 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 highly sensitive 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.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

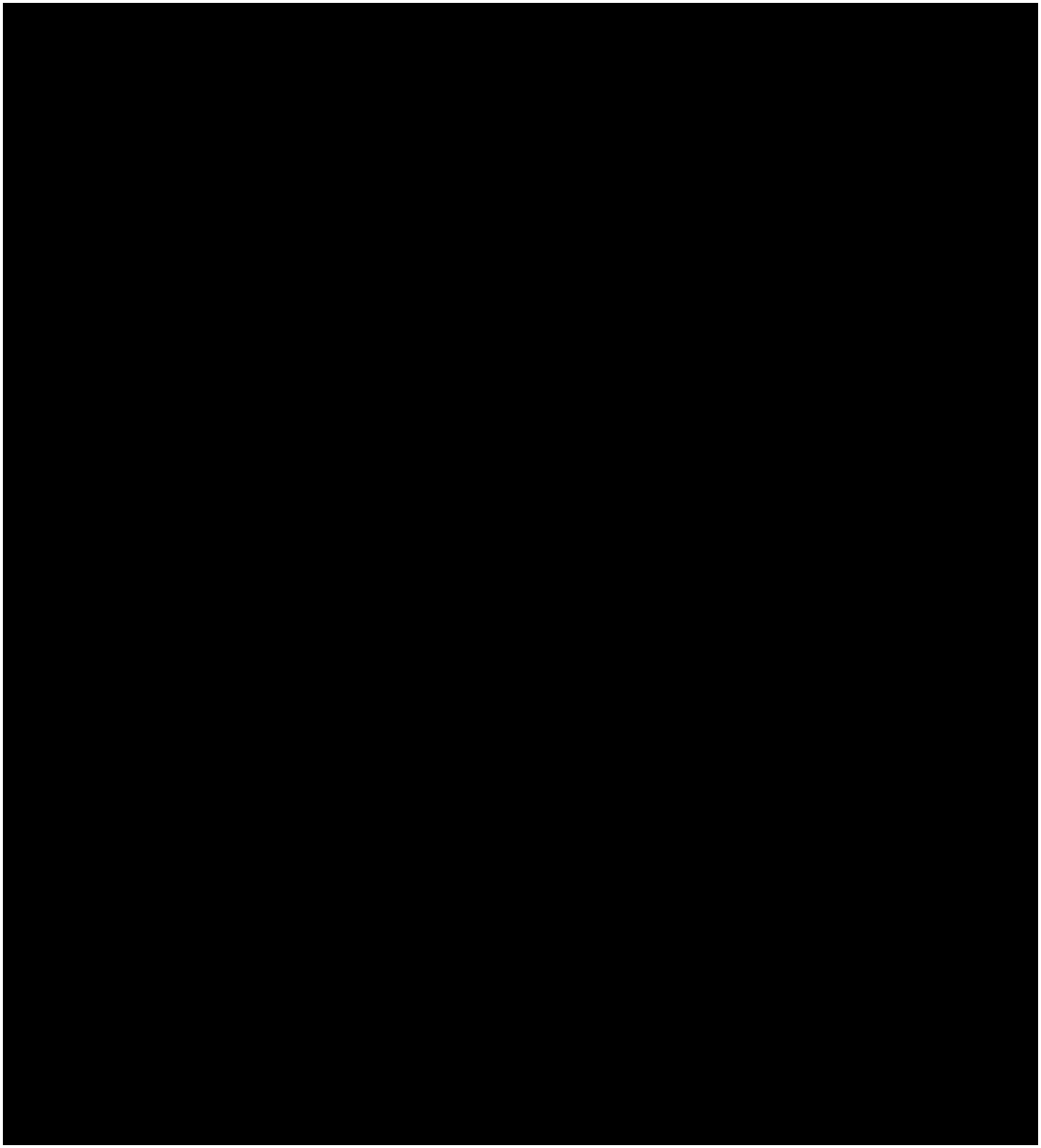
10.7.4. Collection of Pregnancy Information

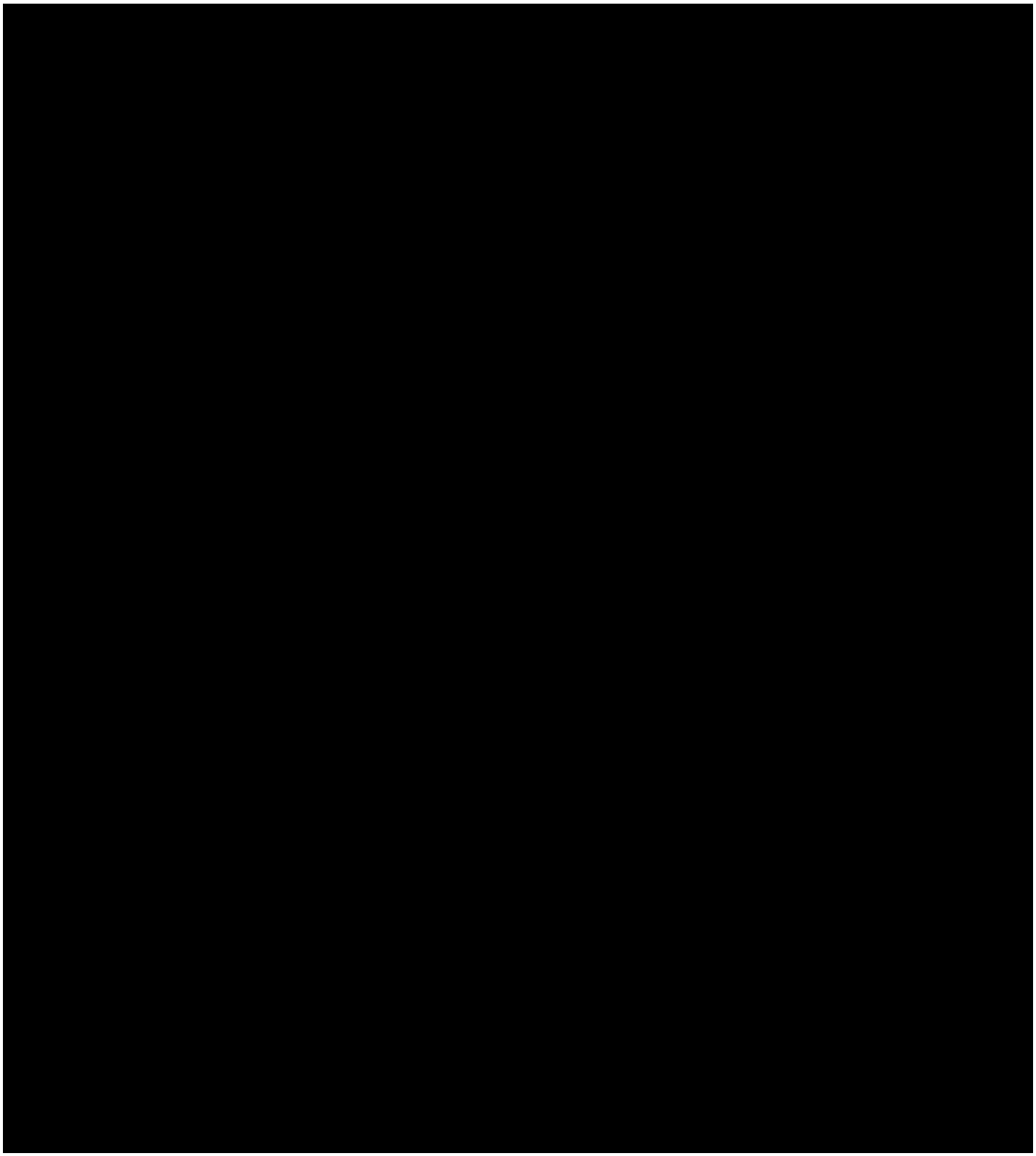
Female Participants Who Become Pregnant

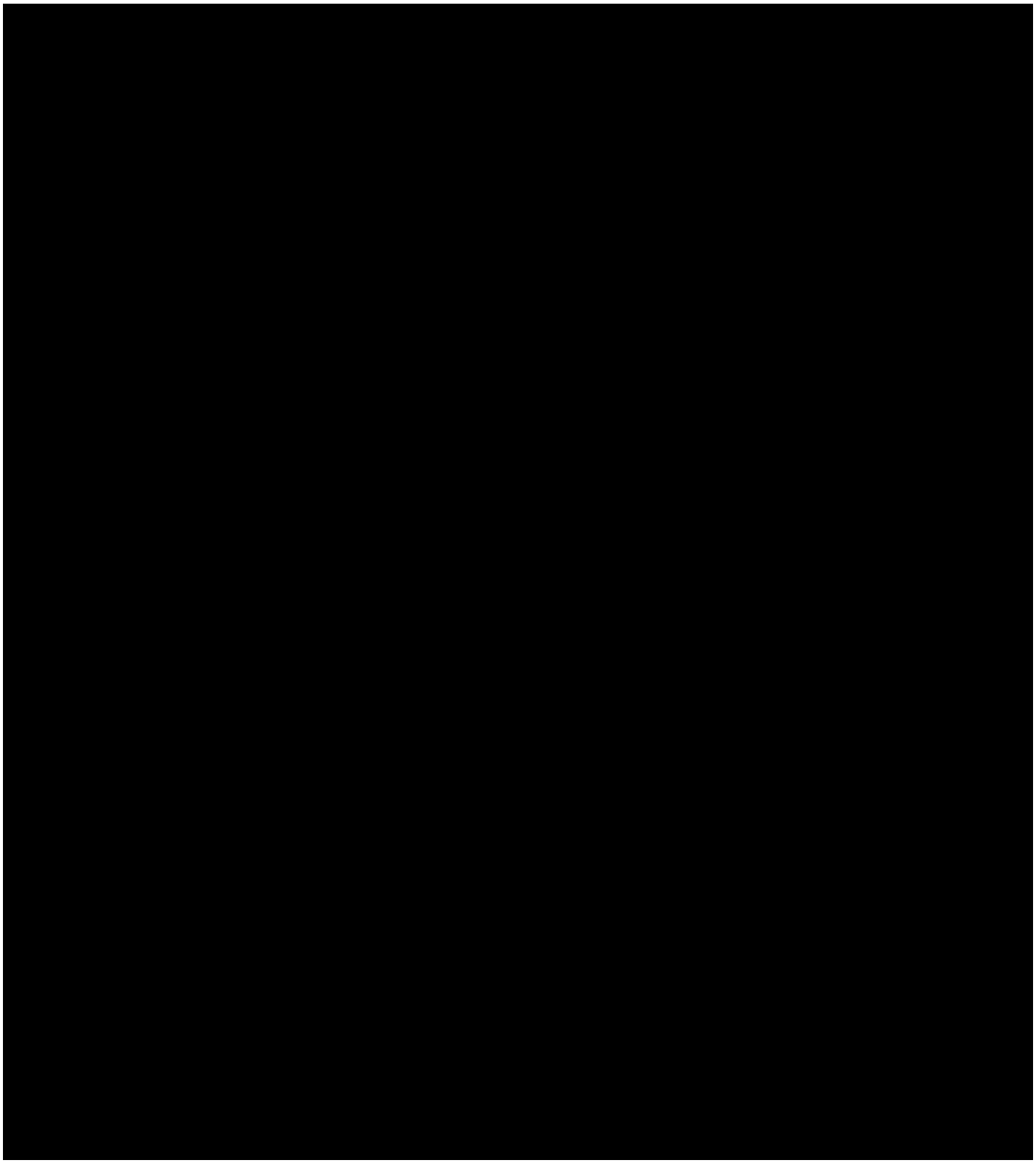
- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed 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 abnormalities, ectopic pregnancy) or genetic abnormalities (whether leading to an elective abortion or not) are always considered to be an SAE 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

