Clinical Study Protocol

STUDY TITLE:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Dose-Ranging, Multi-Center Trial to Evaluate the Efficacy and Safety of DaxibotulinumtoxinA for Injection for the Treatment of Upper Limb Spasticity in Adults After Stroke or Traumatic Brain Injury (JUNIPER)
SPONSORS:	REVANCE THERAPEUTICS, INC. 7555 Gateway Boulevard Newark, California 94560, USA Telephone: (510) 742-3400
STUDY NUMBER:	1820203
STUDY PHASE:	Phase 2
STUDY DRUG:	DaxibotulinumtoxinA for Injection
INDICATION	Upper Limb Spasticity in Adults
PROTOCOL VERSION/DATE:	Amendment 3 / 29 June 2020
VERSION HISTORY	Version 1, 13 July 2018 Version 2, 27 August 2018 Version 3, 14 September 2018 (Original Protocol) Amendment 1, 29 November 2018 Amendment 2, 04 November 2019

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

Confidentiality Statement

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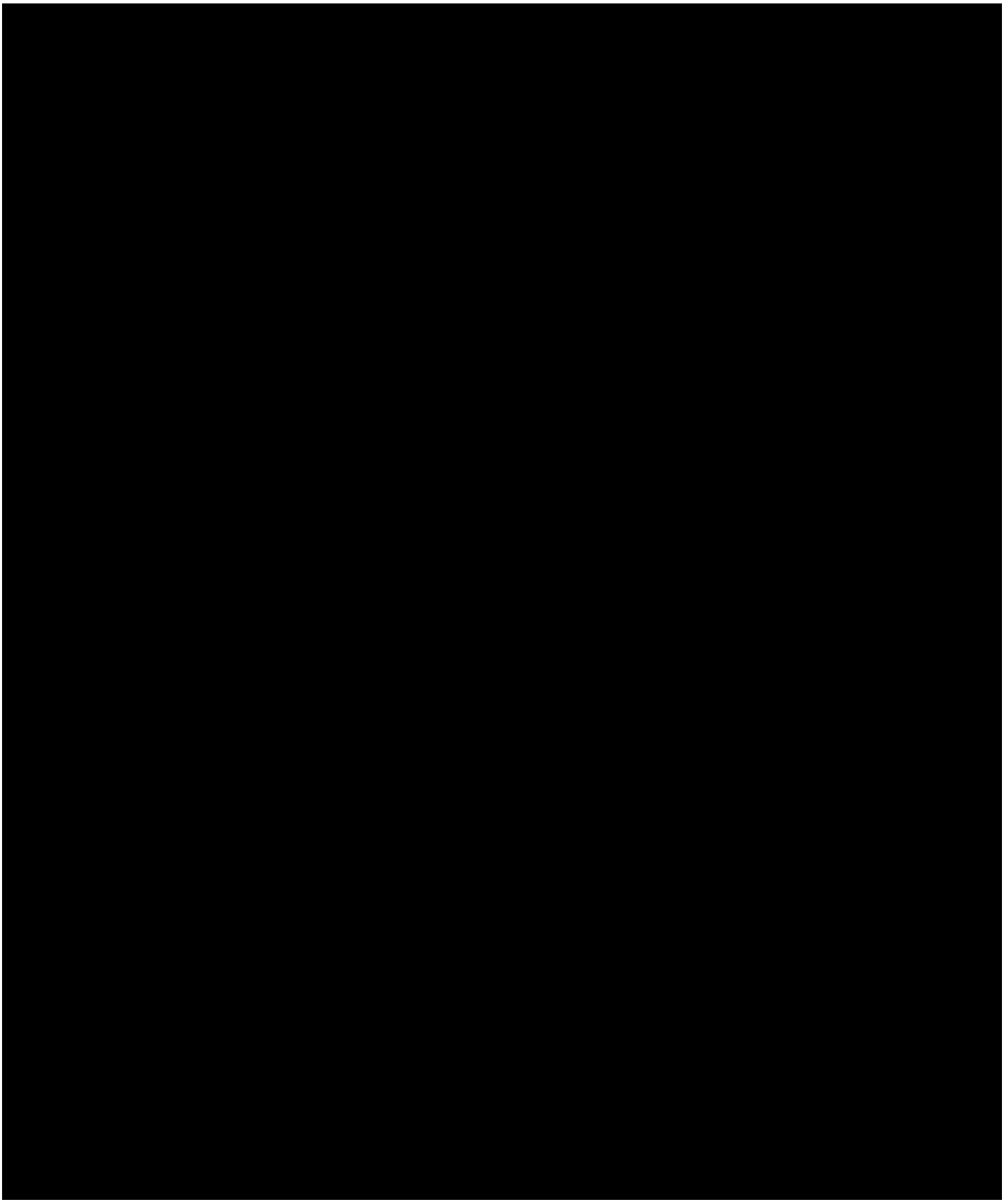

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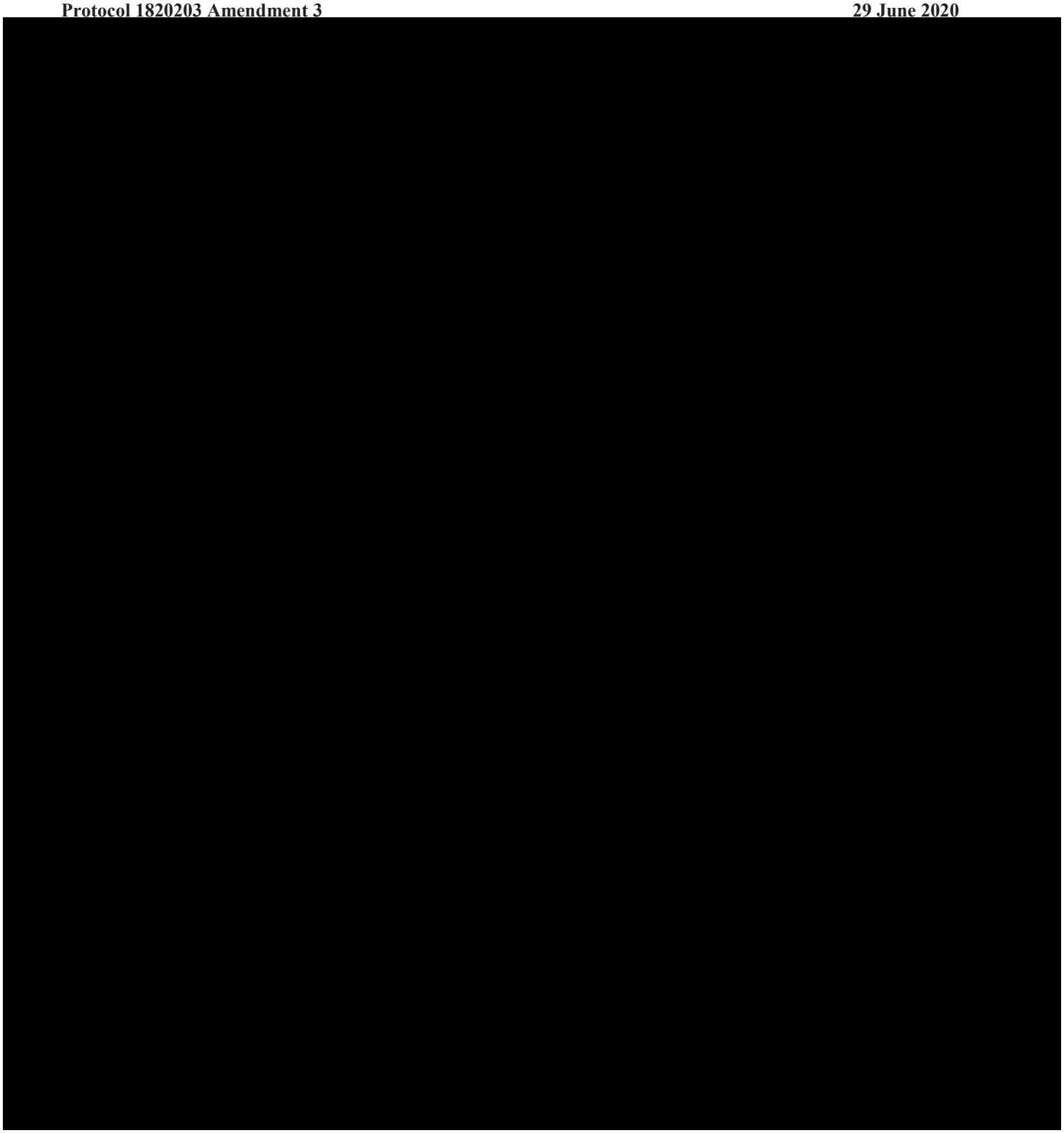


INVESTIGATOR SIGNATURE

Protocol Number: 1820203

A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Dose-Ranging, Multi-Center Trial to Evaluate the Efficacy and Safety of DaxibotulinumtoxinA for Injection for the Treatment of Upper Limb Spasticity (ULS) in Adults After Stroke or Traumatic Brain Injury (JUNIPER)

I have read this protocol and agree that it contains all the necessary details for performing the study in accordance with the Declaration of Helsinki and the International Conference on Harmonization (ICH) for Good Clinical Practice (GCP).

I will provide copies of the protocol and of the clinical and preclinical information on the investigational product, which was furnished to me by the Sponsor, to all members of the study team responsible to me who participate in the study. I will discuss this material with them to assure that they are fully informed regarding the study drug and the conduct of the study.

I will perform the study according to specifications outlined in the protocol and agree to implement protocol requirements only after the protocol and patient information/Informed Consent form have been approved by the Institutional Review Board/Ethics Committee (IRB/EC). I will submit any protocol modifications (amendments) and/or any Informed Consent form modifications to the IRB/EC, and approval will be obtained before any modifications are implemented.

I understand that the information presented in this study protocol is confidential, and I hereby assure that no information based on the conduct of the study will be released without prior consent from the Sponsor, Revance Therapeutics, Inc. unless this requirement is superseded by a regulatory authority (e.g., FDA).

_____

Investigator Name (PLEASE PRINT)

Signature: _____ Date _____

SYNOPSIS

TITLE OF STUDY: A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Dose-Ranging, Multi-Center Trial to Evaluate the Efficacy and Safety of DaxibotulinumtoxinA for Injection for the Treatment of Upper Limb Spasticity in Adults After Stroke or Traumatic Brain Injury (JUNIPER)	
NAME OF SPONSOR(S): Revance Therapeutics, Inc	
NAME OF INVESTIGATIONAL PRODUCT: DaxibotulinumtoxinA for Injection	
STUDY CENTERS: Up to 35 study centers across the United States	
PLANNED NUMBER OF SUBJECTS: Approximately 128 subjects	
DURATION OF STUDY: Up to 39 weeks, including 3 weeks for screening	Clinical Phase: 2

OBJECTIVES

Primary Objective

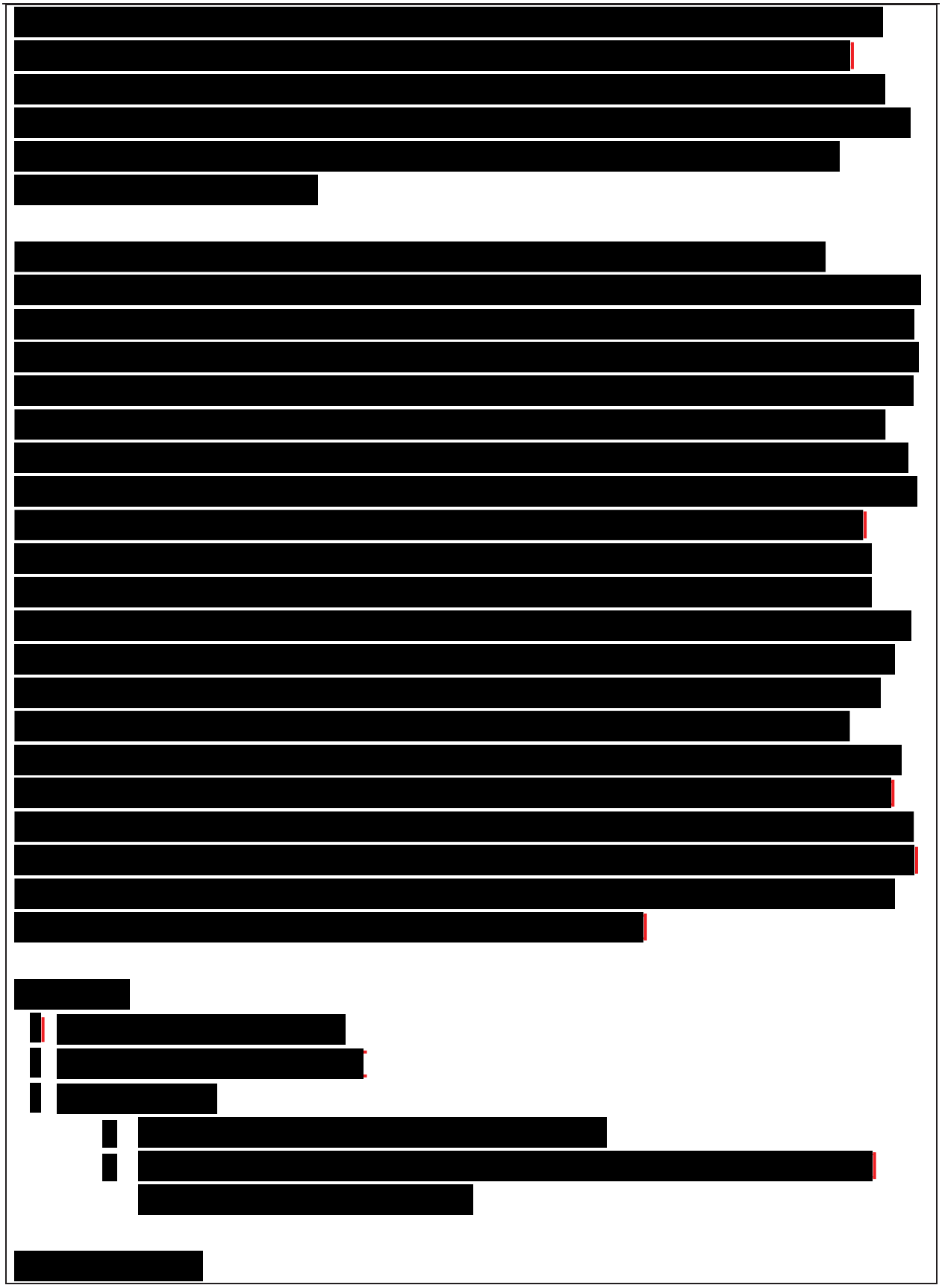
- To compare the safety and efficacy of a single treatment of DaxibotulinumtoxinA for Injection (DAXI for injection) at three dose levels (250 U, 375 U, 500 U) versus placebo in reducing muscle tone of adult subjects with upper limb spasticity after stroke or traumatic brain injury

[redacted]

STUDY DESIGN

This randomized, double-blind, placebo-controlled trial will evaluate the dose-related efficacy and safety of 3 doses of DAXI for injection for the treatment of upper limb spasticity (ULS) in adult subjects.