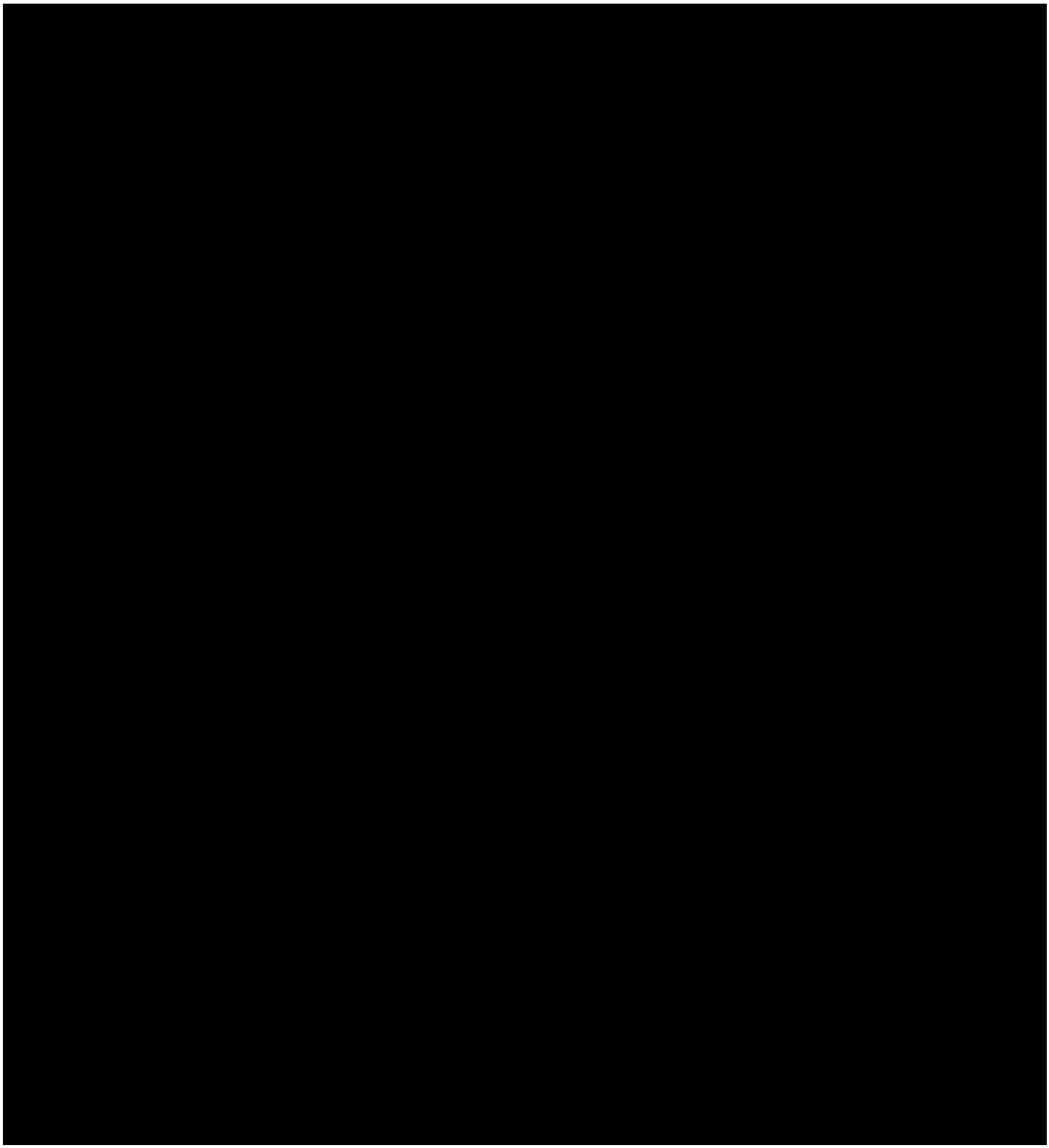
sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

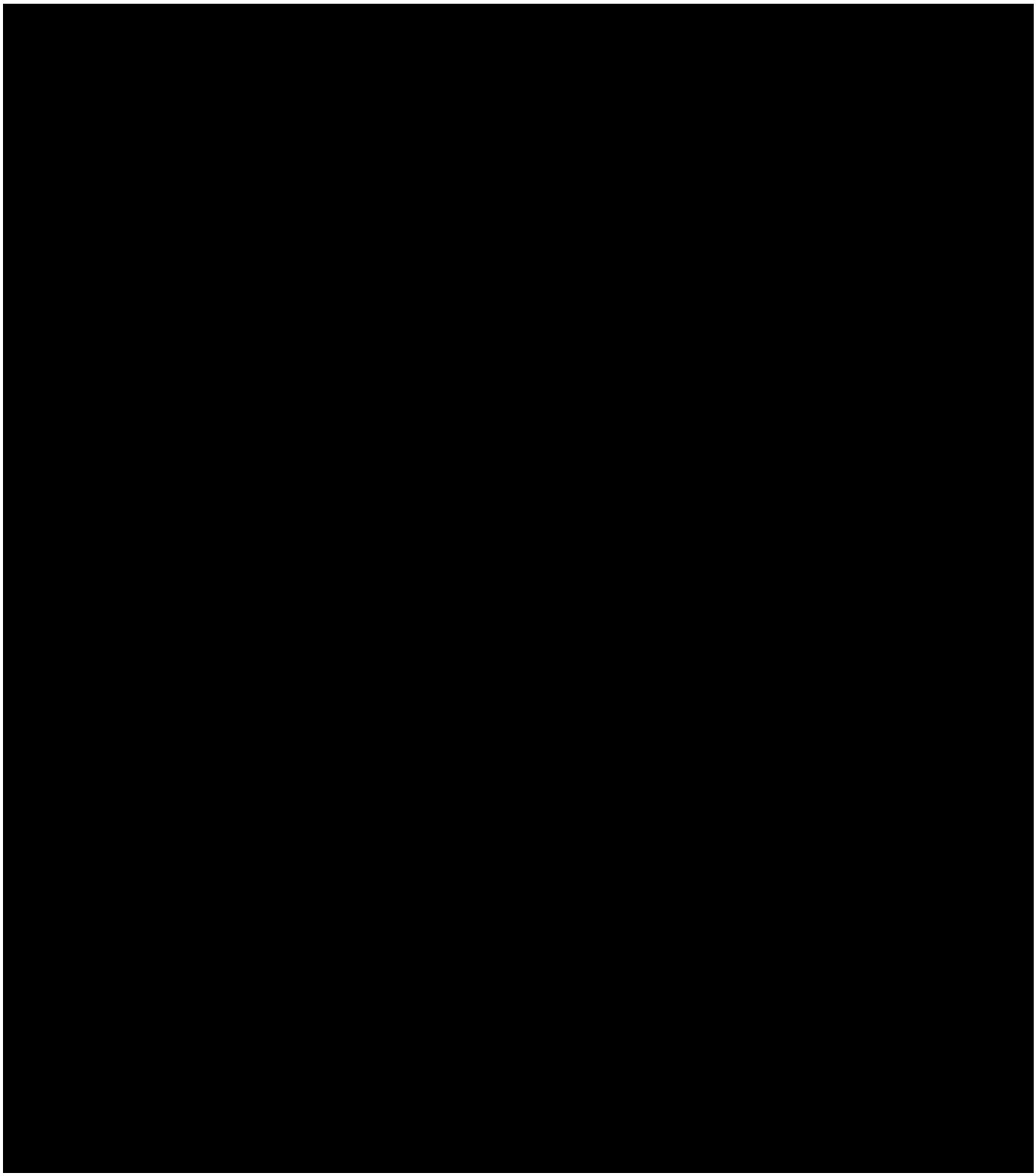
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention and be withdrawn from the study.