Approximately 128 adult subjects with upper limb spasticity after stroke or traumatic brain injury will be recruited from up to 35 study centers across the United States (US). The Screening period will be up to 21 days.



[redacted]
d.

SUBJECT REPLACEMENT STRATEGY: Subjects who discontinue from the study will not be replaced.

[redacted]

ELIGIBILITY CRITERIA

Inclusion Criteria

1. Adults, 18 to 75 years of age, inclusive.
2. Written informed consent including authorization to release health information.
3. Focal upper limb spasticity (ULS) after a stroke (as defined by WHO criteria) or traumatic brain injury (TBI), last stroke or TBI > 24 weeks prior to Screening.
4. ULS with the primary aggregate posture (AP): flexed elbow + flexed wrist + clenched fist (flexed fingers) and ≥ 1 other clinical pattern(s): adducted and internally rotated shoulder, pronated forearm, and/or thumb-in-palm deformity.
5. Moderate to severe ULS with a MAS score ≥ 2 at the elbow, wrist, and finger flexors; with the exception that the MAS score is ≥ 3 at the suprahypertonic muscle group (SMG) for subjects with previous injections of BoNTA in the paretic limb.
6. Moderate to severe functional disability (DAS score ≥ 2) on the principal target of treatment (1 of 4 functional domains: hygiene, dressing, malposition of the arm/wrist/fingers, and pain).
7. Has sufficient cognitive and communication ability to be able to give informed consent including authorization to release health information.

Exclusion Criteria

1. Upper limb spasticity attributable to an etiology other than stroke or TBI.
2. Bilateral upper limb paresis or quadriplegia.
3. Initiated in physiotherapy of the upper extremities ≤ 30 days prior to Screening or planned to start physiotherapy of the upper extremities during the course of the study.
4. Previous treatment with any BoNT product for any condition ≤ 16 weeks prior to Screening.
5. Botulinum neurotoxin treatment-experienced subjects who have historically required < 200 U of Botox/Xeomin or its equivalent to effectively treat the upper limb spasticity.
6. Botulinum neurotoxin treatment-experienced subjects who had suboptimal or no treatment response to the most recent BoNTA injection for spasticity, as determined by the investigator; or history of primary or secondary non-response to BoNTA injections, known to have neutralizing antibodies to BoNTA; or have a history of botulinum toxin type B (rimabotulinumtoxinB [Myobloc/Neurobloc]) injection for spasticity due to non-response or suboptimal response to BoNTA.
7. Change in oral medications for spasticity including dosage and dosing frequency ≤ 30 days prior to Screening.
8. Previous or planned treatment of the spastic upper limb with phenol, alcohol injection or surgery.

9. Profound muscular atrophy or fixed contracture (spasticity angle, per the Tardieu Scale, <10 degrees in the most hypertonic muscle group {elbow, wrist or finger flexors}) of the spastic limb leading to marked limitation on passive range of motion or any other known conditions of the upper limb that could confound muscle tone or functional assessment.
10. Current or prior treatment with intrathecal baclofen pump.

[redacted]

[redacted]

EFFICACY ASSESSMENTS

- Modified Ashworth Scale (MAS)
- Physician Global Impression of Change (PGIC)
- Disability Assessment Scale (DAS)
- Patient or Caregiver Global Impression of Change (P/CGIC)
- Tardieu Scale (TS)
- Active Range of Motion (AROM)
- Fugl-Meyer Upper Extremity (FMUE) Assessment (measure of active motor function)
- EuroQoL Five Dimension Scale (EQ-5D-5L)
- Short Form Health Survey (SF-36)

SAFETY ASSESSMENTS

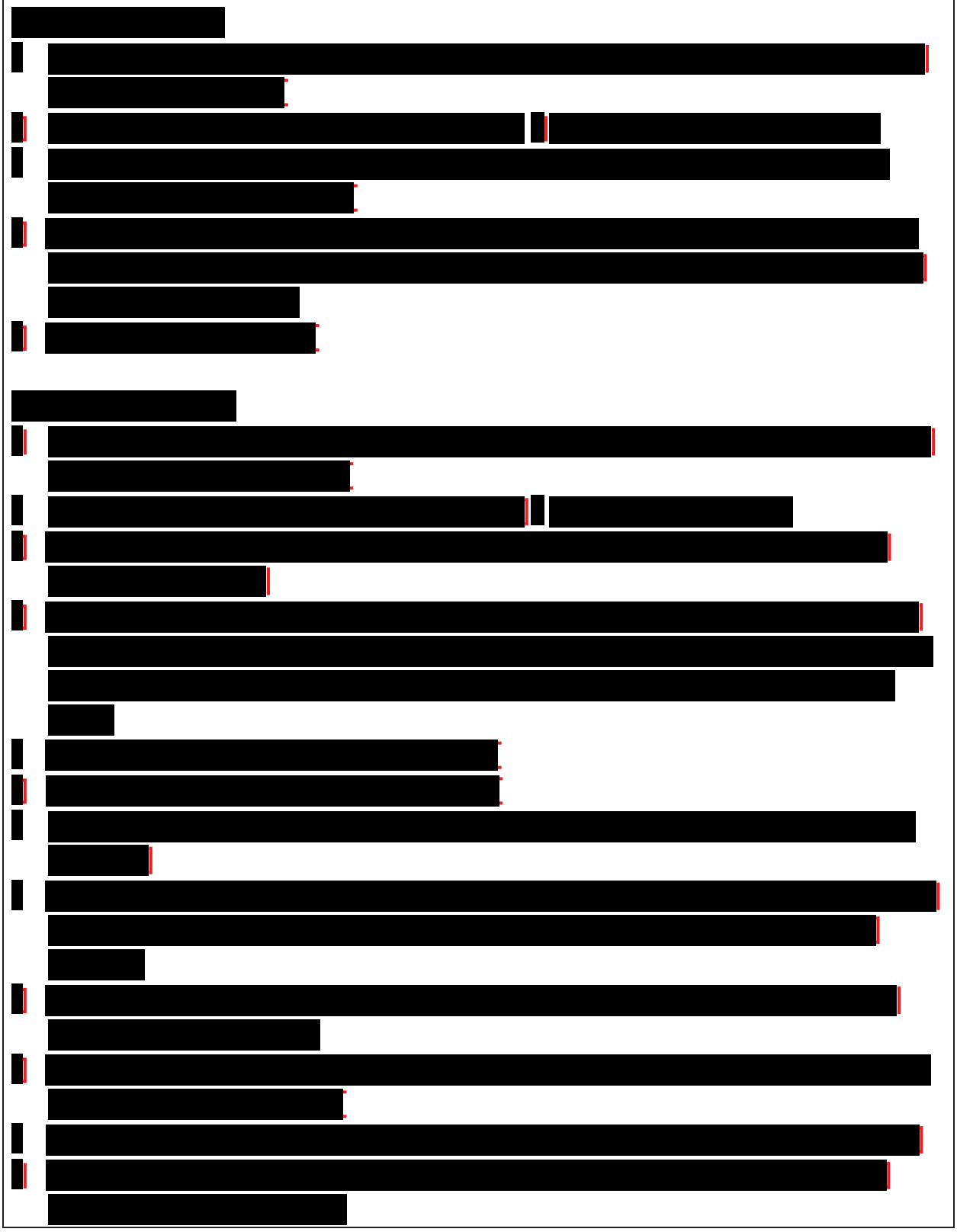
- Adverse events including [redacted]
- Vital signs, physical and neuro examination findings
- Injection site evaluations
- Spirometry (discontinued 20 March 2020 due to COVID-19)
- Lab tests (CBC, PT, chemistry panel, UA, urine pregnancy test [WOCBP])
- 12-lead ECG
- Concomitant medications
- Columbia-Suicide Severity Rating Scale (C-SSRS)

ENDPOINTS

Co-Primary Endpoints

- Mean change from baseline in muscle tone measured using the MAS in the suprahypertonic muscle group (SMG) of the elbow, wrist, OR finger flexors at Week 6

- Mean score on the PGIC at Week 6



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PLANNED ANALYSES

Analyses of Co-Primary Endpoints

1) Mean change from baseline in muscle tone measured by MAS in the suprahypertonic muscle group (SMG: elbow flexors, wrist flexors, or finger flexors) at Week 6
2) Mean score on the PGIC at Week 6

The SMG is the one with the highest MAS score at baseline. In case two or three muscle groups have the same highest MAS scores, the selection of the SMG will be at the discretion of the investigator, based upon his/her clinical judgement. Change from baseline in muscle tone of the SMG at Week 6 and mean PGIC score at week 6 will be compared between each dose group and placebo beginning with DAXI 500 U vs placebo, then DAXI 375 U vs placebo, and DAXI 250 U vs placebo with control of the family-wise type 1 error rate using a 6-step hierarchical testing procedure. The significance of each comparison will be tested only if the previous step reached significance.

[redacted]

STATISTICAL ANALYSIS

Sample Size Calculations

The treatment effect size for the primary endpoint (mean change from baseline in MAS in the SMG) was observed in a BoNTA product registration study (de) for the treatment of ULS.

[redacted]

Analysis Populations

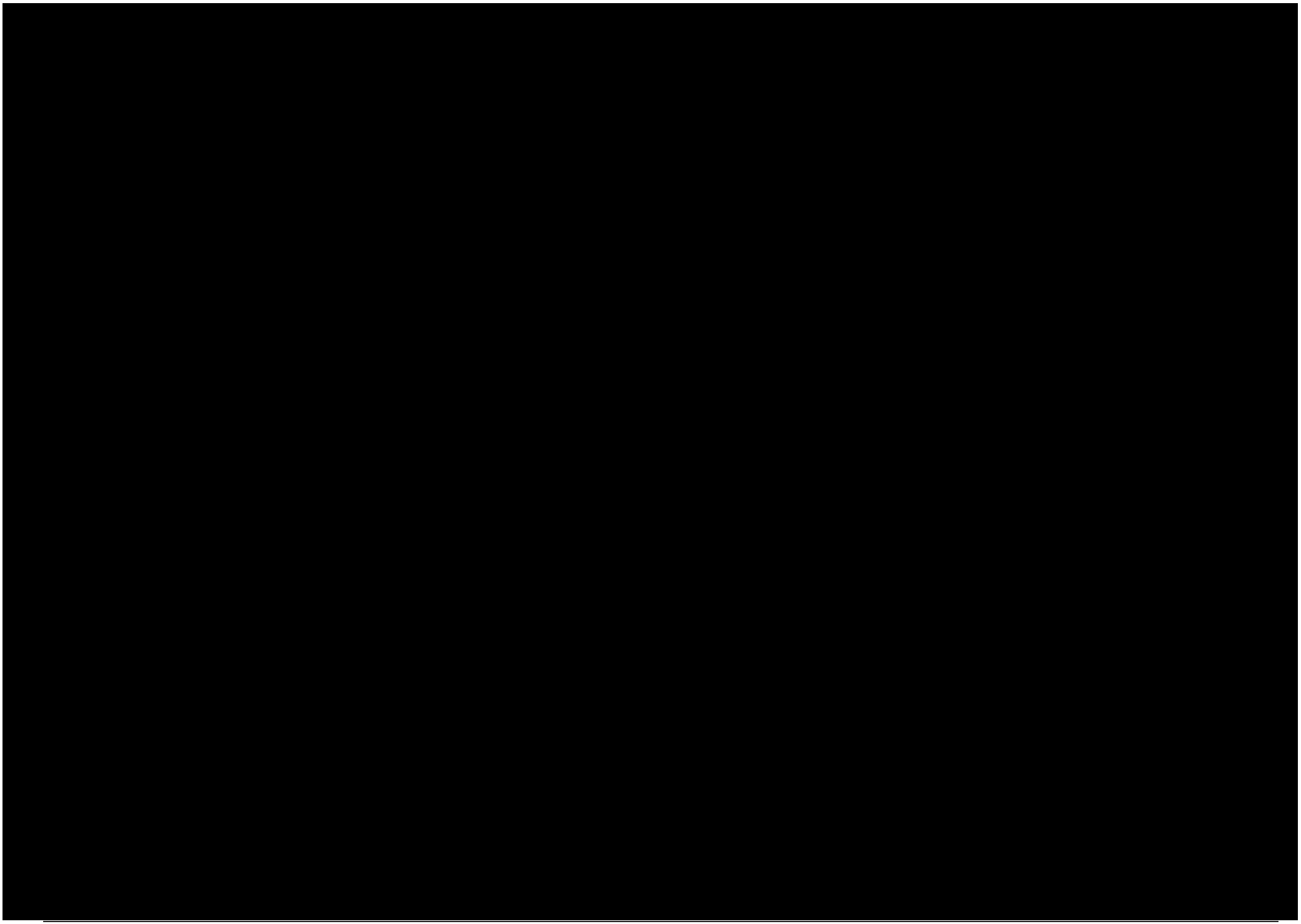
- Intention-to-Treat Population: Efficacy analysis will be performed using the intention-to-treat analysis set. This population includes all subjects randomized, given one injection session of the study medication and have a MAS score in the SMG at baseline and at least one post-baseline MAS assessment