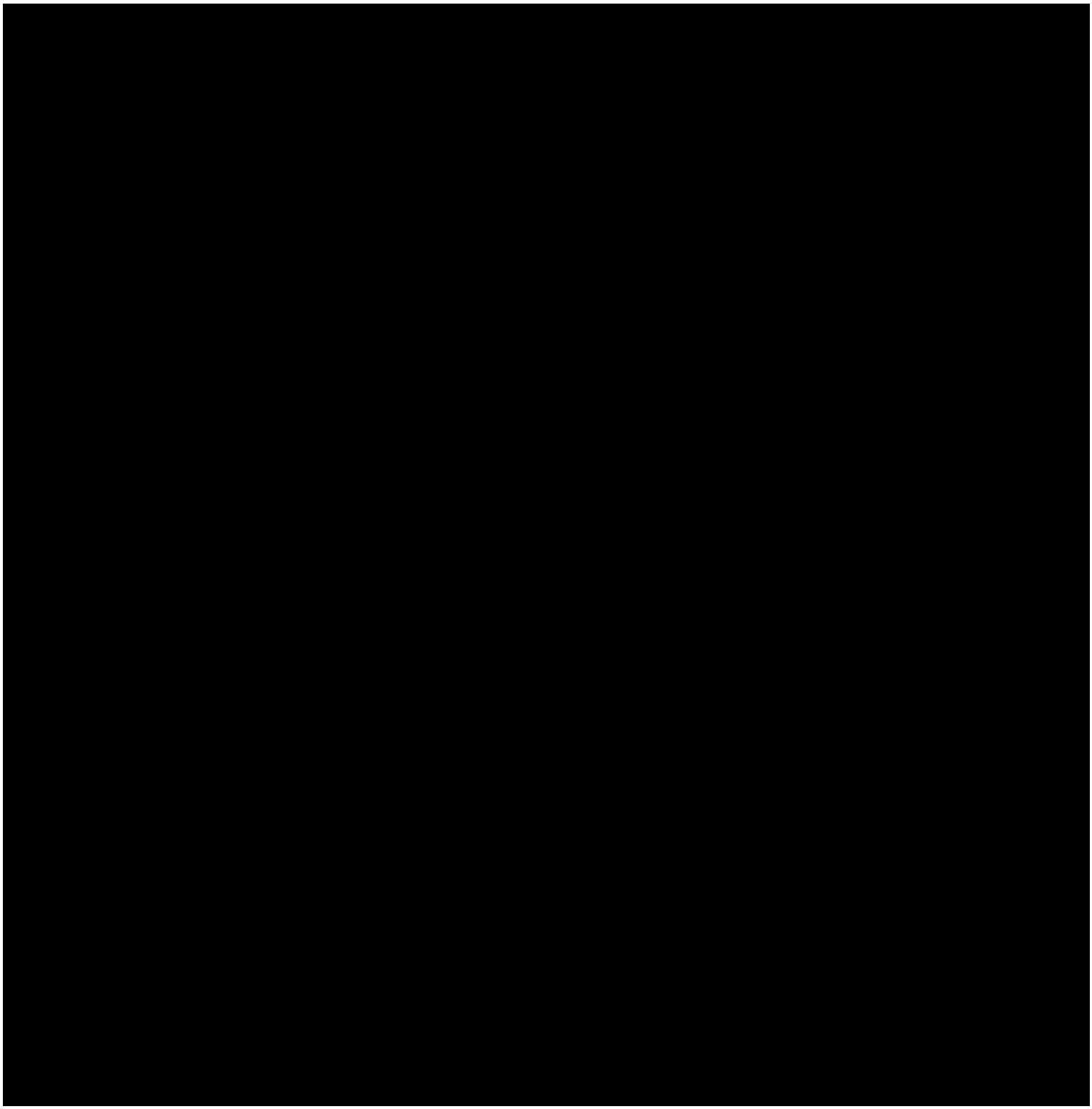


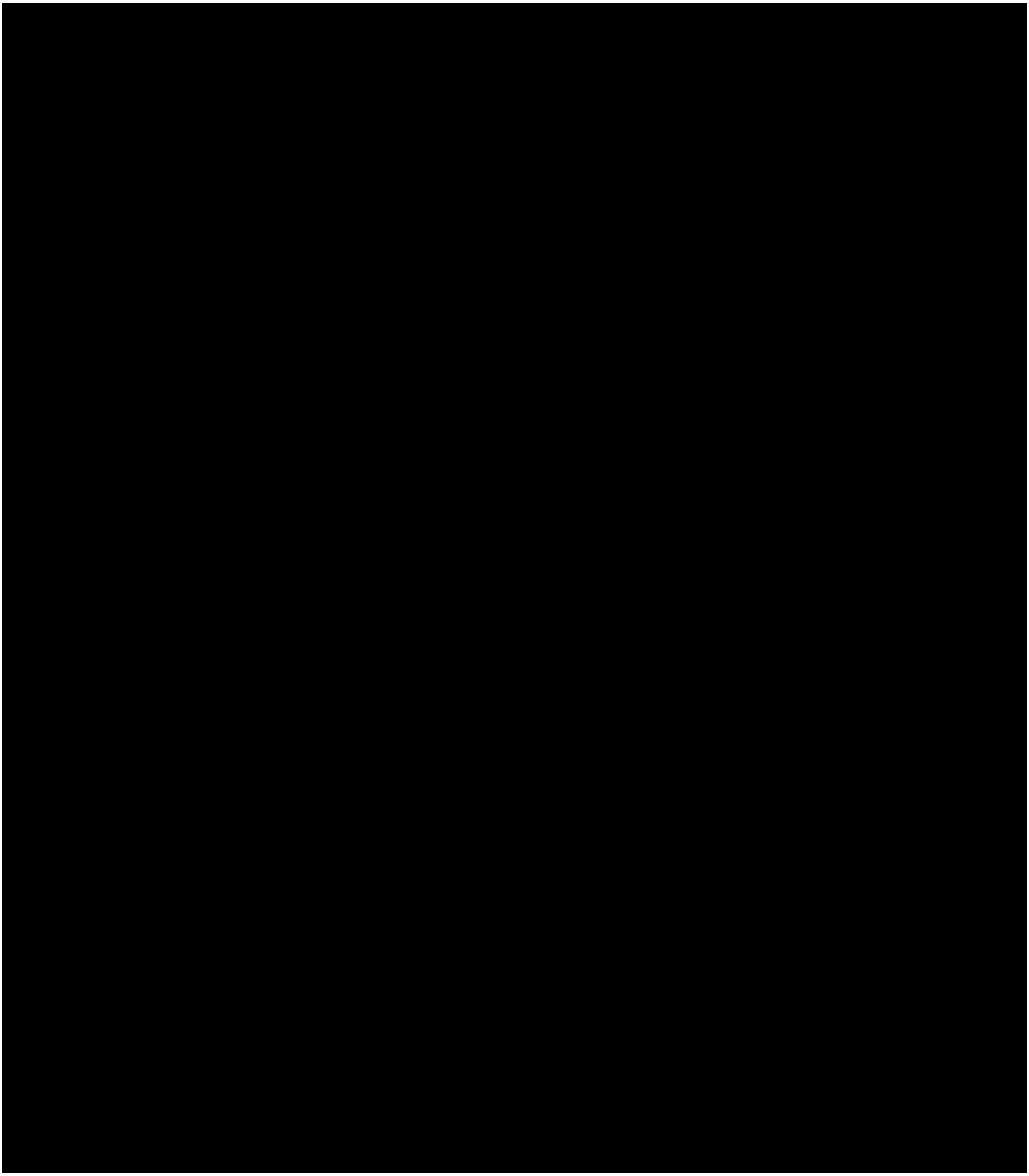


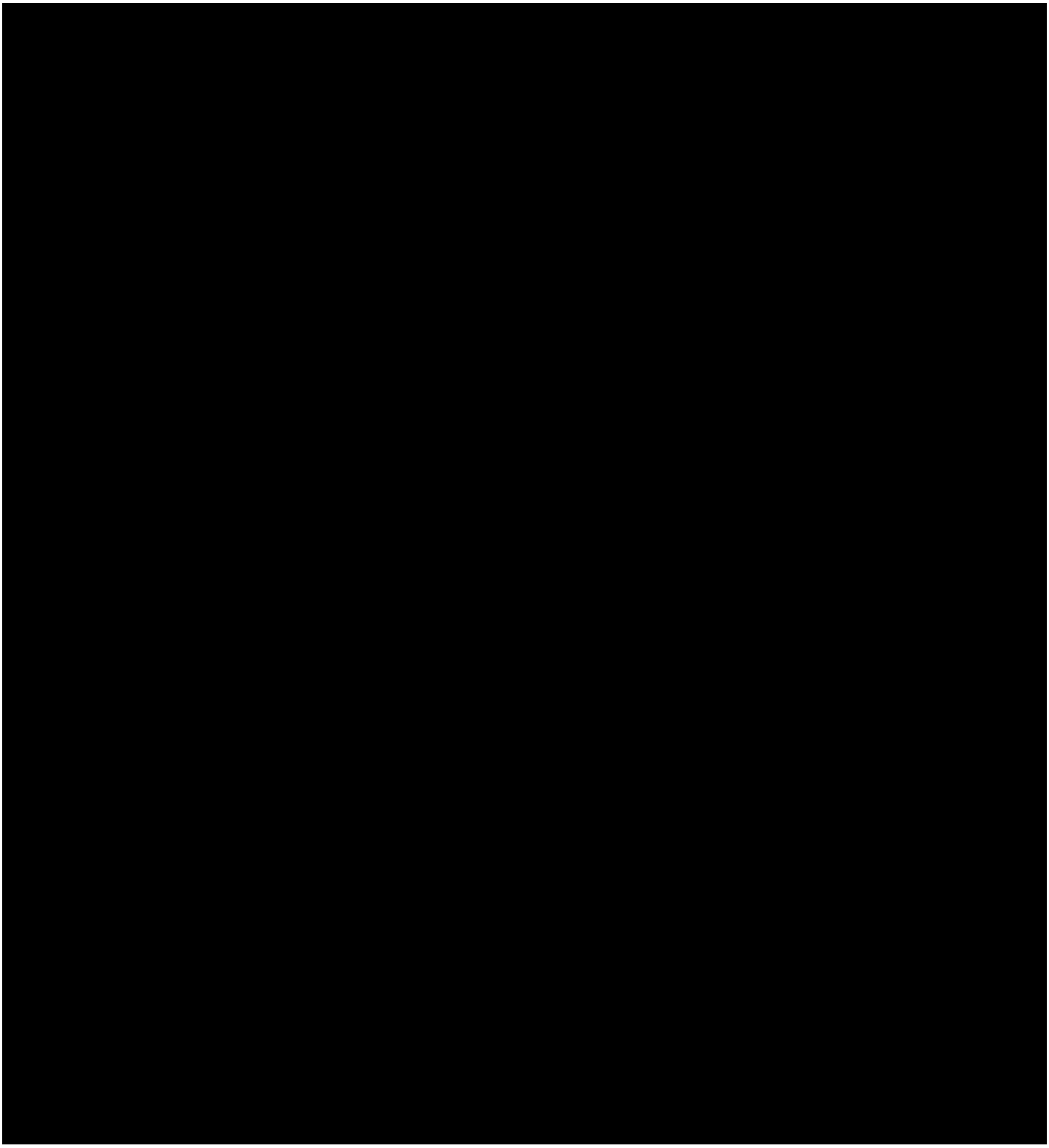


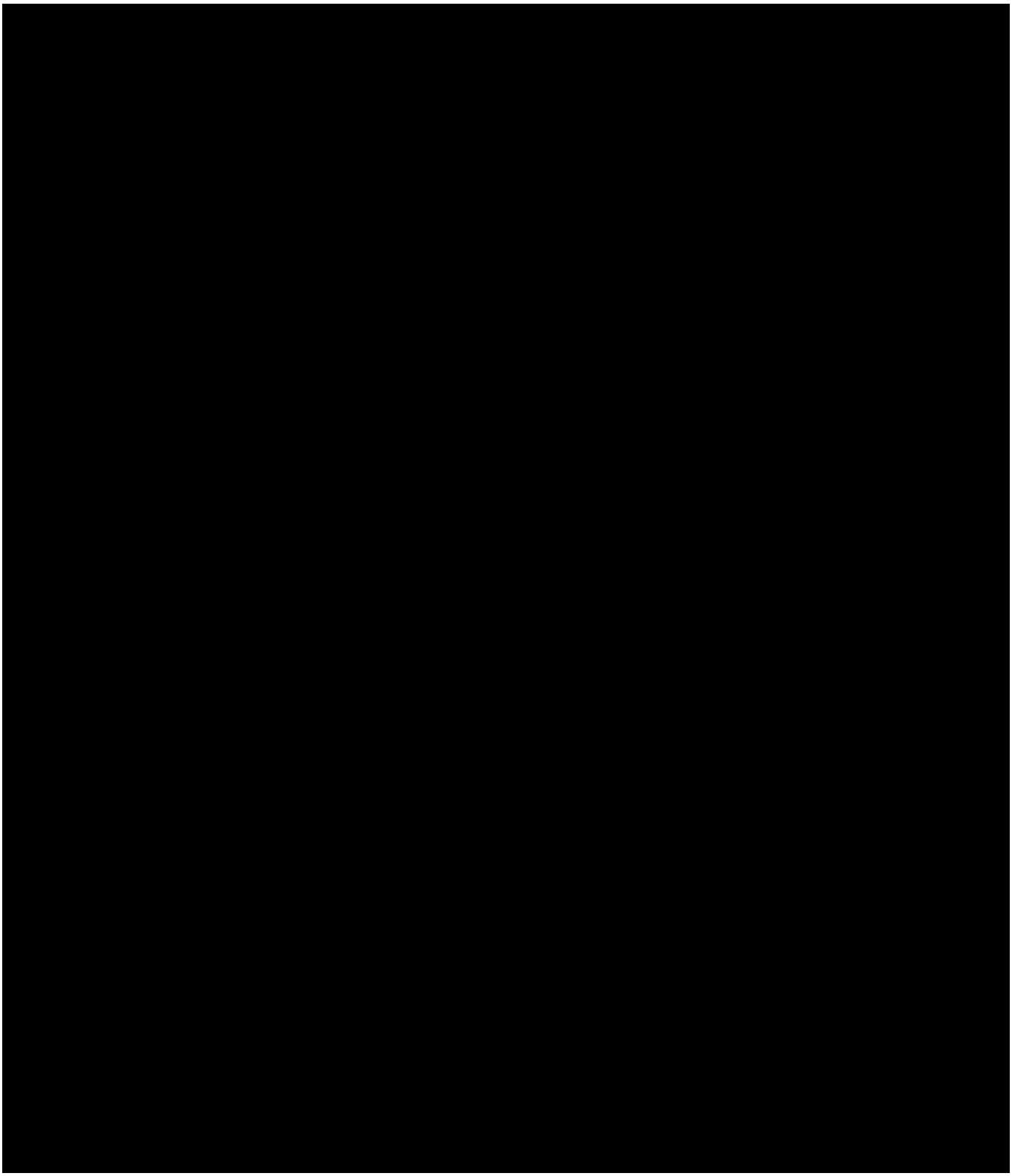


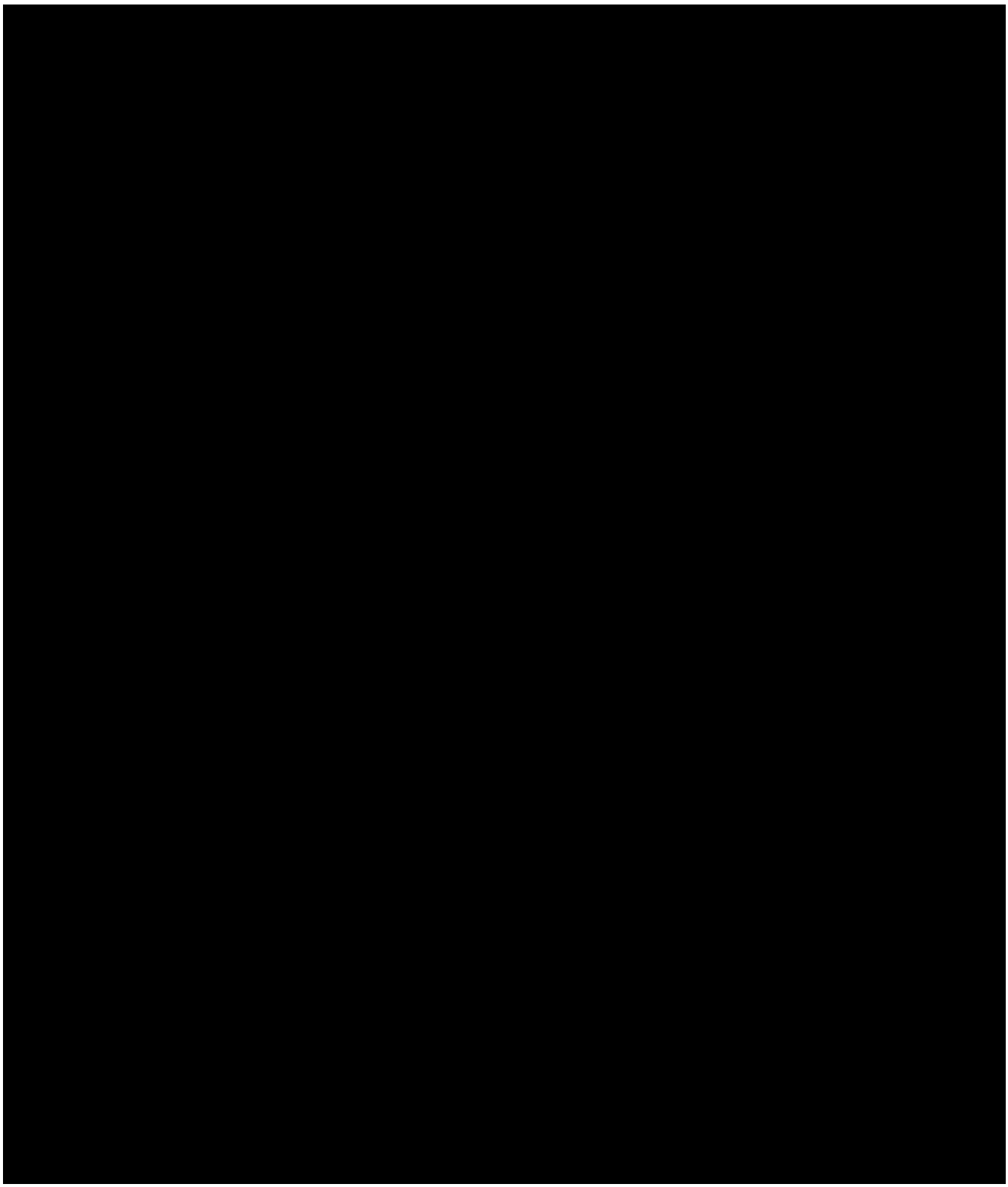


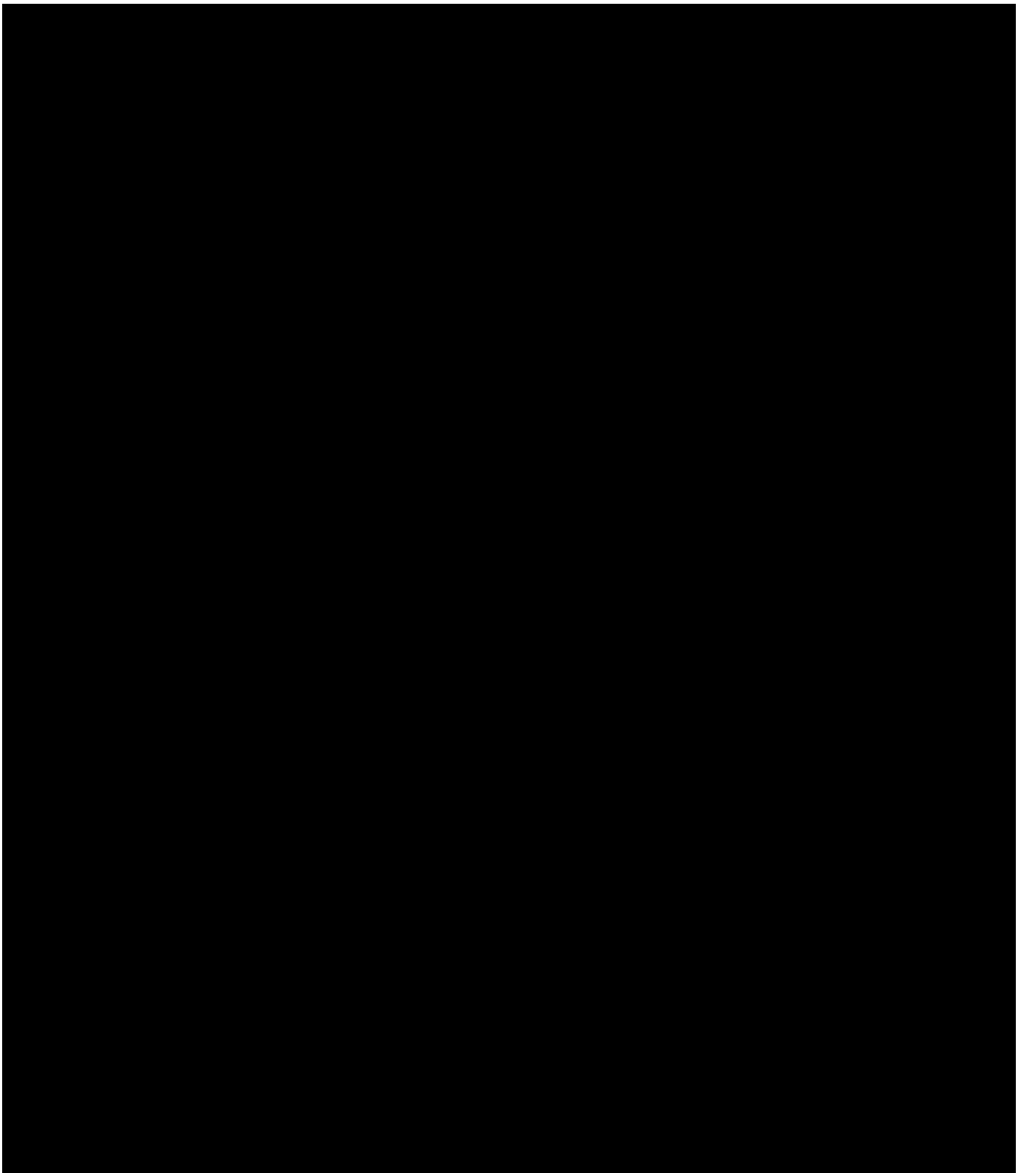


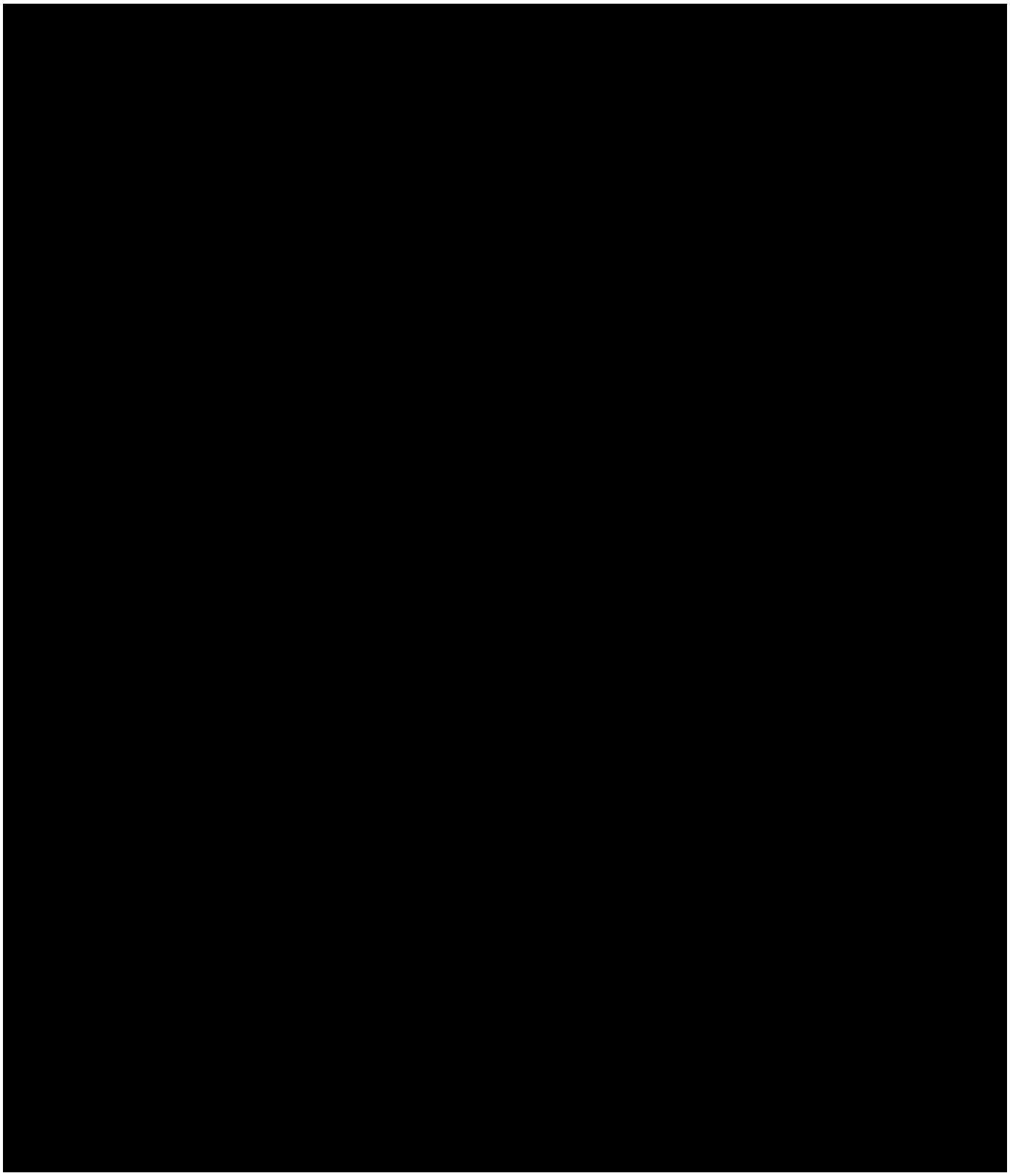