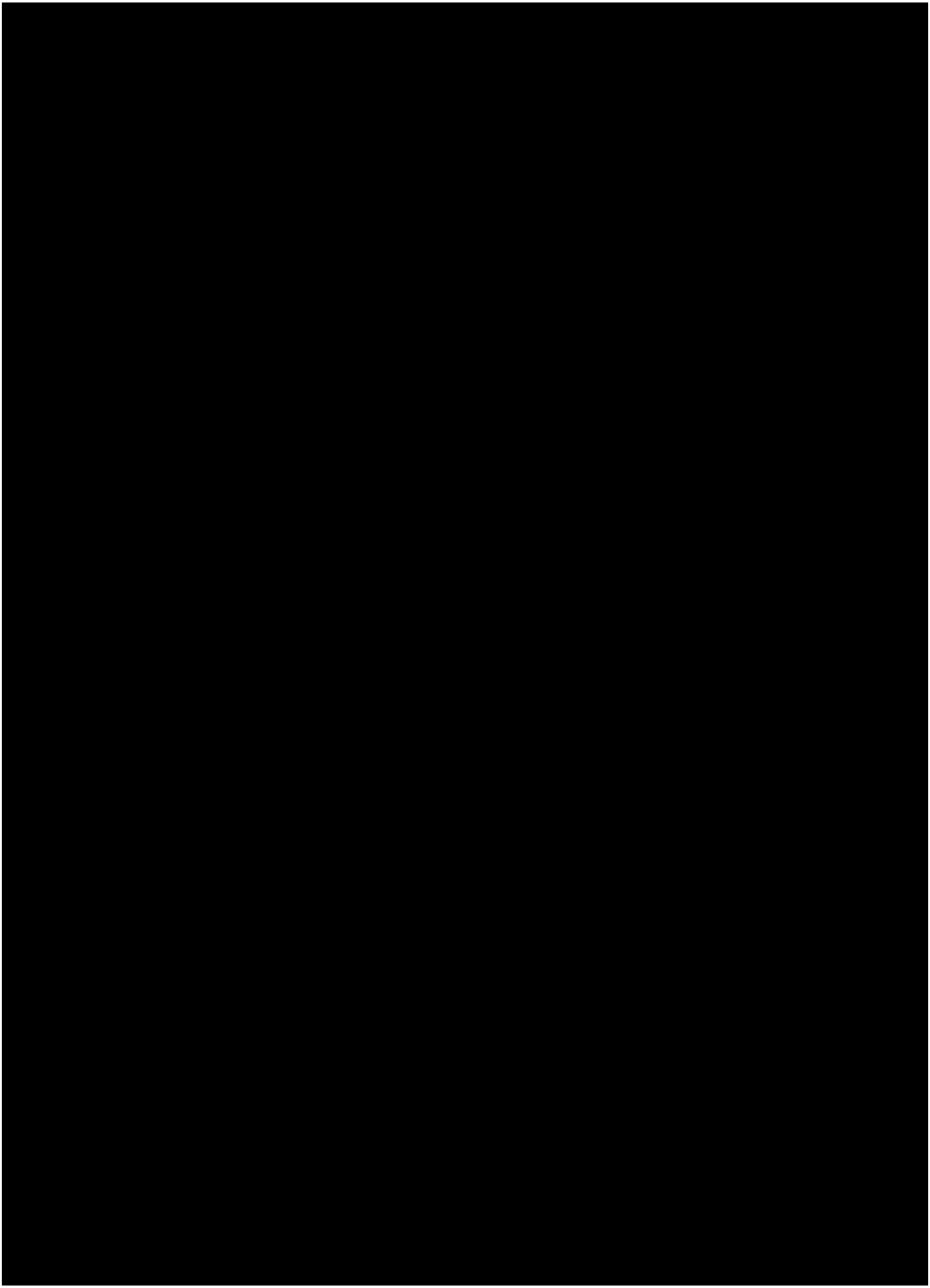
[redacted]

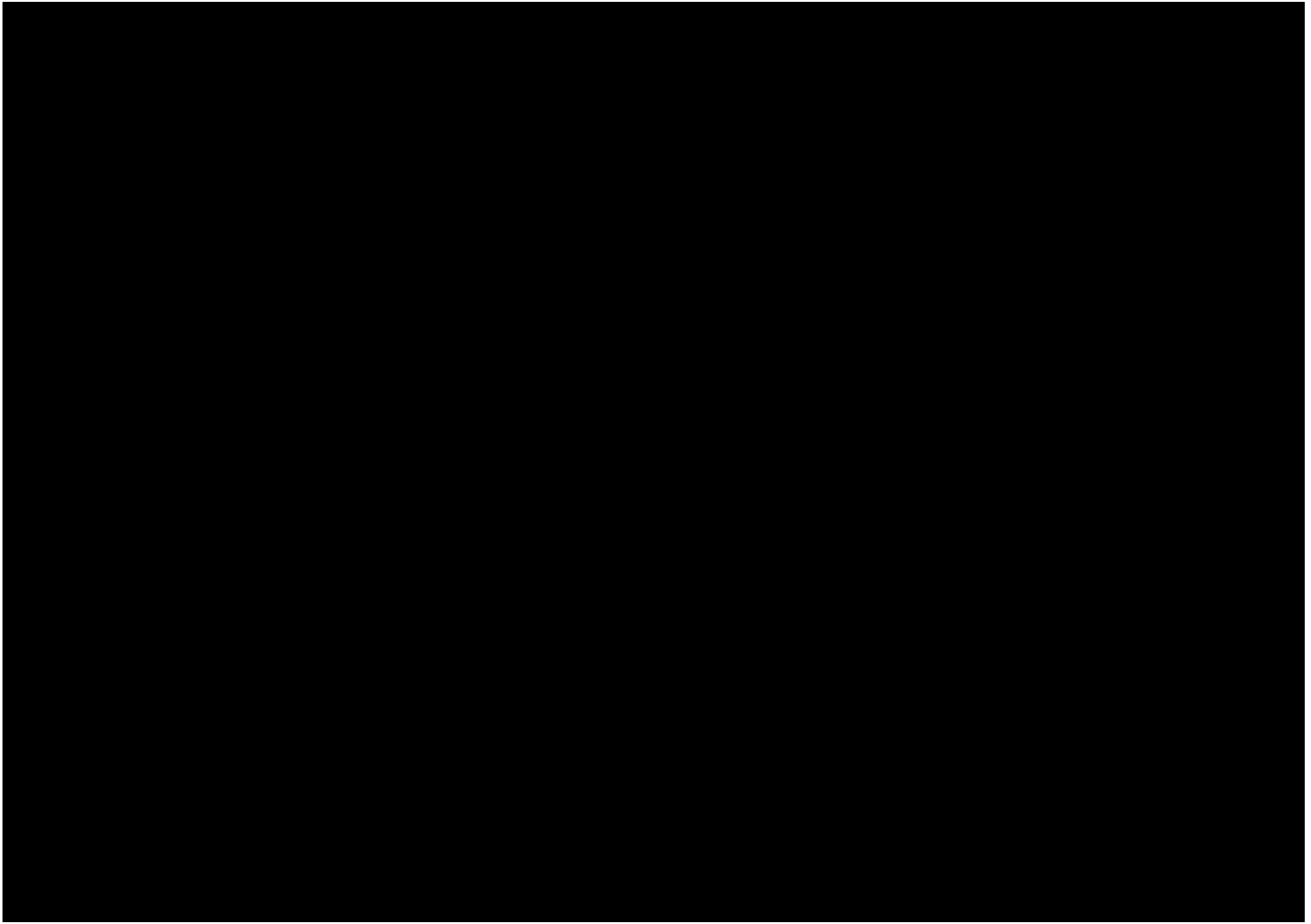
[redacted]

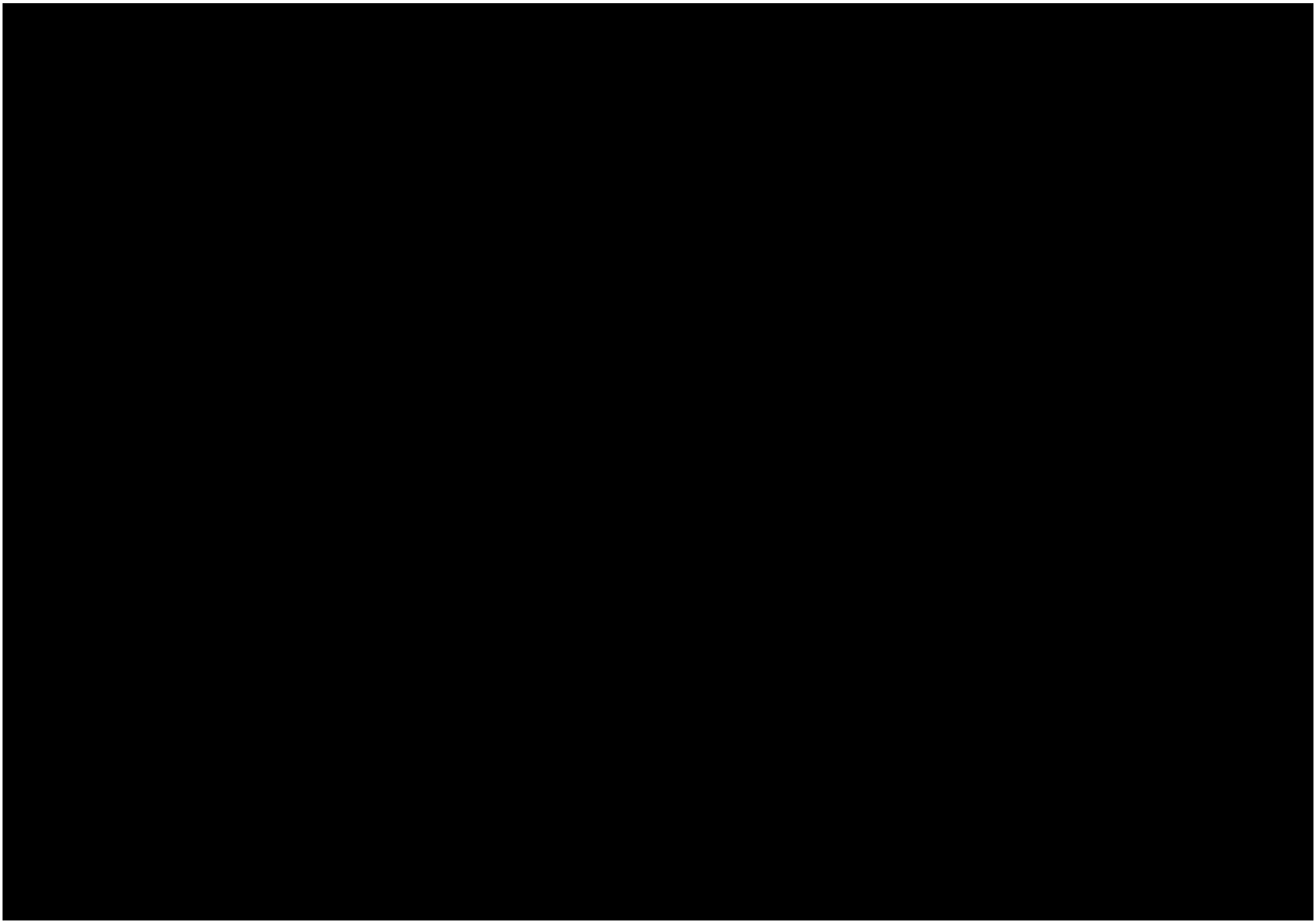
- Safety Population: all randomized subjects who received a study treatment.
- Pre-COVID-19 ITT Population: a subset of the ITT population, subjects who were enrolled before COVID-19 enrollment hold (20MAR2020).
- Pre-COVID-19 PP Population: a subset of the PP population, subjects who were enrolled before COVID-19 enrollment hold (20MAR2020).

Protocol Version/Date: Amendment 3/ 29 June 2020









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LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
AE	adverse event
AP	aggregate posture
AROM	active range of motion
BoNT	botulinum neurotoxin
BoNTA	botulinum neurotoxin type A
C-SSRS	Columbia-Suicide Severity Rating Scale
CD	cervical dystonia
CI	confidence interval
COVID-19	Coronavirus disease 2019
CS	clinically significant
DAS	Disability Assessment Scale
DAXI	daxibotulinumtoxinA, RTT150
DAXI for injection	daxibotulinumtoxinA for injection
DCC	Data Coordinating Center
DMC	Data Monitoring Committee
DSFS	Drooling Severity and Frequency Scale
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	electronic case report form
EQ-5D-5L	EuroQoL Five Dimension Scale (EQ-5D-5L)
ET	early termination
FMUE	Fugl-Meyer Upper Extremity
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IM	Intramuscular
INR	International Normalized Ratio

Abbreviation	Definition
IRB	Institutional Review Board
ITT	intent-to-treat
IWRS	Interactive Web Randomization System
kDa	Kilodalton
MAS	Modified Ashworth Scale
MMRM	mixed model repeated measures
NOAEL	no observed adverse effect level
PI	principal investigator
PP	per protocol
PT	prothrombin time
PTT	principal treatment target
QoL	quality of life
QT	time from start of the ECG q wave and the end of the t wave
Revance	Revance Therapeutics, Inc.
RT002	previous name for daxibotulinumtoxinA for injection
RTP004	Revance proprietary stabilizing excipient
RTT150	previous drug substance (daxibotulinumtoxinA) name
SAE	serious adverse event
SDST	Serious Distant Spread of Toxin
SF-36	Short-Form 36
SMG	suprahypertonic muscle group
SOA	Schedule of Activities
SOP	standard operating procedure
TS	Tardieu Scale
TdP	Torsade de Pointe
TEAE	treatment-emergent adverse event
U	units (botulinum toxin)
UP	unanticipated problem
UPT	urine pregnancy test
US	United States

Abbreviation	Definition
WOCBP	women of child bearing potential

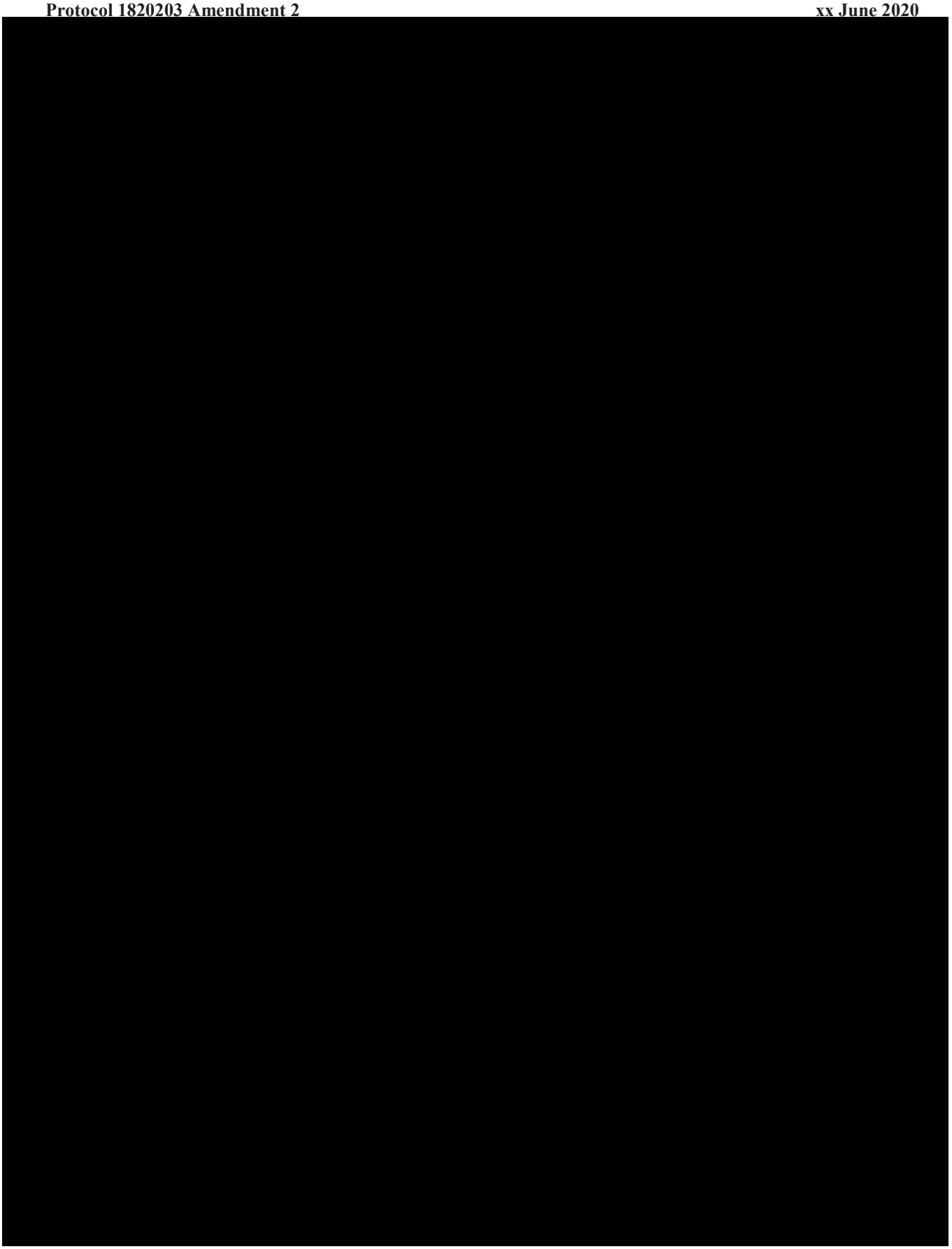
1 INTRODUCTION

1.1 Pathophysiology of Spasticity

Spasticity is a motor symptom characterized by an increase in velocity dependent stretch reflexes, with exaggerated tendon jerks resulting from hyperexcitability of the stretch reflex, as one component of the upper motor neuron syndrome (Brashear, 2016). Spasticity is one of several abnormalities of muscle tone, and is characterized by rigidity, muscle tightness, joint stiffness, involuntary jerky movements, exaggeration of reflexes, unusual posture, abnormal positioning of fingers, wrists, arms, or shoulders, and muscle spasms. Primary causes of spasticity are anoxia secondary to cerebrovascular ischemia (stroke), trauma to the brain or spinal cord, and neurodegenerative diseases such as multiple sclerosis. (Brashear, 2011**).** Essentially spasticity can result from a lesion or injury anywhere along the corticospinal (pyramidal) tracks including the motor cortex, basal ganglia, thalamus, brainstem, cerebellum, central white matter or spinal cord. Fatigue, impaired coordination, impaired motor control, impaired motor planning, and muscle weakness often accompany spasticity and contribute to functional motor impairment, discomfort, and pain.

Effective treatment of spasticity is lacking. Pharmacotherapy has included baclofen (oral and intrathecal), benzodiazepines, dantrolene, phenol or alcohol injections, gabapentin, lamotrigine, cyproheptadine and cannabinoids, all with minimal success. Physical therapy, splints, casts and functional electrical stimulation have been useful to stimulate or stretch muscles and minimize soft tissue contractures. The most affected subjects may need to undergo orthopedic or neurological surgery. However, none of these methods of treating spasticity have been effective.

Recent studies have demonstrated that intramuscular injections (IM) of botulinum toxin type A shows promise in effectively relieving many spastic symptoms, particularly when combined with physical therapy (Royal College of Physicians, 2009). By preventing acetylcholine release from the presynaptic nerve terminal and thus blocking cholinergic transmission at the neuromuscular junction, botulinum toxins (BoNTs) induce a reduction in muscle contraction and muscle tone. As a result, BoNTA has become the treatment of choice for multifocal spasticity (Kaku & Simpson, 2016).



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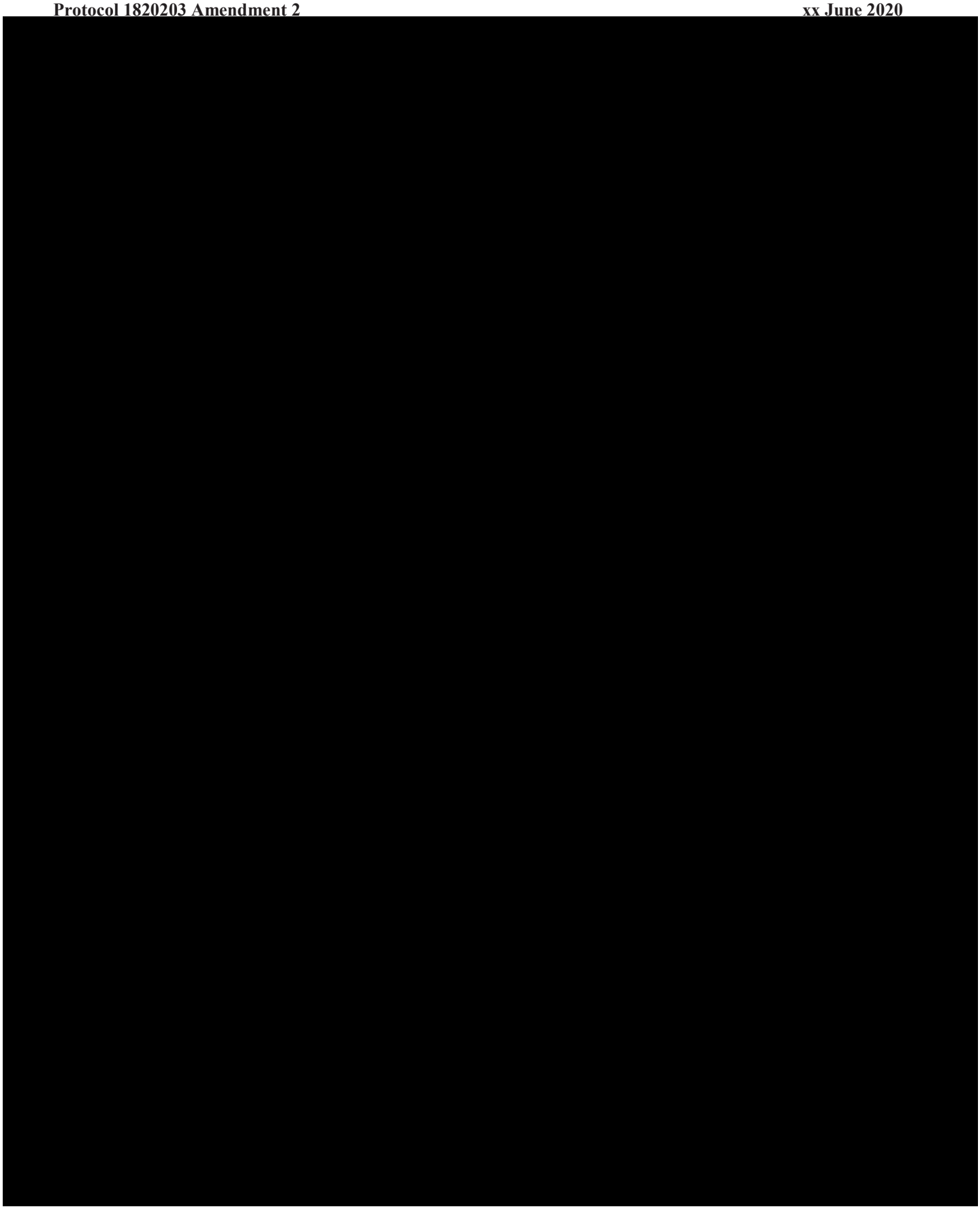

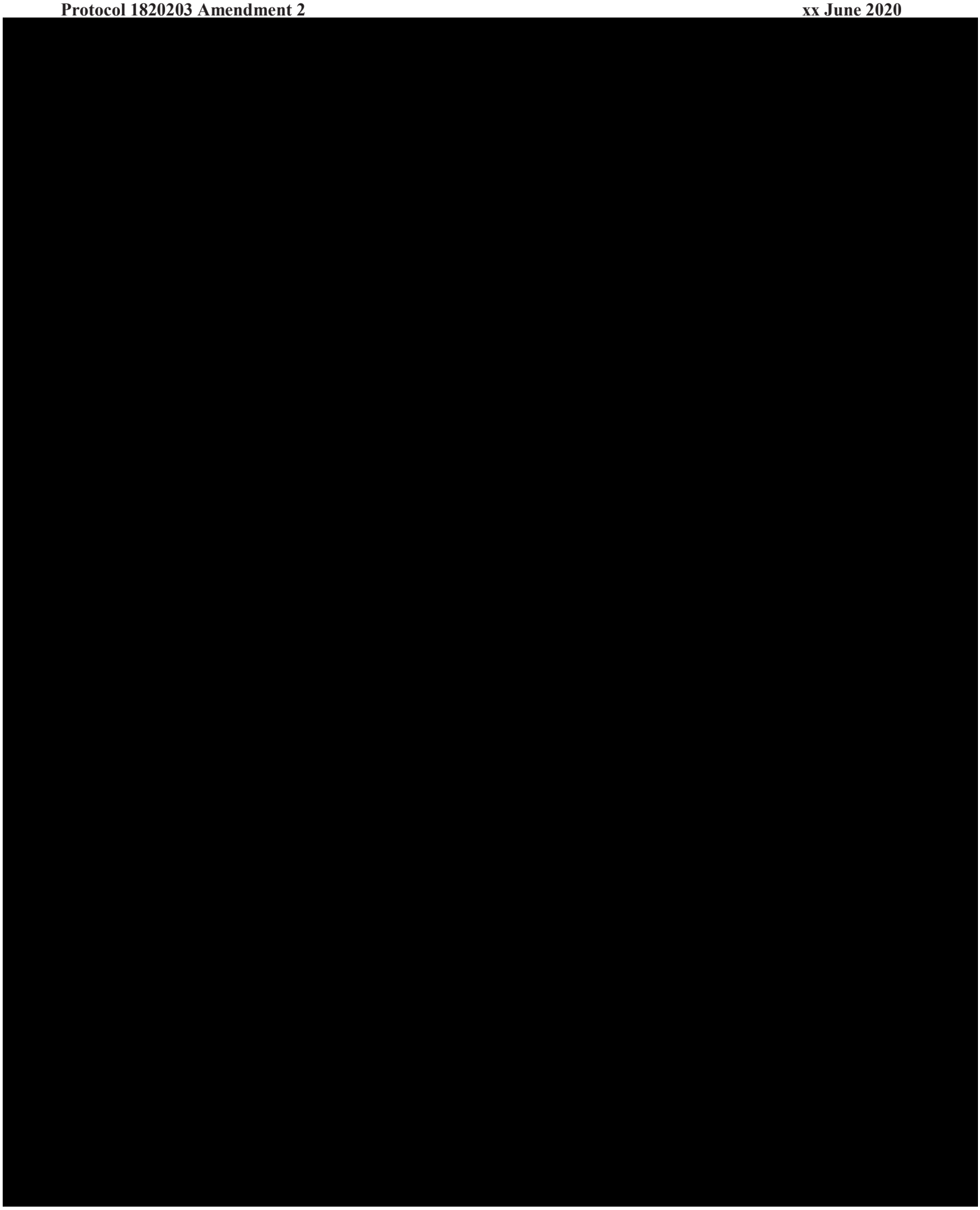

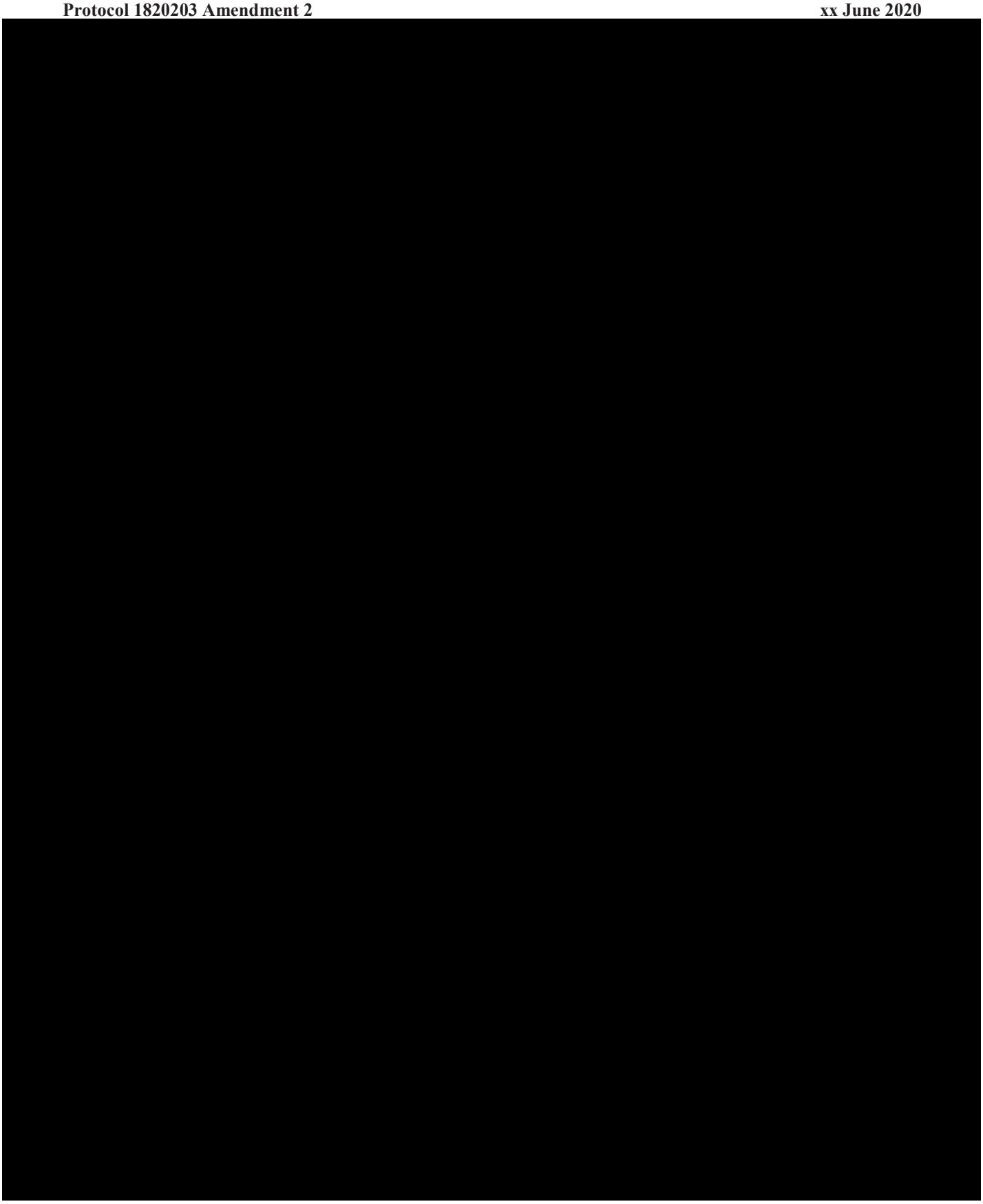

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2.1 Primary Objective

- To compare the safety and efficacy of a single treatment of DAXI for injection at three dose levels (250 U, 375 U, 500 U) versus placebo in reducing muscle tone of adult subjects with upper limb spasticity due to stroke or TBI

[redacted]

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design

JUNIPER is a randomized, double-blind, placebo-controlled trial will evaluate the efficacy and safety of DAXI for injection (3 dose levels) vs placebo for the treatment of ULS after stroke or TBI in adult subjects.