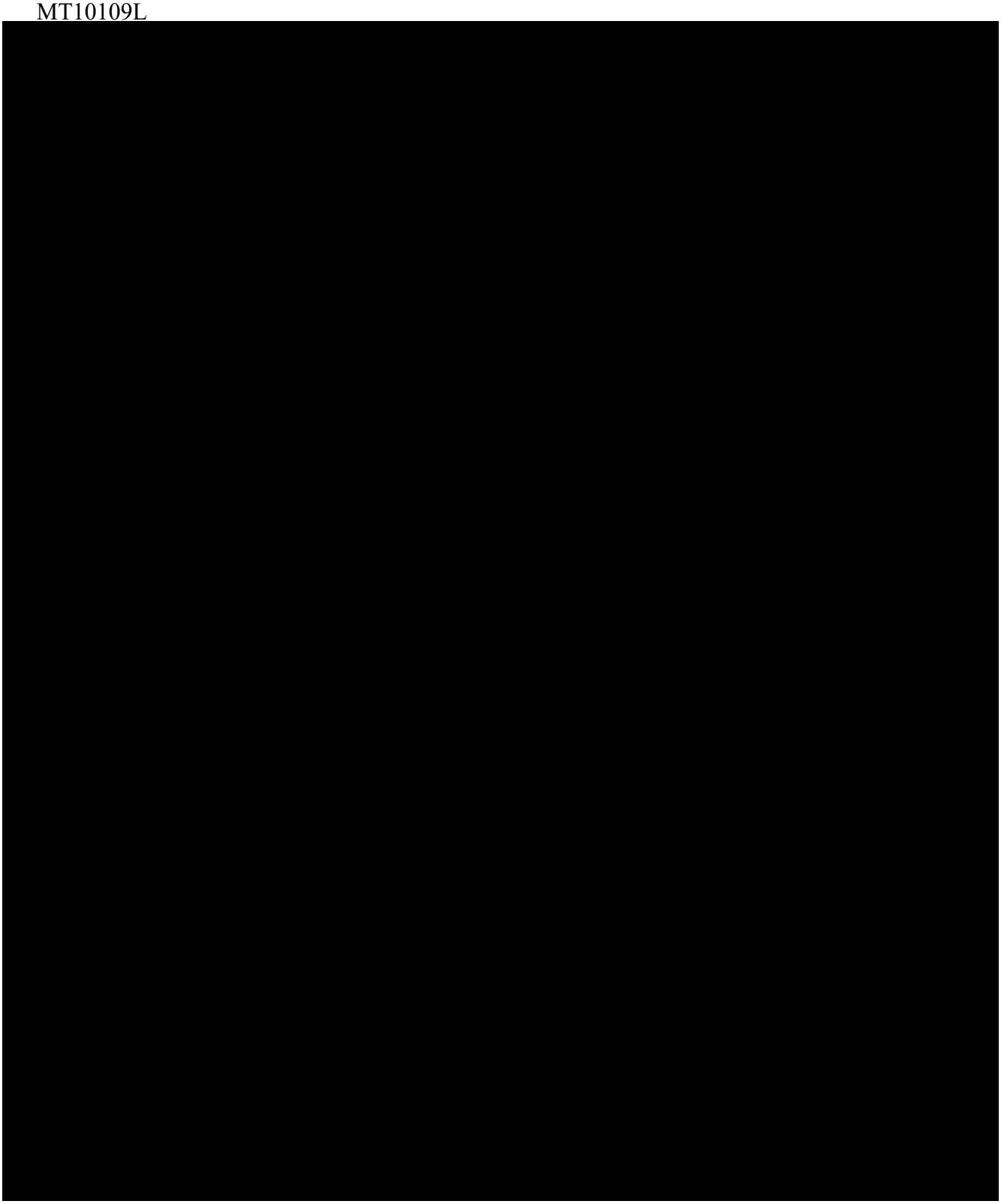


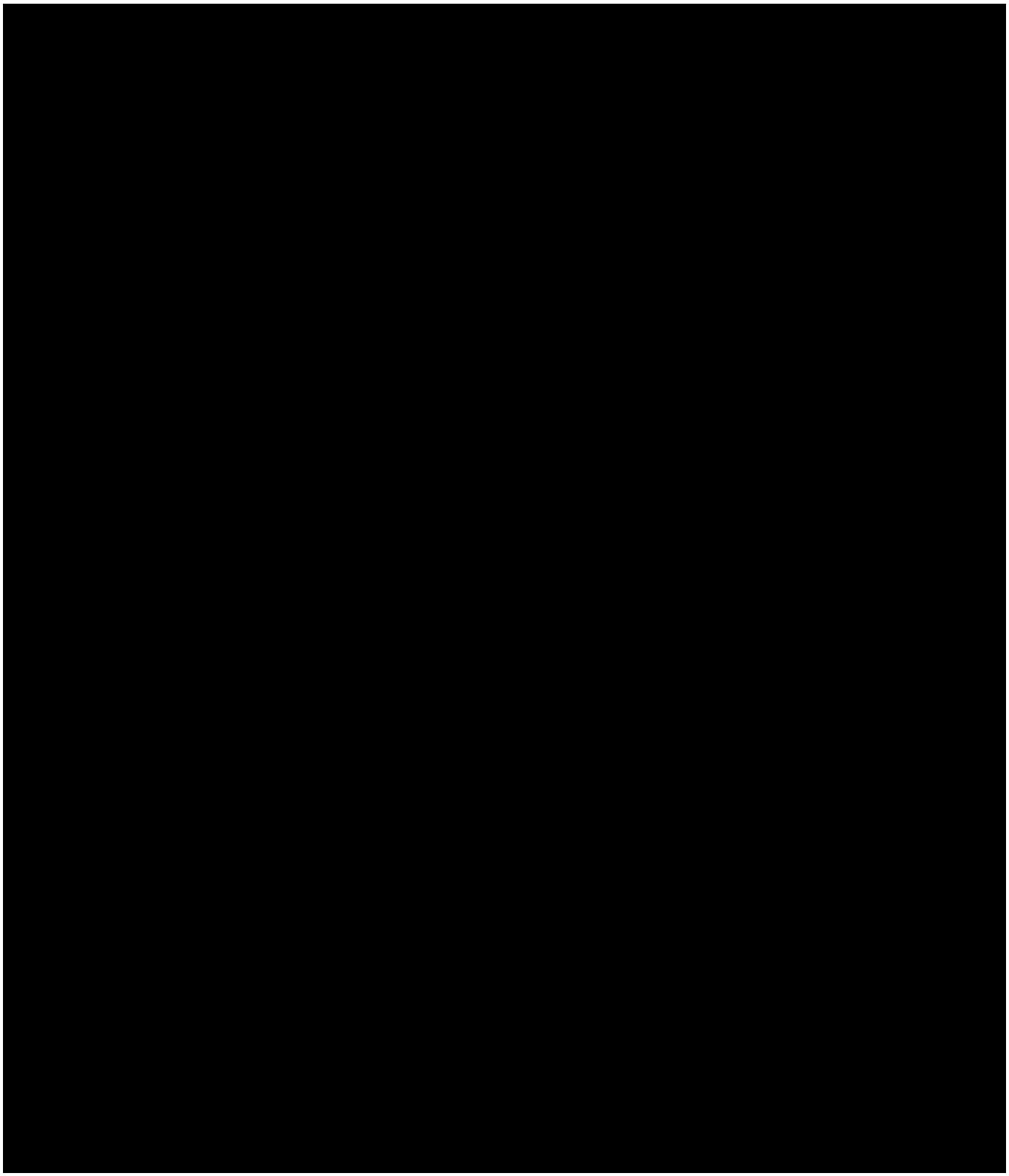


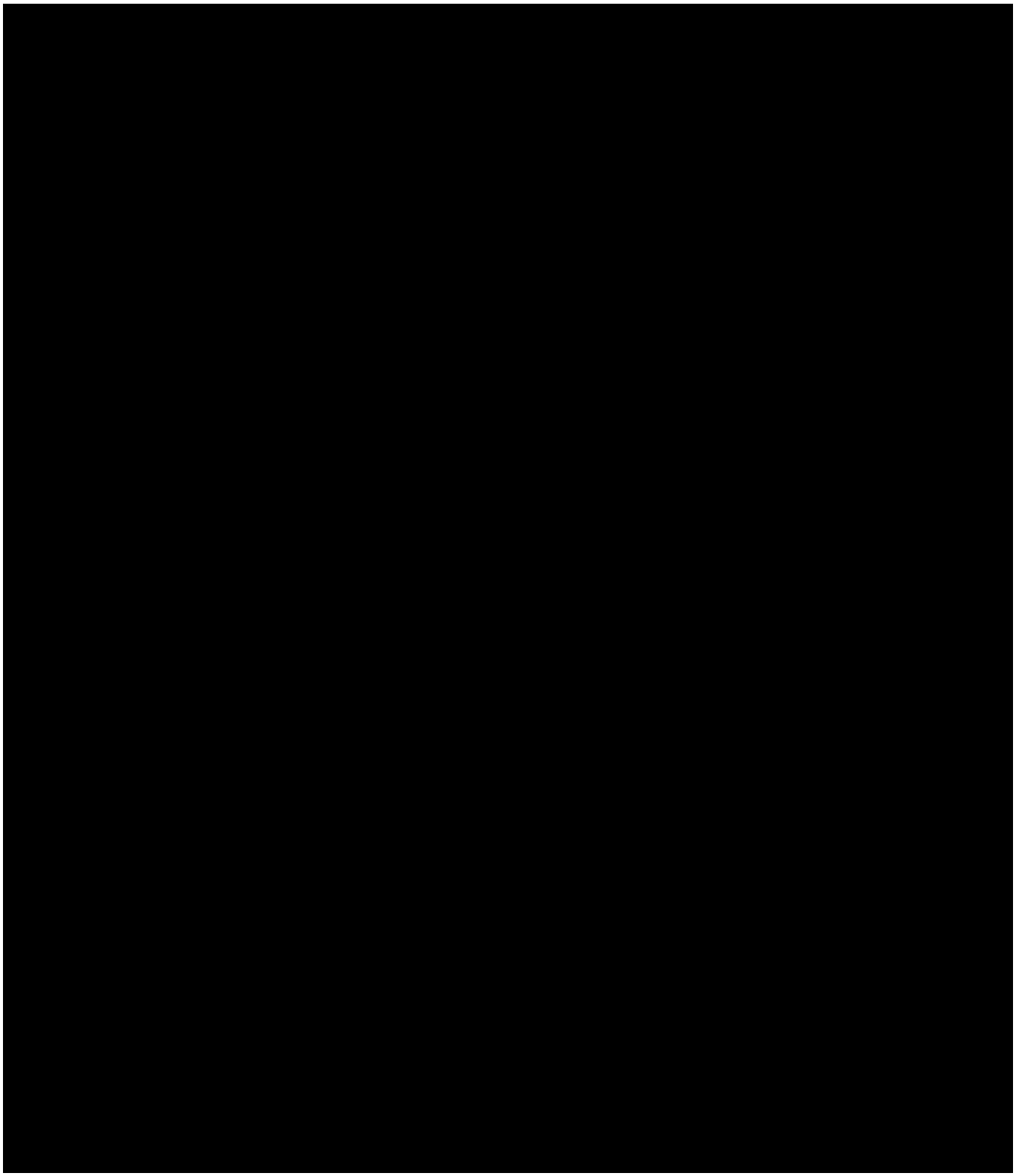


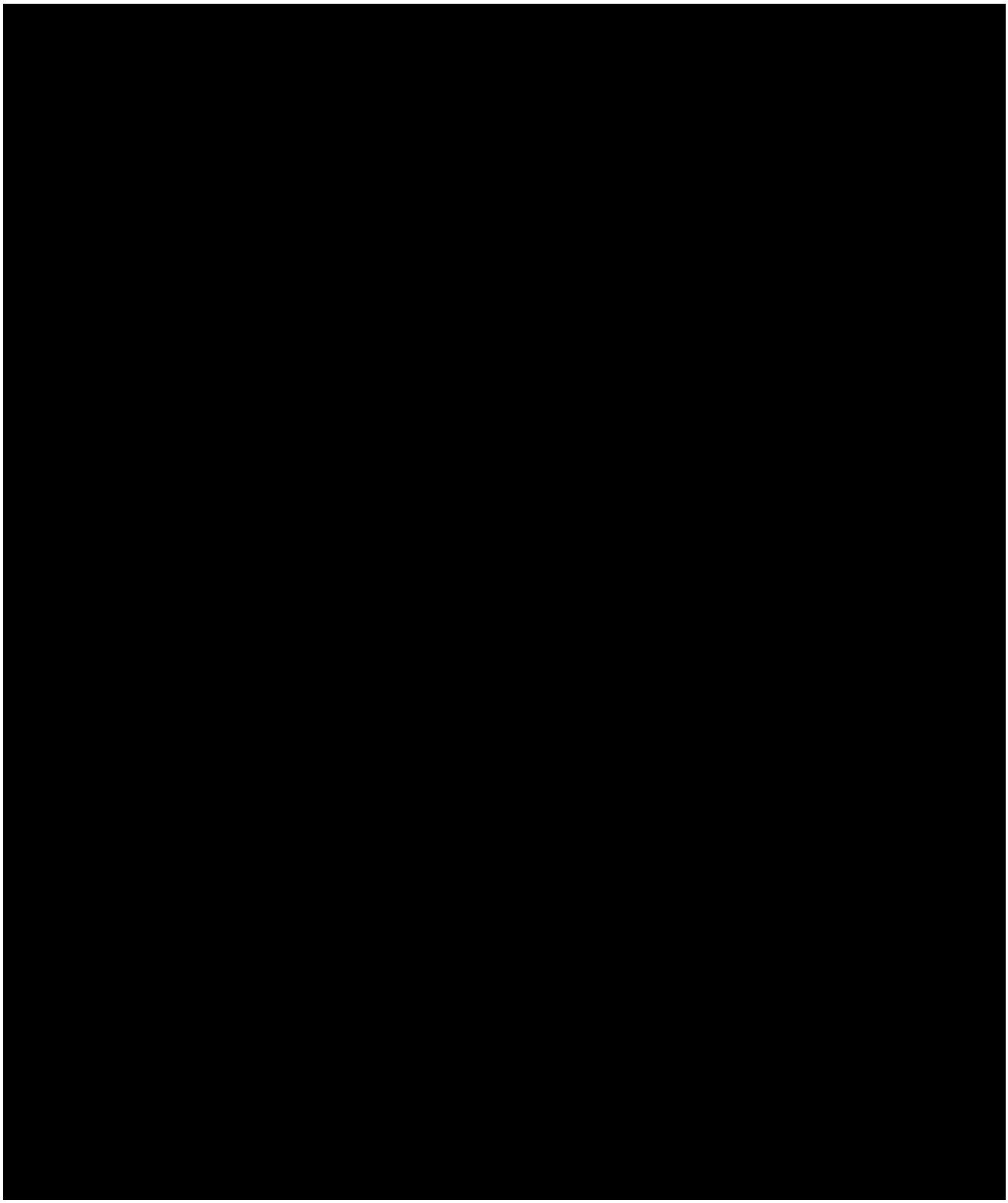