[redacted]

Approximately 128 adult subjects with ULS after stroke or TBI will be recruited from study centers across the US.[redacted]

[redacted]

3.2 Efficacy Measures

- Modified Ashworth Scale (MAS)
- Disability Assessment Scale (DAS)
- Physician Global Impression of Change (PGIC)

- Patient or Caregiver Global Impression of Change (P/CGIC)
- Spasticity per the Tardieu Scale (TS)
- Active Range of Motion (AROM)
- Active function via the Fugl-Meyer Upper Extremity (FMUE) Assessment
- EuroQoL Five Dimension Scale (EQ-5D-5L)
- Short Form Health Survey (SF-36)

3.3 Safety Measures

- Adverse events
- [redacted]
- Vital signs, physical and neuro examination findings
- Injection site evaluations
- Spirometry (pre-COVID-19 only)
- Laboratory tests (CBC, PT/INR, chemistry panel, urinalysis)
- 12-lead ECGs
- Concomitant medications
- [redacted]
- Columbia-Suicide Severity Rating Scale (C-SSRS)

3.4 Endpoints

- Co-Primary Endpoints
  - Mean change from baseline in muscle tone measured with the MAS in the suprahypertonic muscle group (SMG) of the elbow, wrist, OR finger flexors at Week 6
  - Mean score of the PGIC at Week 6

[redacted]

3.5 Duration of Trial

To provide a sufficient amount of time to document the duration of effect and safety profile of DAXI administered doses, all subjects will be prospectively followed for a minimum of 12 weeks and a maximum of 36 weeks. With a median duration of effect of at least 24 weeks experienced by adult subjects with cervical dystonia given a single treatment of DAXI for injection in the RT002-CL005 Study and adults with glabellar lines treated with a single treatment of DAXI for injection from the SAKURA Studies, it is scientifically justifiable to follow adult subjects with upper limb spasticity treated with DAXI for injection for up to 36 weeks.

Due to the COVID-19 pandemic impact study enrollment, visits, and conduct, subjects enrolled after the 20 March 2020 screening and enrollment hold will complete the study at Week 12. Subject participation may be terminated early for continuing or emergent safety concerns related to COVID-19. Sufficient results should be available to make informed decisions for program development.

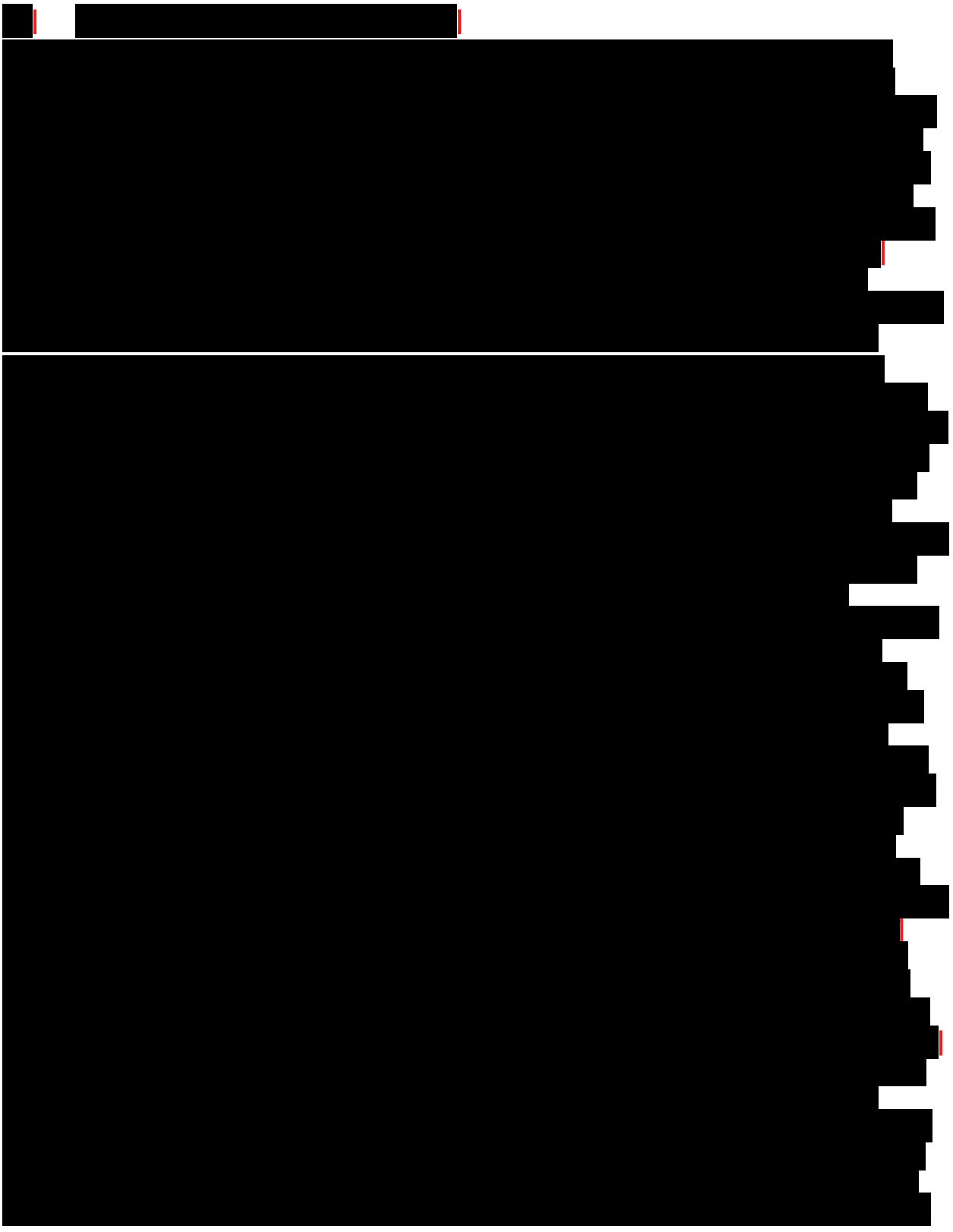
3.6 End of Study Definition

For subjects enrolled before COVID-19, the EOS visit for a given subject can occur at Week 12 if the change in MAS score in the SMG is < 1-point reduction from baseline AND the PGIC score is ≤ 0.

The EOS visit will occur after Week 12 when there is loss of muscle tone improvement in the SMG (i.e., a reduction from baseline in MAS score of < 1-point) AND the PGIC score is ≤ 0.

Week 36 will be the end of study for all subjects even those who maintain the muscle tone improvement in the SMG (i.e., a reduction from baseline in MAS score of ≥ 1-point) OR the PGIC score is ≥ 1.

For subjects enrolled after the COVID-19 20 March 2020 screening and randomization hold the end of study will be at Week 12.



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4 STUDY POPULATION

4.1 Diagnosis and Main Eligibility Criteria

Adult subjects with a diagnosis of upper limb spasticity after stroke or traumatic brain injury meeting the full eligibility criteria may participate in the study. Major inclusion and exclusion criteria are presented below.

4.1.1 Inclusion Criteria

All subjects must meet the following inclusion criteria:

1. Adults, 18 to 75 years of age, inclusive.
2. Written informed consent including authorization to release health information.
3. Focal ULS after a stroke (as defined by WHO criteria) or TBI, last stroke or TBI > 24 weeks prior to Screening.
4. Upper limb spasticity with the primary aggregate posture (AP): flexed elbow + flexed wrist + clenched fist (flexed fingers) and ≥ 1 other clinical pattern(s): adducted and internally rotated shoulder, pronated forearm, thumb-in-palm and/or intrinsic plus hand.
5. Moderate to severe ULS with a MAS score ≥ 2 at the elbow, wrist, and finger flexors; with the exception that the MAS score is ≥ 3 at the suprahypertonic muscle group (SMG) for subjects with previous injections of BoNTA in the paretic limb.
6. Moderate to severe functional disability (DAS score ≥ 2) on the principal target of treatment (1 of 4 functional domains: hygiene, dressing, malposition of the arm/wrist/fingers, and pain).
7. Has sufficient cognitive and communication ability to be able to give informed consent including authorization to release health information.

4.1.2 Exclusion Criteria

1. Upper limb spasticity attributable to an etiology other than stroke or TBI.
2. Bilateral upper limb paresis or quadriplegia.
3. Initiated in physiotherapy of the upper extremities ≤ 30 days prior to Screening or planned to start physiotherapy of the upper extremities during the course of the study.
4. Previous treatment with any BoNT product for any condition ≤ 16 weeks prior to Screening.
5. Botulinum neurotoxin treatment-experienced subjects who have historically required < 200 U of Botox/Xeomin or its equivalent to effectively treat the upper limb spasticity.
6. Botulinum neurotoxin treatment-experienced subjects who had suboptimal or no treatment response to the most recent BoNTA injection for spasticity, as determined by the investigator; or history of primary or secondary non-response to BoNTA injections, known to have neutralizing antibodies to BoNTA; or have a history of botulinum toxin type B (rimabotulinumtoxinB [Myobloc/Neurobloc]) injection for spasticity due to non-response or suboptimal response to BoNTA.
7. Change in oral medications for spasticity including dosage and dosing frequency ≤ 30 days prior to Screening.
8. Previous or planned treatment of the spastic upper limb with phenol, alcohol injection or surgery.
9. Profound muscular atrophy or fixed contracture (spasticity angle, per the Tardieu Scale, <10 degrees in the most hypertonic muscle group [elbow, wrist or finger flexors]) of the spastic limb leading to marked limitation on passive range of motion or any other known conditions of the upper limb that could confound muscle tone or functional assessment.
10. Prior or current treatment with intrathecal baclofen pump.

[redacted]

(e.g., amyotrophic lateral sclerosis and motor neuropathy, and neuromuscular junctional

[redacted]

4.4 Concomitant Medications

Concomitant medications are any prescription or over-the-counter preparations, including herbs, vitamins, or other nutritional supplements, used by subjects during participation in the study. Use of concomitant medications will be recorded on the Concomitant Medications electronic case report form (eCRF) from Screening through end of study. Subjects are allowed to be on a stable dose of medications (if any) used for spasticity treatment (e.g., anticholinergics, muscle relaxants, benzodiazepines) for at least 4 weeks prior to screening and continuing through end of study.

[redacted]

4.5 Screen Failures

A screen failure subject will be an individual from whom informed consent is obtained and is documented in writing (i.e., subject signs an informed consent form) but who does not meet the study eligibility requirements.

Individuals who do not meet the criteria for participation in this study (screen failure) because of failure to meet an eligibility criterion that may requalify them after a waiting period (such as a clinically significant out of range clinical laboratory result, prohibited medication use, etc.), or because the treatment was not performed within the 21-day window after screening, may be rescreened once. Rescreened subjects may be assigned a different subject number from the one assigned at initial Screening.

4.6 Subject Discontinuation/Withdrawal Criteria

Study subjects will receive a one (1) time only treatment for this study. Discontinuation of study treatment is not applicable. However, subjects may choose to discontinue their participation in the follow-up phase at any time.

- If the subject withdraws consent and discontinues from the trial, the Investigator will attempt to determine the reason for discontinuation and record the reason in the subject's trial records and on the case report form (CRF).
- If a subject withdraws consent because of an AE, that AE should be indicated as the reason for withdrawal. In the event of early discontinuation, (i.e., prior to the Final Evaluation) and whenever possible, the subject should be asked to return to the trial center to complete the assessments specified in the Week 12/Early Termination visit. Subjects who withdraw from the trial will not be replaced.
- If at any time during the trial, the Investigator determines that it is not in the best interest of the subject to continue, the subject will be discontinued from participation.
- The Investigator can discontinue a subject from study participation at any time if medically necessary or if the subject has failed to follow trial procedures or to keep follow-up

appointments. Appropriate documentation in the subject's trial record and CRF regarding the reason for discontinuation must be completed. Prior to discontinuing a subject from study participation, the Investigator will discuss his/her intentions with the Medical Monitor or designee.

All subjects who fail to return to the trial center for the required follow-up visits will be contacted by phone to determine the reason(s) why the subject failed to return for the necessary visit or elected to discontinue from the trial. If a subject is unreachable by telephone after a minimum of two (2) documented attempts (one [1] attempt on two [2] different days), a registered letter will be sent requesting that contact be made with the Investigator.

Revance can terminate or to stop the trial at any time. Should this be necessary, both Revance and the Investigator will ensure that proper study discontinuation procedures are completed.

4.7 Lost to Follow-Up

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

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

The site will attempt to contact the participant and reschedule the missed visit(s) and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.

Before a participant is deemed lost to follow-up, the Investigator or designee will make every effort to regain contact with the participant (where possible, three (3) telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.

Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

5 STUDY VISITS AND PROCEDURES

5.1 Screening Visit (Day -21 to -1)

Subjects presenting with upper limb spasticity will be examined to verify the diagnosis of spastic hemiparesis. Then, subjects with upper limb spasticity will be screened to determine if they meet the study eligibility criteria. Prospective study participants will be informed of the study, and the requirements for study participation will be explained to them. Subject informed consent must be obtained prior to conducting screening procedures. Refer to **Table 1.1. Schedule of Study Assessments and Procedures** for activities to be performed.

At screening, protocol-specified procedures include:

- Physical and neurological examinations
- Laboratory: serum chemistry, hematology, PT/INR, [redacted]
- Urinalysis
- [redacted]
- Concomitant medications

- Medical/surgical and neurological history
- 12-lead electrocardiogram
- Columbia-Suicide Severity Rating Scale (C-SSRS) – Baseline/Screening version
- Modified Ashworth Scale (MAS)
- Disability Assessment Scale (DAS)
- Tardieu Scale (TS)
- Active Range of Motion (AROM)

Results from clinical laboratory tests and centrally-read ECGs must be obtained and reviewed by the investigator. WOCBP with a positive pregnancy test must be excluded from study entry.