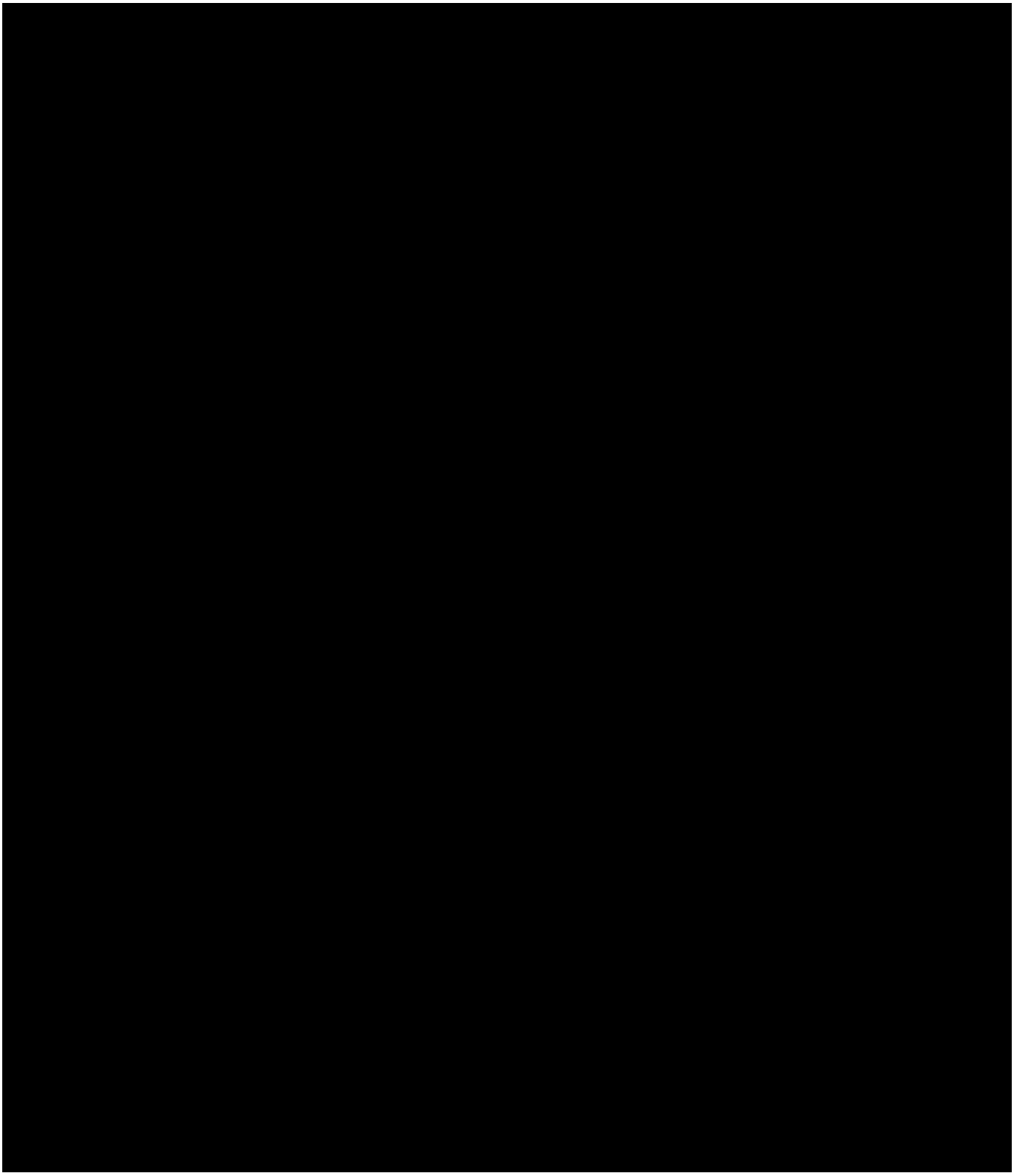


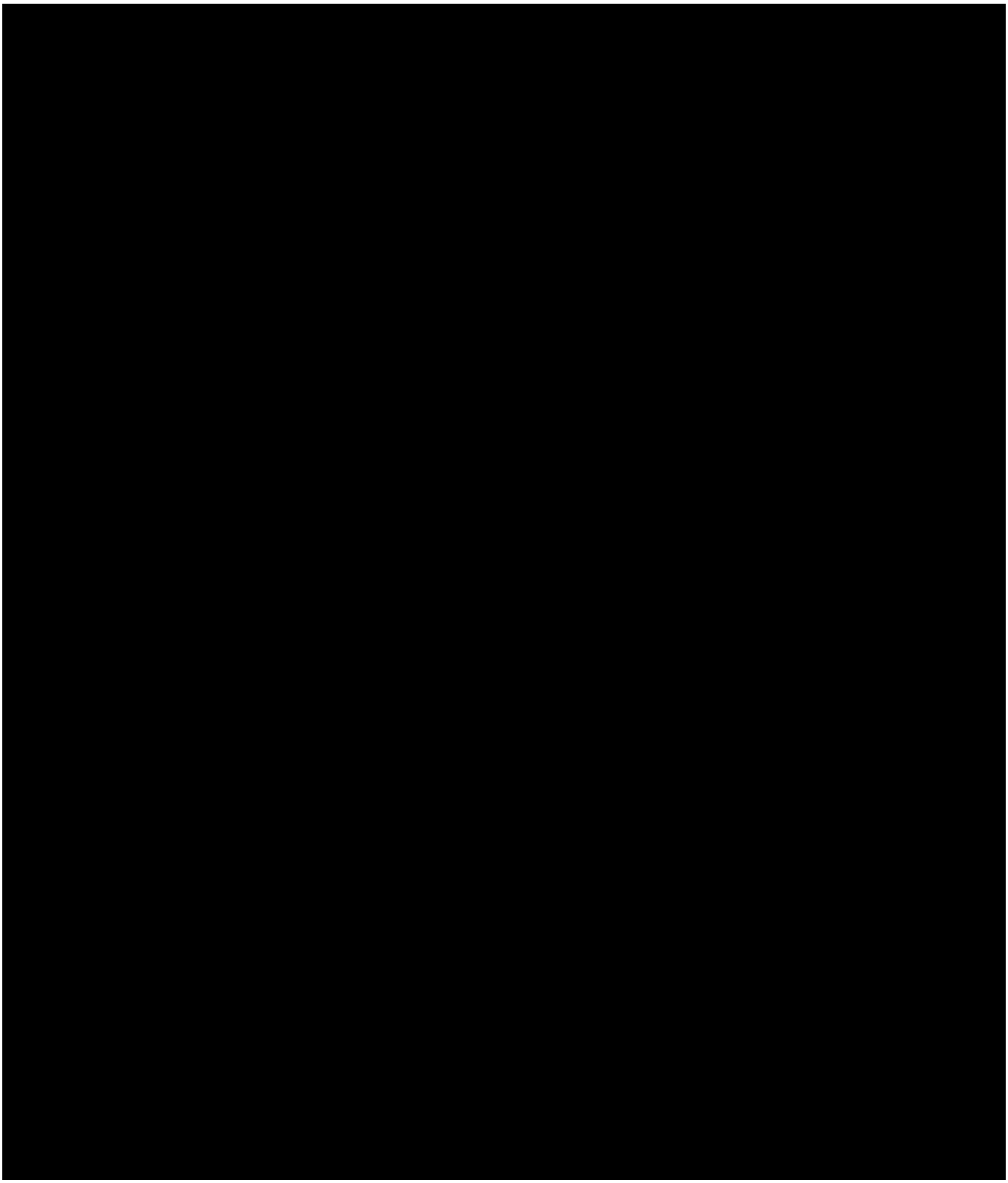




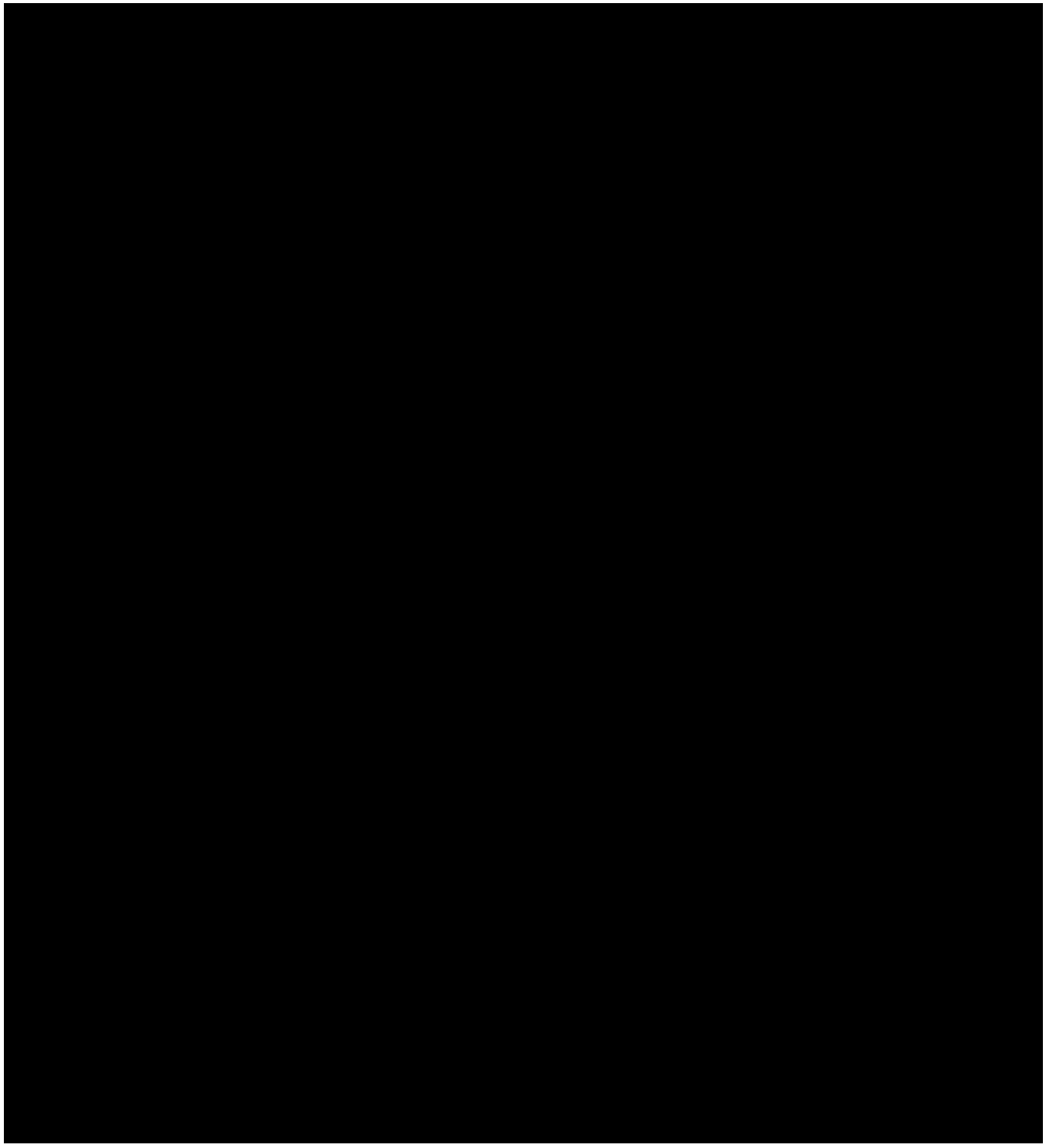


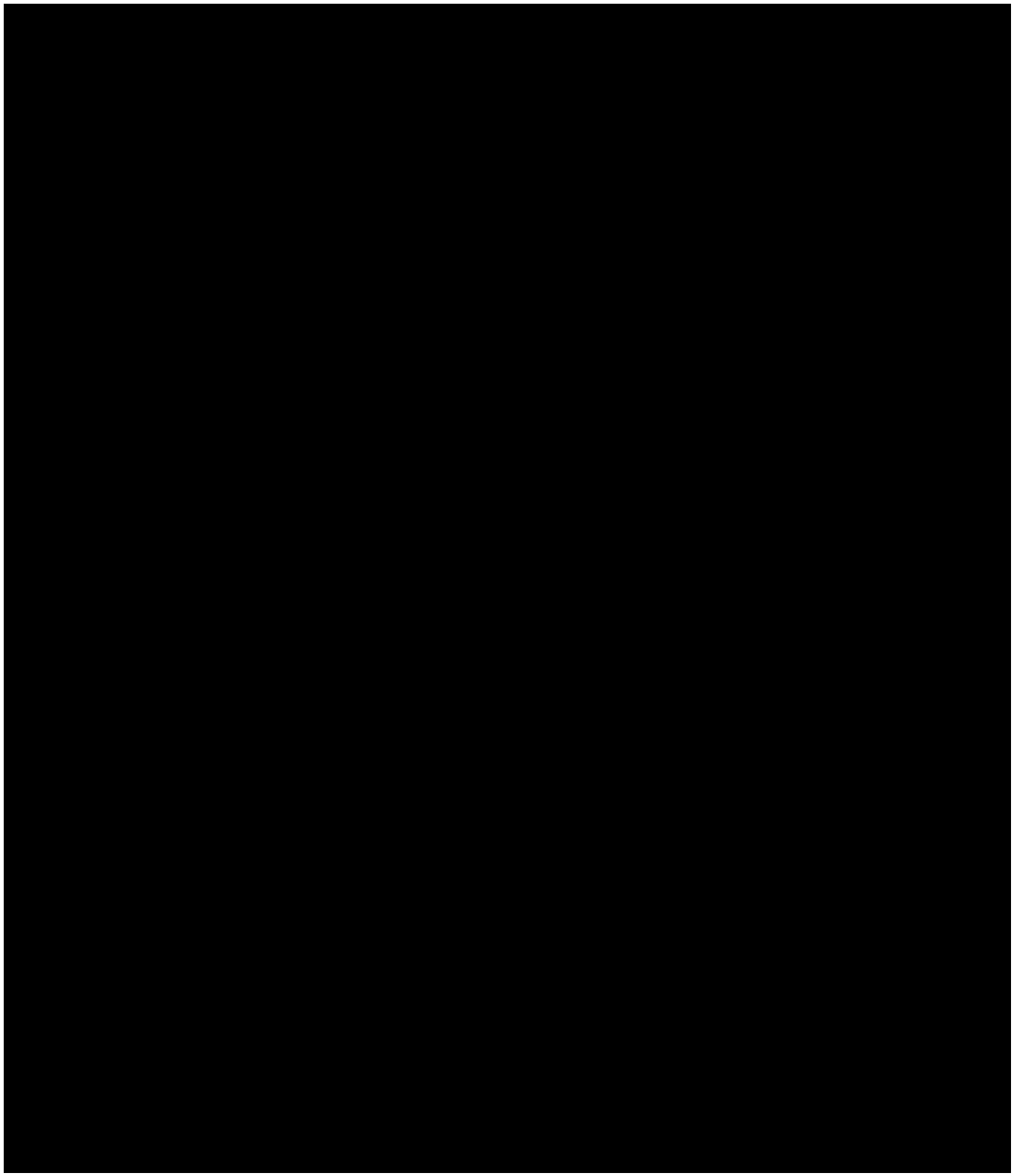


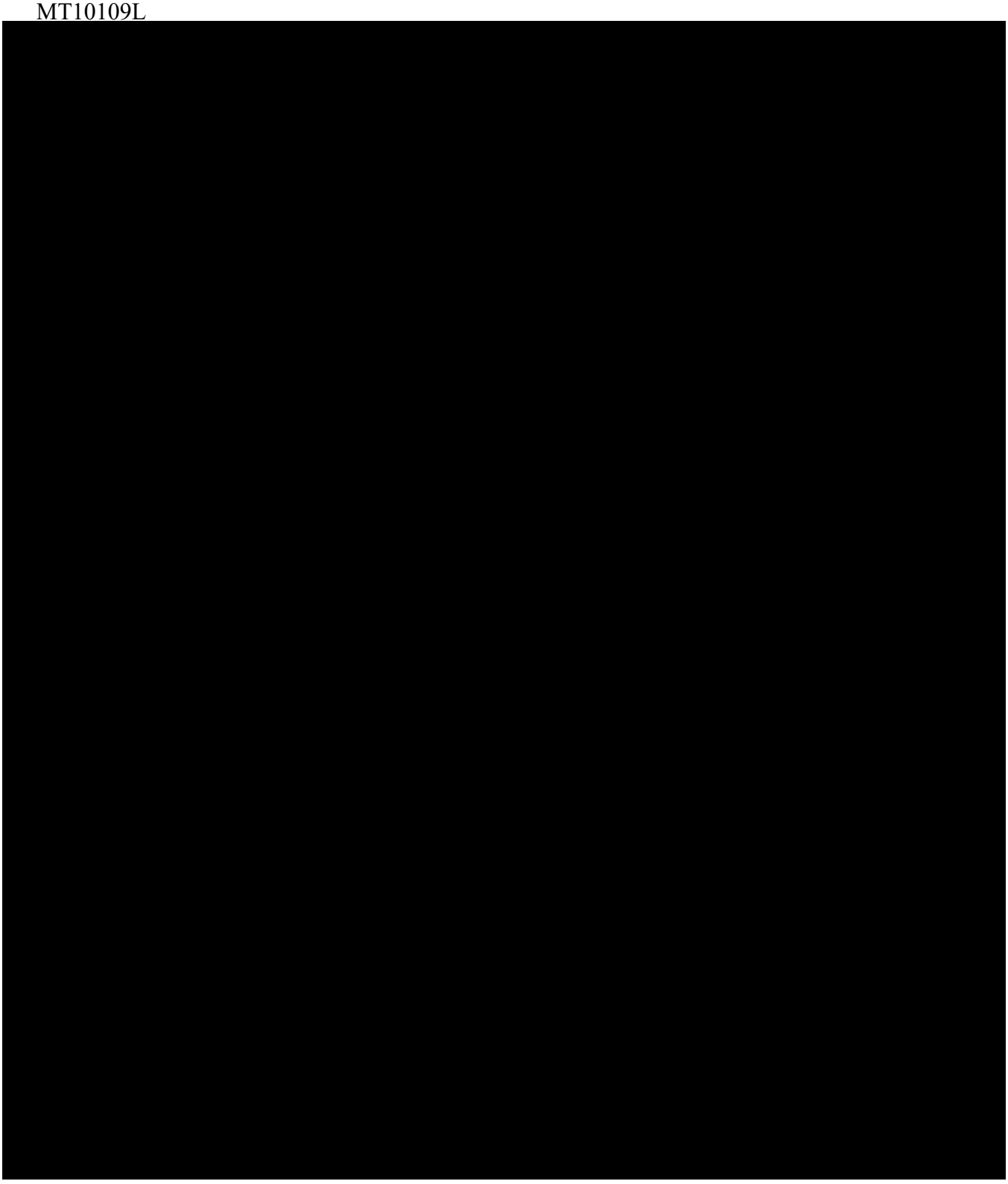


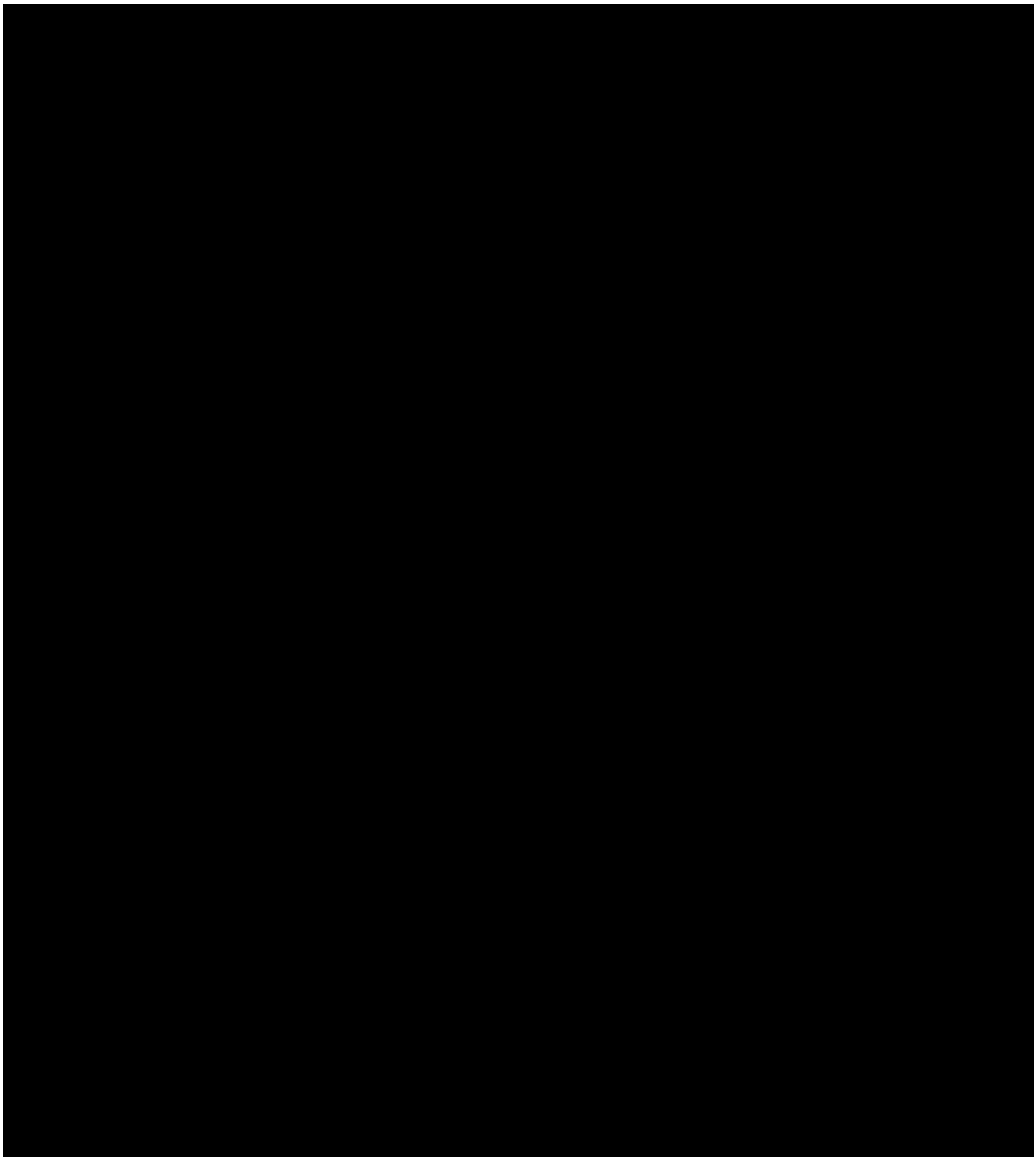


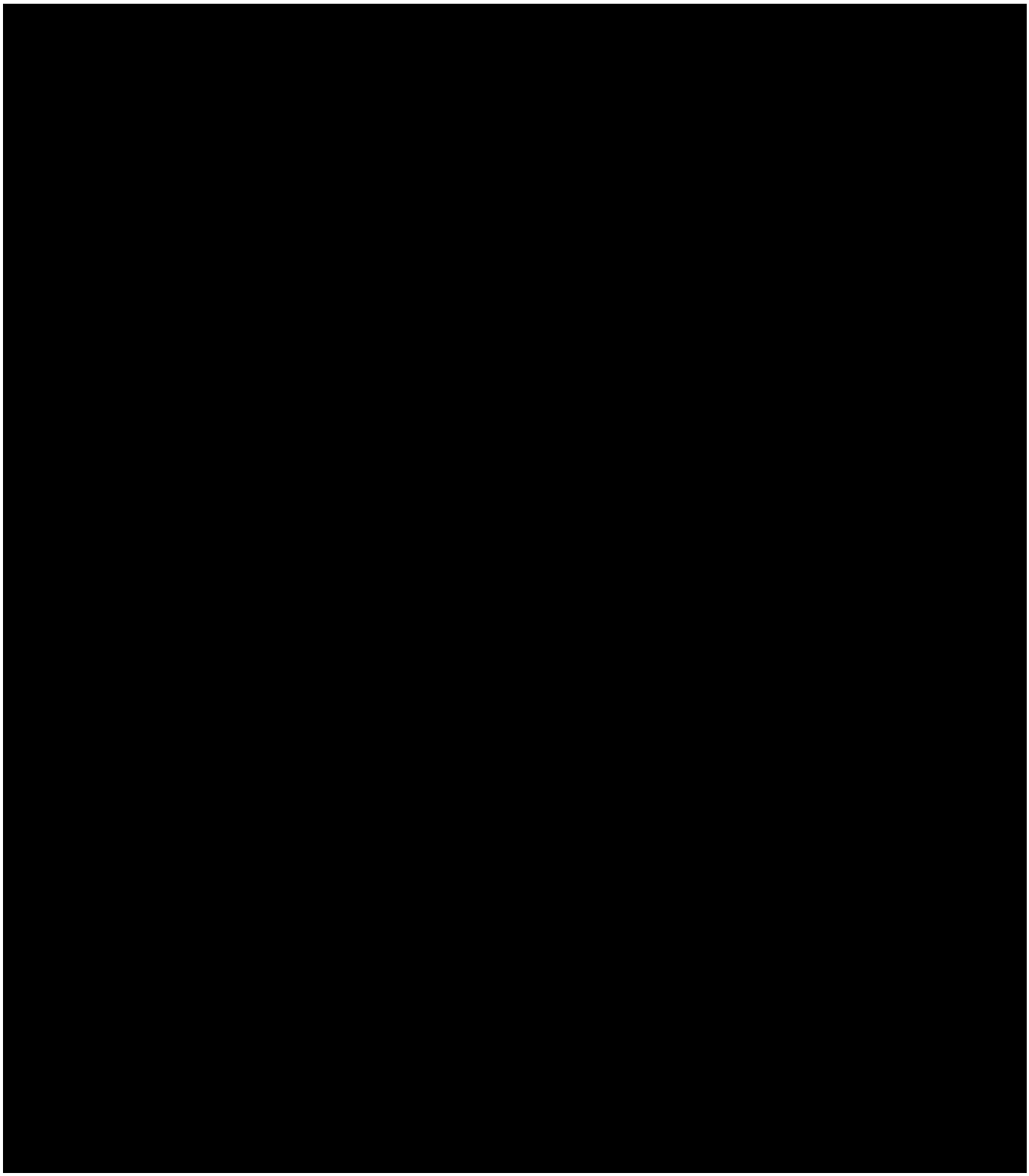