Before enrolling WOCBP in this clinical trial, investigators must review guidelines about study participation for WOCBP. The topics should generally include:

- Informed consent document
- Pregnancy prevention information
- Risks to unborn children
- Any drug interactions with hormonal contraceptives
- Contraceptives in current use
- Guidelines for the follow-up of a reported pregnancy

A female is considered to be of childbearing potential UNLESS she is post-menopausal (no menses for 12 consecutive months) or without a uterus and/or both ovaries.

WOCBP and male subjects must, accordingly, use an effective method of birth control such as oral contraceptive, injection, implant, patch, vaginal ring, intrauterine coil or device, tubal ligation, and female/male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods). True abstinence (i.e. no heterosexual intercourse) when it is in line with preferred and usual lifestyle, or having a vasectomized partner is considered acceptable methods of contraception. Effective methods of contraception must be used from the start of study, Screening visit, to 30 days after the end of study participation.

Prior to study enrollment, WOCBP and male subjects must be advised of the importance of avoiding pregnancy during participation in this clinical study from the Baseline visit to 30 days after the end of study participation, and the potential risk factors for an unintentional pregnancy. The subject must sign the informed consent document stating that the above-mentioned risks/consequences were discussed with her/him.

During the study, all WOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual cycle). The investigator must immediately notify the sponsor or the authorized representative of any female subject who becomes pregnant any time during study participation. The site will be asked to follow-up with the subject periodically during the pregnancy for ongoing health and safety information through term, as applicable. Given that this is a single treatment administration study, subjects who become pregnant after receiving their study treatment will not be automatically discontinued from the study.

After the required screening procedures are completed and study eligibility is confirmed, the subject is enrolled in the study and randomized to a treatment arm.

5.2 Baseline/Treatment Visit (Day 1)

The Baseline/Treatment Visit must be performed within 21 days of the Screening Visit.

[redacted]

The following procedures will be completed **pre-treatment on Day 1** (refer to the SOA):

- Vital signs (blood pressure [BP], pulse, temperature) and weight
[redacted]
- Columbia-Suicide Severity Rating Scale (C-SSRS) – Baseline/Screening version
[redacted]

[redacted]

5.3 Follow-up Visits

[redacted]

The following procedures will be completed at follow-up visits:

[redacted]

- Vital signs (blood pressure [BP], pulse, temperature) and weight

[redacted]

- Columbia- Suicide Severity Rating Scale (C-SSRS)- Since Last Visit version

[redacted]

5.4 End of Study Visit

A participant is considered to have completed the study when the MAS score has returned to baseline levels and the PGIC ≤0, or the Week 36 visit whichever comes first and has completed the last scheduled procedure shown in Table 1.1. Schedule of Study Assessments and Procedures.

Subjects enrolled post COVID-19, after 20 March 2020 will have the EOS Visit at Week 12 as shown in Table 1.2. Table 1.1. Schedule of Study Assessments **and Procedures**.

The EOS Visit may also occur when a subject prematurely withdraws from the study for specific reasons (e.g., AEs, pregnancy, or withdraws consent).

6 SAFETY ASSESSMENTS

6.1 Clinical Laboratory Tests

A central laboratory will be used to process all clinical specimens. The clinical laboratory parameters that will be evaluated in the study are listed in Table 3.

Table 4. Clinical Laboratory Parameters

Hematology	Chemistry	Urinalysis	Additional Tests
Hemoglobin	Sodium	Specific gravity	[redacted]
Hematocrit	Potassium	pH	
Leukocyte count (total)	Chloride	Glucose	
Leukocyte count (differential)	CO_2	Protein	[redacted]
Red blood cell count	Calcium	Blood	
Platelet count	Albumin	Bilirubin	[redacted]
	Glucose	Ketones	PT/INR
	Total bilirubin		
	Alanine aminotransferase		

	Aspartate aminotransferase Alkaline phosphatase Blood urea nitrogen Creatinine		

CO_2=carbon dioxide; ET=early termination; WOCBP=women of childbearing potential.

It is the Investigator's responsibility to review the results of all laboratory tests as they become available. For each laboratory test result outside the reference range, the Investigator must ascertain if the abnormal lab result is a clinically significant result for that individual subject. Likewise, if laboratory tests are taken at follow-up visits, the Investigator must ascertain if this is an abnormal and clinically significant change from pre-treatment for that individual subject. The Investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory test. The Investigator must sign and date all written laboratory results (e.g., urinalysis, hematology, chemistry, and pregnancy tests) and note Not Clinically Significant (NCS) or Clinically Significant (CS) for each out of range laboratory value.

If a laboratory value is determined to be a clinically significant result for that subject, this may be considered an AE to be assessed according to severity. Refer to Section 6.2 for further information.

[redacted]

6.2 Adverse Events

6.2.1 Assessment of Adverse Events:

Adverse Events (AEs) will be graded as mild, moderate, or severe as defined in Section 6.2.2.3 of this protocol.

AEs will be evaluated at the Injection visit post-treatment, follow-up Weeks 2, 4, 6, 8, 12,16, 20, 24, 28, 32 and 36/EOS, if applicable.

Adverse events will be reported by the Sponsor in accordance with "21CRF part 312.32 and Guidance for Industry and Investigators: Safety Reporting Requirements." The Investigator will report any serious adverse events (SAEs) to the IRB.

Subjects should be told to seek immediate medical attention if they experience any abnormal symptoms after investigational product administration, especially:

- Generalized loss of strength and muscle weakness
- Difficulty swallowing, breathing or speaking
- Extreme tiredness
- Loss of bladder control
- Symptoms of allergic reaction (rash, itching, etc.)

6.2.2 Adverse Events and Serious Adverse Events

6.2.2.1 Definition of Adverse Events

For this protocol, an adverse event (AE) is any untoward medical occurrence (e.g., sign, symptom, disease, syndrome, intercurrent illness, clinically significant abnormal laboratory finding, injury or accident) that emerges or worsens following administration of investigational product and until the end of trial participation that may not necessarily have a causal relationship to the administration of the investigational product. An AE can therefore be any unfavorable and/or unintended sign (including a clinically significant abnormal laboratory result), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. A treatment-emergent AE (TEAE) is one that occurs after any period of exposure to treatment.

Pre-existing conditions, which increase in frequency or severity or a change in nature as a consequence of an investigational product use will also be considered an adverse event.

An unexpected AE is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product). Any clinically significant change in the study safety evaluations, (e.g., vital signs, laboratory results, ECG, injection site evaluation, physical/neurological examinations, etc.) post-treatment must be reported as an AE.

6.2.2.2 Definition of Serious Adverse Events (SAE)

A **serious adverse event (SAE)** is any untoward medical occurrence that results in any of the following outcomes:

- Death
- Life-threatening, (i.e., the subject was, in the opinion of the Investigator, at immediate risk of death from the event as it occurred. It does not apply to an AE that hypothetically might have caused death if it were more severe)
- Persistent or significant disability/incapacity or substantial disruption of the subject's ability to carry out normal life functions
- Requires in-patient hospitalization or prolongs hospitalization (i.e., a prolonged hospitalization beyond the expected length of stay; hospitalizations for elective medical/surgical procedures, scheduled treatments, or routine check-ups are not SAEs by this criterion)
- Congenital anomaly/birth defect (i.e., an adverse outcome in a child or fetus of a subject exposed to the molecule or investigational product before conception or during pregnancy)
- Does not meet any of the above serious criteria but based upon appropriate medical judgement may jeopardize the subject or may require medical or surgical intervention to prevent one (1) of the outcomes listed above (i.e., is a significant or important medical event)

6.2.2.3 Classification of an Adverse Event

Relationship of an AE to investigational product will be assessed as follows:

- **Definite:** There is a clinically plausible time sequence between the onset of the AE and the administration of investigational product; when the event responds to withdrawal of investigational product and/or recurs with re-administration of investigational product
- **Probable:** There is a clinically plausible time sequence between the onset of the AE and the administration of investigational product; the AE is unlikely to be caused by the concurrent/underlying illness, other drugs or procedures
- **Possible:** There may or may not be a clinically plausible time sequence between the onset of the AE and the administration of investigational product and a cause cannot be ruled out
- **Unrelated:** There is not a temporal or causal relationship to investigational product administration

The investigator is responsible for evaluating all AEs and determining the severity of the event. Severity will be categorized as mild, moderate, or severe according to the following definition:

- **Mild:** Event may be noticeable to subject; does not influence daily activities; usually does not require intervention
- **Moderate:** Event may be of sufficient severity to make a subject uncomfortable; performance of daily activities may be influenced; intervention may be needed
- **Severe:** Event may cause severe discomfort; usually interferes with daily activities; subject may not be able to continue in the study; treatment or other intervention usually needed

Expectedness

The Sponsor medical monitor will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention. Expectedness is further defined in the Investigator's Brochure (IB) under Anticipated Risks and Side Effects. The list of AEs found in the IB can be considered to be expected AEs.

6.2.2.4 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of

resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. The investigator will assess subject post-treatment and at each subsequent study visit for the occurrence of AEs. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The investigator should follow the SAE until it resolves or is determined by the investigator to be stable, or the subject is lost to follow-up. The investigator should continue to report any significant follow-up information to the sponsor or the authorized representative, and the IRB, up to the point the event has resolved, or is determined to be stable. Resolution means the subject has returned to the baseline state of health, and stable means the investigator does not expect any further improvement or worsening of the subject's condition.
Any new SAEs reported by the subject to the investigator that occur after the last scheduled contact and are determined by the investigator to be reasonably associated with the administration of investigational product should be reported to the sponsor or the authorized representative, and the IRB, as required.

6.2.2.5 Adverse Event Reporting

The Investigator will assess subjects for post-treatment AEs at each subsequent trial visit. In order to avoid bias in eliciting AEs, subjects should be asked the following non-leading question: "How have you felt since your last visit?" All AEs (serious and non-serious) reported by the subject must be recorded on the source documents and CRFs. Adverse events related to COVID19 should be documented.

6.2.2.6 Serious Adverse Event Reporting

An Investigator must report an SAE to Revance or the designated CRO representative within **24 hours** of their awareness of the event:

1. Complete and return an SAE Form with all information known to date; including the Investigator's assessment of causality.
2. A fatal or life-threatening SAE must be telephoned to Revance or the authorized representative as soon as the Investigator learns of the event.
3. All pertinent medical records (discharge summary, autopsy report, etc.) should be obtained and judgments of all medical personnel who assisted in subject's treatment and follow-up.
4. Provide follow-up information to Revance or the authorized representative.

All SAEs will be followed until satisfactory resolution or until the Investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the Data Coordinating Center (DCC)/study sponsor and should be provided as soon

as possible. **The study sponsor will be responsible for notifying the FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information**. In addition, the sponsor must notify FDA and all participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting. Regulatory authorities, IRBs, and Investigators will be notified of SAEs in accordance with applicable regulations and requirements (e.g., GCPs, ICH Guidelines, national regulations and local requirements).

6.2.2.7 Reporting Events to Participants

Revance will disclose clinical trial data to individuals, to investigators at clinical sites, and publicly as aggregate summaries, in accordance to Regulatory and local legal requirements.

Follow-up of Non-Serious Adverse Events

Non-serious AEs that are identified during the last scheduled trial visit (or early discontinuation, if applicable) must be recorded on the AE CRF as ongoing.

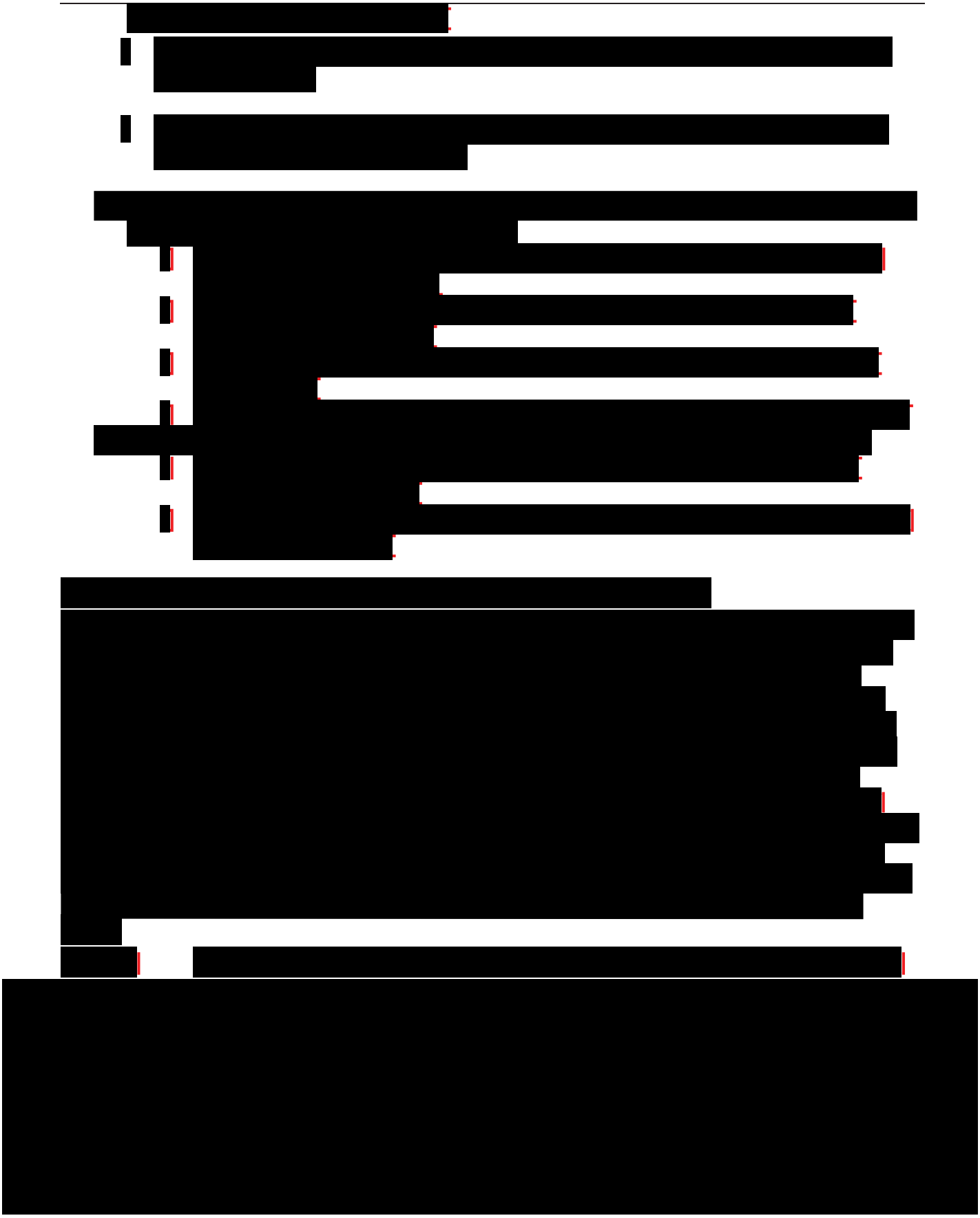
Any clinically significant abnormal test results, e.g., laboratory findings, at the Week 12/Early Termination visit should be followed to resolution or until determined by the Investigator to be stabilized. Repeat tests may be indicated to establish this. If a subject has any clinically significant, trial-related abnormalities at the end of the trial, the Medical Monitor should be notified, and every effort made by the Investigator to arrange follow up evaluations at appropriate intervals to document the course of the abnormalities.

Follow-up of Post-Trial Serious Adverse Events

SAEs that are identified on the last scheduled contact (or early discontinuation, if applicable) must be recorded on the AE CRF page and reported to the CRO and Revance according to the reporting procedures outlined in Section 6.2.2.6. This may include unresolved previously reported SAEs, or new SAEs. The Investigator should follow these SAEs until the events are resolved, or the subject is lost to follow-up. The Investigator should continue to report any significant follow-up information to the Medical Monitor, Revance, and the IRB up to the point the event has been resolved. Resolution means the subject has returned to the baseline state of health, or the Investigator does not expect any further improvement or worsening of the subject's condition.

Any new SAEs reported by the subject to the Investigator that occur after the last scheduled contact and are determined by the Investigator to be reasonably associated with the administration of investigational product should be reported to Revance and the IRB.

[redacted]



[redacted]

6.3 Injection Site Evaluation:

The injection sites will be evaluated at Injection Visit (Day 1) pre- and post- treatment (to determine if there is an immediate reaction to the investigational product), follow-up visits (Weeks 2, 4, and 36 or Early Termination visit), if applicable. The assessment will be done as a global evaluation of the injection sites to be performed pre-treatment on Injection visit.

Table 5. Injection Site Evaluation

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

6.4 Reporting of Pregnancy

During the trial, all WOCBP should be instructed to contact the Investigator immediately (within 24 hours) if they suspect they might be pregnant (e.g., missed or late menstrual cycle). The Investigator must immediately notify Revance or designated Contract Research Organization (CRO) of any female subject who becomes pregnant any time during study participation, record the information on the Pregnancy Notification Form and send the form to the CRO. The site will be asked to follow-up with the subject periodically during the pregnancy for ongoing health and safety information through term, as applicable. Subjects will remain on the trial.

6.5 Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a questionnaire that prospectively assesses Suicidal Ideation and Suicidal Behavior using a semi-structured interview to probe subject responses (Posner, 2008) (**APPENDIX K**). The C-SSRS is to be administered at Screening and each study visit, including unscheduled ones. Both the Baseline/Screening and Since Last Visit versions will be utilized. All assessors will receive formal training in the use of this tool.

A subject who endorses "suicidal ideation" must be referred to a mental health professional for further assessment and/or treatment.

7 UNANTICIPATED ADVERSE EVENTS

7.1 Definition of Unanticipated Adverse Events

Unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the

- Characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Revance will comply with these criteria for reporting Unanticipated Adverse Events.

7.2 Unanticipated Adverse Event Reporting

The Investigator will report unanticipated Adverse Events to the reviewing Institutional Review Board (IRB) and the Sponsor. The unanticipated adverse event report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number.
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an unanticipated adverse event;

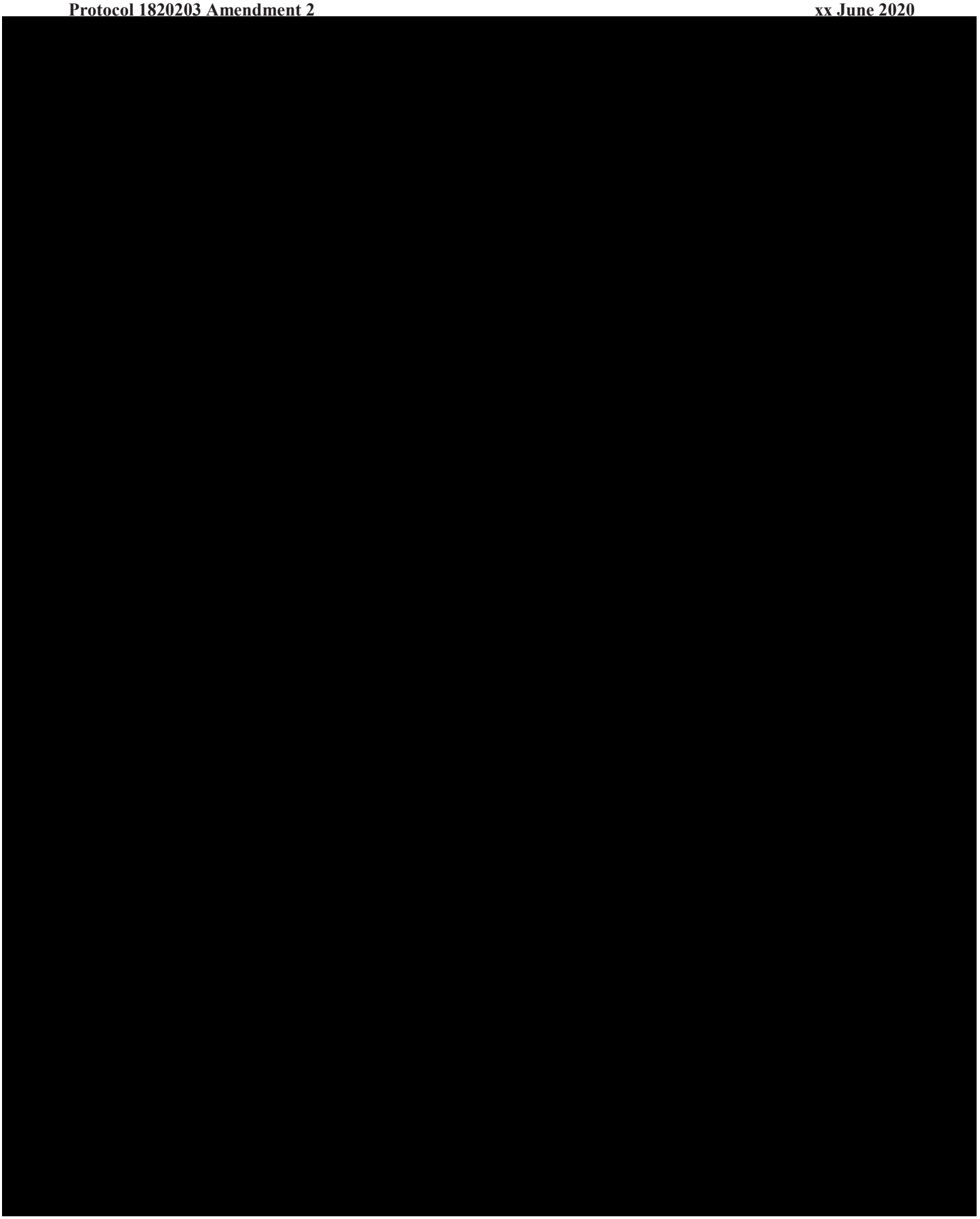
- A description of any changes to the protocol by the Sponsor or other corrective actions that have been taken or are proposed in response to the unanticipated adverse event.
- The Sponsor will update the IB or provide Dear Doctor letter should these actions be deemed required.

To satisfy the requirement for prompt reporting, unanticipated adverse events will be reported using the following timeline:

- Unanticipated adverse events that are fatal and life-threatening serious adverse events (SAEs) will be reported to the IRB and to the Sponsor within seven (7) days of the Investigator becoming aware of the event.
- Any other unanticipated adverse events that are SAEs will be reported to the IRB and to the Sponsor within 15 days of the Investigator becoming aware of the problem.
- All unanticipated adverse events that non-serious AEs are not required to be reported to the IRB or to the Sponsor.
- All unanticipated serious adverse events should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) if applicable.

7.3 Reporting Unanticipated Adverse Events to Participants

Revance will disclose clinical trial data to individuals, to investigators at clinical sites, and publicly as aggregate summaries, in accordance to Regulatory and local legal requirements.



[redacted]

9 STATISTICAL PLAN

This section contains a brief overview of the statistical analyses planned for this study. A formal statistical analysis plan (SAP) will be finalized before database lock.

9.1 Sample Size

The sample size calculation is based on the effect size that was observed for the primary endpoint (change from baseline in MAS in the SMG) from the registration study of Dysport (Gracies J, 2015) for the treatment of ULS. [redacted]

[redacted]

9.2 Analysis Populations

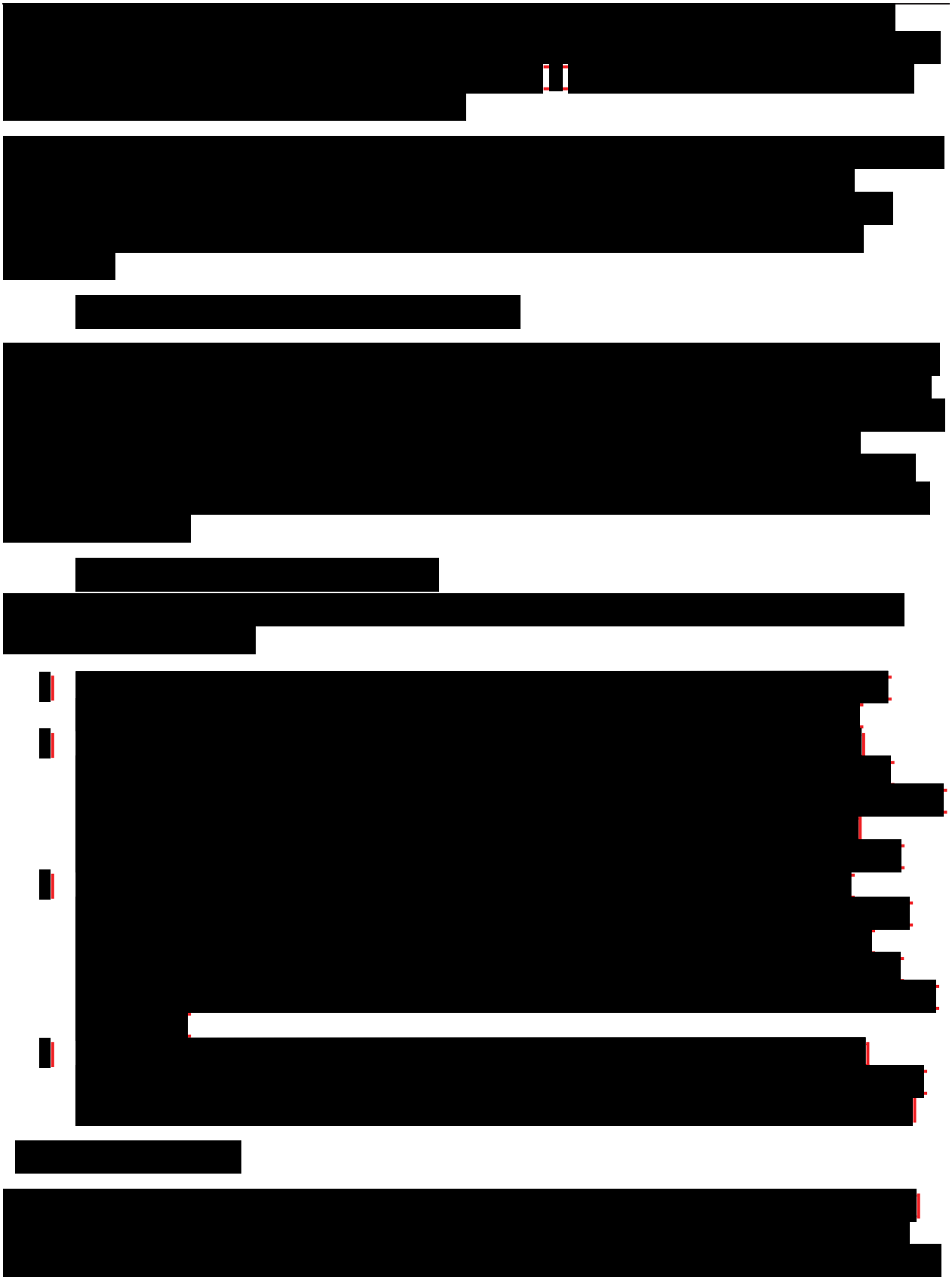
- Intent-to-Treat Population: Efficacy analysis will be performed using the intention-to-treat analysis set. This population includes all subjects randomized, given one injection session of the study medication and have a MAS score in the SMG at baseline and 6 weeks after treatment and a PGIC score at least one post-baseline MAS assessment.

[redacted]

- Pre-COVID-19 ITT Population: a subset of the ITT population, subjects who were enrolled before COVID-19 enrollment hold (20MAR2020).
- Pre-COVID-19 PP Population: a subset of the PP population, subjects who were enrolled before COVID-19 enrollment hold (20MAR2020).

9.2.1. Primary Analyses

Efficacy analysis will be performed using the intention-to-treat analysis set. This population includes all subjects randomized, given one injection session of the study medication and have a MAS score in the SMG at least one post-baseline MAS assessment.



[redacted]

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Good Clinical Practice

It is the responsibility of the Principal Investigator to oversee the safety of the subject at their site. The Investigator will ensure that this study is conducted in full compliance with the principles of the "Declaration of Helsinki" (as amended in Tokyo, Venice, Hong Kong, and South Africa), ICH guidelines, or with the laws and regulations of the country in which the research is conducted. By signing the US Form FDA 1572, "Statement of Investigator", the Investigator commits to adhere to applicable sections of the US 21CFR parts 50 "Protection of Human Subjects", 54 "Financial Disclosure by Clinical Investigators", 56 "Institutional Review Boards", and 312 subpart D "Responsibilities of Sponsors and Investigators". All Investigators will ensure adherence to ICH guidelines for GCP and Clinical Safety Data Management.

10.2 Institutional Review Board/Ethics Committee Approval

The institution's IRB, or other committee functioning in a similar capacity, will review and approve the protocol and any protocol amendments, initial and any revised IC documents, protocol amendments, and safety items. After approval by the IRB, documentation of approval and the approved Informed Consent document will be sent to Revance/designee before any subject is enrolled into this study.

10.3 Informed Consent

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Written informed consent will be obtained from all subjects before any study-related procedures (including any pre-treatment screening procedures) are performed. The investigator may discuss the study and the possibility for entry with a potential subject without first obtaining consent. However, a subject wishing to participate must give written informed consent prior to any study-related procedures being conducted, including those performed solely for the purpose of determining eligibility for study participation, and including withdrawal from current medication (if required prior to study entry). The investigator has both the ethical and legal responsibility to ensure that each subject being considered for inclusion in this study has been given a full explanation of the procedures and expectations for study participation.