10.9. Appendix 9: Protocol Amendment History

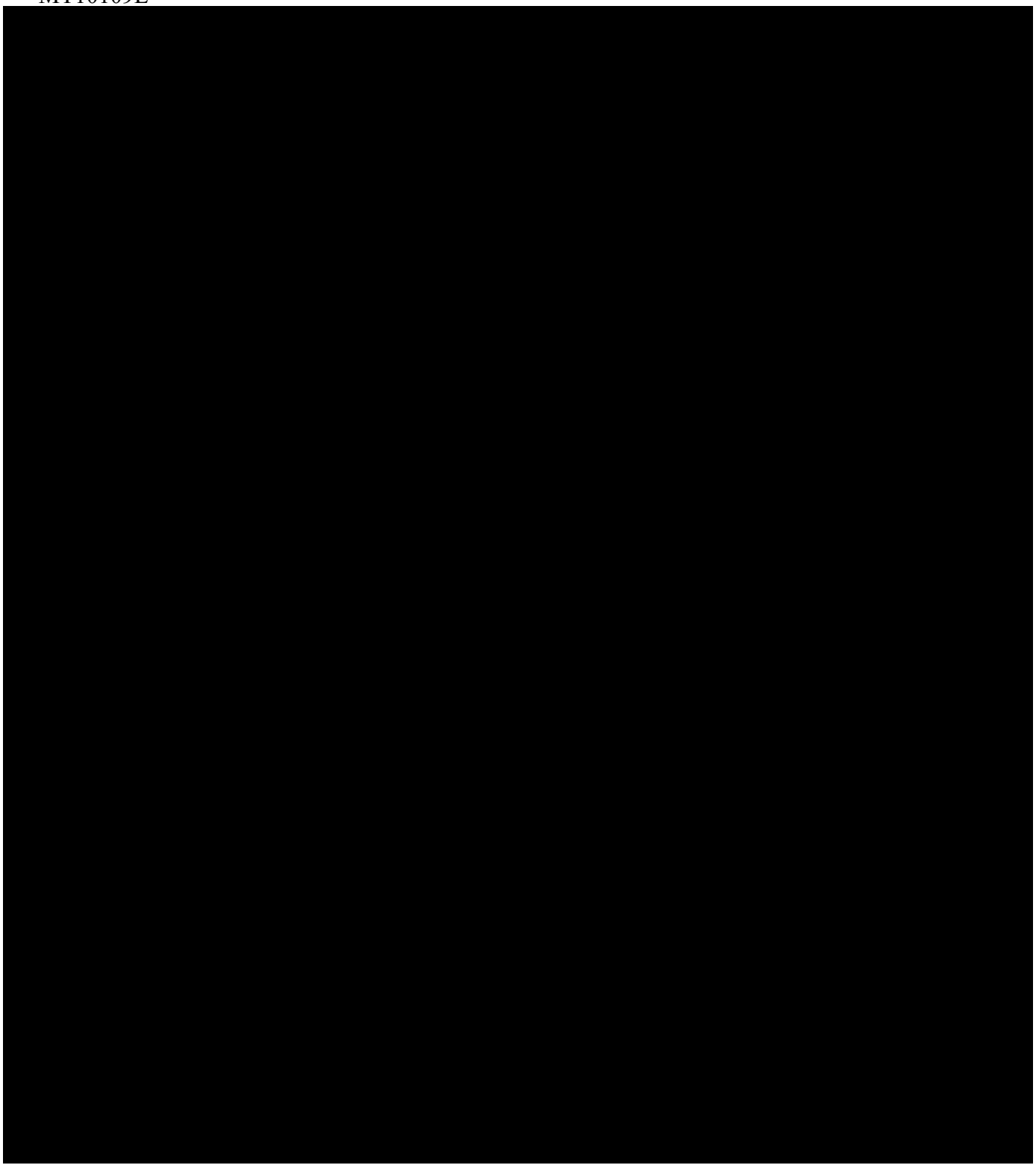












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12. Sponsor Signature