When applicable, the site-specific informed consent must be forwarded to the sponsor for approval prior to submission to an IRB that is registered with appropriate local or federal agencies as required. Each subject will sign the consent form that has been approved by the same IRB that was responsible for protocol approval. Each informed consent document must adhere to the ethical principles stated in the Declaration of Helsinki and will include the elements required by FDA regulations in 21 CFR Part 50, Health Canada's Food and Drug Regulations, Division 5, European Medicines Agency (EMA), as well as the elements required by the ICH-GCP guideline, and applicable national and local regulatory requirements. The consent form must also include a statement that the sponsor, their designees, and auditing regulatory agencies will have direct access to the subject's records and medical history for study related purposes.

Once the appropriate essential information has been provided to the subject and fully explained by the investigator (or a qualified designee) and it is felt that the subject understands the implications and risks of participating in the study, the IRB approved consent document shall be signed and dated by both the subject and the person obtaining consent (investigator or designee), and by any other parties required by the IRB or other Regulatory Authorities. The subject will be given a copy of the signed informed consent document with the original kept on file by the investigator. All of the above activities must be completed before any study related procedures are conducted (including any screening study procedures).

10.4 Recording and Collecting of Data

In accordance with ICH and GCP guidelines, the Investigator will maintain complete, accurate, legible, and easily retrievable data, and will allow personnel authorized by Revance access to all study data at any time. Such data shall also be secured in order to prevent loss of data**.**

10.4.1 Case Report Forms

At scheduled monitoring visits, CRFs will be verified against source documentation and submitted as final data.

10.4.2 Protocol Deviations and Compliance

A protocol deviation is any noncompliance with the clinical trial protocol. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations as soon as possible. All deviations must be entered in the eCRFs and must be sent to the reviewing IRB per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

This study will be conducted as described in this protocol, except for an emergency situation in which the protection, safety, and well-being of the subject requires immediate intervention, based on the judgment of the investigator (or a responsible, appropriately trained professional designated by the investigator). In the event of a significant deviation from the protocol due to an emergency, accident, or mistake, the investigator or designee must contact the medical monitor and the sponsor at the earliest possible time by telephone. This will allow an early joint decision regarding the subject's continuation in the study. This decision will be documented by the investigator and the medical monitor.

10.5 Safety Oversight

Safety oversight will be under the direction of an independent Data Monitoring Committee (DMC) composed of individuals with the appropriate expertise, including indication and/or neuromodulators and/or data management. The DMC will be appointed to review safety data during the study and will monitor quality and completeness of the safety data, as well as signals and outcomes (SAEs, AEs, laboratories, and other outcome data). Data will be reviewed in both blinded and unblinded manners, as appropriate.

The DMC will consist of 5 members, including a chair, a biostatistician, two neurologists, a pulmonologist, and a cardiologist. Details of the composition, identity of members, and scope of the committee's mandate will be presented in a DMC charter document.

[redacted]

10.7 Clinical Monitoring

All aspects of the study will be monitored by the sponsor or authorized representatives of the sponsor according to GCP and Standard Operating Procedures (SOPs) for compliance with

applicable government regulations, (i.e., Informed Consent Regulations [US 21CFR, Part 50] and Institutional Review Board regulations [US 21CFR, Part 56.103]). Access to all records, both during the trial and after trial completion, should be made available to the sponsor at any time for review and audit to ensure the integrity of the data. The investigator must notify sponsor immediately if the responsible IRB has been disqualified or if proceedings leading to disqualification have begun.

The investigator must conduct the protocol in accordance with applicable GCP regulations and guidelines; applicable informed consent regulations (US 21CFR, Part 50); and in compliance with the Declaration of Helsinki. Every attempt must be made to follow the protocol and to obtain and record all data requested for each subject at the specified times. If data is not recorded per protocol, the reasons must be clearly documented on the eCRF/records.

Before study initiation, at a site initiation visit or at a meeting with the investigator(s), a representative from the sponsor will review the protocol and study eCRFs with the investigator(s) and their staff. During the study, the study monitor will visit the site regularly to check the completeness of subject records, the accuracy of entries on the eCRFs, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that consent is being sought and obtained in compliance with applicable regulations, and that the investigational product is being stored, dispensed and accounted for according to specifications. The investigator and key trial personnel must be available to assist the monitor during these visits.

The investigator must give the monitor access to relevant hospital or clinical records, to confirm their consistency with the eCRF entries. No information in these records about the identity of the subjects will leave the study center. Monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of primary efficacy and safety variables. Additional checks of the consistency of the source data with the eCRFs will be performed according to the study-specific monitoring plan.

The investigator must promptly complete the eCRFs after the subject's visit. The monitor is responsible for reviewing them and clarifying and resolving any data queries. A copy of the eCRFs will be retained by the investigator who must ensure that it is stored in a secure place with other study documents, such as the protocol, the Investigator's Brochure, and any protocol amendments.

11 DATA HANDLING AND RECORD KEEPING

11.1 Data Collection and Management Responsibilities

For this study, all protocol-specified data will be recorded in the source documents, and data will be entered on the eCRFs from the source documents. In addition to signature confirmation that a subject meets the study eligibility criteria, upon each subject's completion of the study, the investigator will sign a statement indicating that all pages of the subject's case report have been reviewed. Signature stamps and "per signatures" are not acceptable.

It is sponsor's policy that the study data be verifiable with the source data that necessitates access to all original recordings, laboratory reports, and other records for each subject. The investigator must therefore agree to allow access to subjects' records, and source data must be made available for all study data. Subjects (or their legal representatives) must also allow access to their medical

records. Subjects will be informed of the importance of increased record access and permission granted by signature on the informed consent document prior to Screening.

Checks will be performed to ensure the quality, consistency, and completeness of the data. Instances of missing or uninterpretable data will be resolved with the investigator or study coordinator. Data queries, documented on data query forms, will be sent to the research facility. Site personnel will be responsible for providing resolutions to the data queries and for correcting the eCRFs, as appropriate. All unused sponsor source documents and binders must be returned to the sponsor upon completion of the study.

The investigator must keep written or electronic source documents for every subject participating in the clinical study. The subject file that identifies the study in which the subject is participating must include the subject's available demographic and medical information including:

- Name
- Contact information
- Age
- Sex
- Medical history
- Concomitant diseases
- Concomitant therapies/medication
- Study visit dates
- Performed examinations, evaluations, and clinical findings
- Investigational product administration
- AEs, SAEs, or pregnancy (as applicable)

Additionally, any other documents with source data, especially original printouts of data that were generated by technical equipment must be included in the subject's source document (e.g., laboratory value listings). All these documents must have at least the subject's study number, and the date of the evaluation.

The data recorded during the course of the study will be documented in the eCRF and/or the study-specific forms. Before or at study termination, all data must be forwarded to the sponsor. The data will then be recorded, evaluated, and stored in anonymous or coded form in accordance with data-protection regulations.

Subjects will authorize the use of their protected health information during the informed consent process in accordance with the applicable privacy requirements. Subjects who deny permission to use and disclose protected health information will not be eligible to participate in the study. The investigator will ensure that the study documents forwarded to the sponsor, and any other documents, contain no mention of subject names.

Any amendments and corrections necessary will be undertaken in both the source documents and eCRFs (as appropriate) and countersigned by the investigator, or documented designee, stating the date of the amendment/correction. Errors must remain legible and may not be deleted with correction aids. The investigator must state his/her reason for the correction of any data. In the case of missing data/remarks, the entry spaces provided in the eCRF should be cancelled out so as to avoid unnecessary follow up inquiries.

Regulatory authorities, the IRB and/or the sponsor's Quality Assurance group (or designee) may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. The investigator must guarantee direct access to these documents. Electronic CRFs (eCRFs) will be kept by the sponsor or an authorized designee in a secured area. Clinical data will be recorded in a computer format for subsequent statistical analyses. Data files will be stored on electronic media with a final master data file kept by the sponsor after descriptive and statistical analyses and reports have been generated and are complete.

It is the responsibility of the investigator to ensure that the study center file is maintained in accordance with the ICH Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance, Section 8 – Essential Documents for the Conduct of a Clinical Trial.

11.2 Study Records Retention

It is a sponsor requirement that all investigators participating in clinical studies maintain detailed clinical data for one of the following periods:

- Country-specific requirements, or
- A period of at least two years following the last approval of a marketing application approved by a Regulatory Authority in an ICH region or until there are no pending or contemplated marketing applications in an ICH region, or
- A period of two years after the sponsor notifies the investigator that the data will not be submitted for review by any Regulatory Authority

The investigator must not dispose of any records or essential documents relevant to this study without either (1) written permission from the sponsor, or (2) providing an opportunity for the sponsor to collect such records. The investigator shall take responsibility for maintaining adequate and accurate electronic or hard copy source documents of all observations and data generated during this study. Such documentation is subject to inspection by the sponsor and relevant regulatory agencies. If the investigator withdraws from the study (e.g., relocation, retirement) all study-related records should be transferred to a mutually agreed upon designee. Notice of such transfer will be provided to sponsor in writing.

It is the responsibility of the investigator to ensure that the study center file is maintained in accordance with the ICH Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance, Section 8 - Essential Documents for the Conduct of a Clinical Trial.

11.3 Treatment of Missing Data

A protocol deviation is any noncompliance with the clinical trial protocol. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations as soon as possible. All deviations must be addressed in study source documents and must be sent to the reviewing IRB per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

This study will be conducted as described in this protocol, except for an emergency situation in which the protection, safety, and well-being of the subject requires immediate intervention, based on the judgment of the investigator (or a responsible, appropriately trained professional designated by the investigator). In the event of a significant deviation from the protocol due to an

emergency, accident, or mistake, the investigator or designee must contact the medical monitor and the sponsor at the earliest possible time by telephone. This will allow an early joint decision regarding the subject's continuation in the study. This decision will be documented by the investigator and the medical monitor.

11.6 Access to Information for Monitoring and Auditing

In accordance with ICH GCP guidelines and 21 CFR 312, the CRA/auditor is to have direct access to the subject's source documentation in order to verify the data recorded in the CRFs. The CRA is responsible for routine review of the CRFs at regular intervals throughout the study and to verify adherence to the protocol, as well as the completeness, consistency, and accuracy of the data being recorded. The CRA/auditor is to have access to any subject records needed to verify the entries on the CRFs, as well as access to all other study-related documentation and materials. The Investigator agrees to provide the monitor with sufficient time and facilities to conduct monitoring, and to cooperate with the monitor to ensure that any problems detected in the course of these monitoring/auditing visits are resolved.

11.7 Termination of the Study

For reasonable cause, either the Investigator or the Sponsor (Revance) may terminate the Investigator's participation in this study, provided a written notice is submitted within the time period provided for in the Clinical Trial Agreement (CTA). In addition, Revance may terminate the study at any time upon immediate notice for any reason, including but not limited to, Revance's belief that termination is necessary for the safety of subjects.

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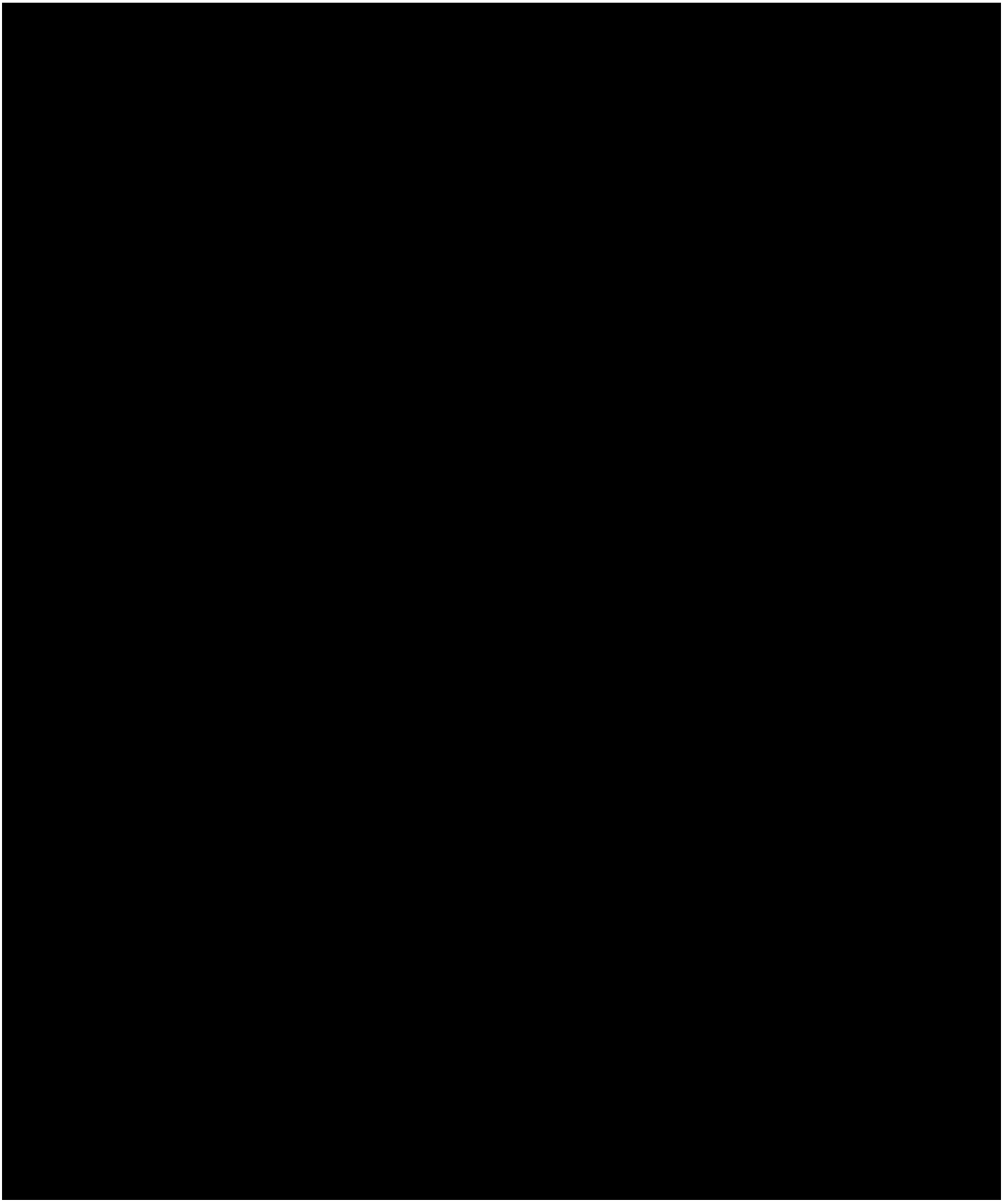

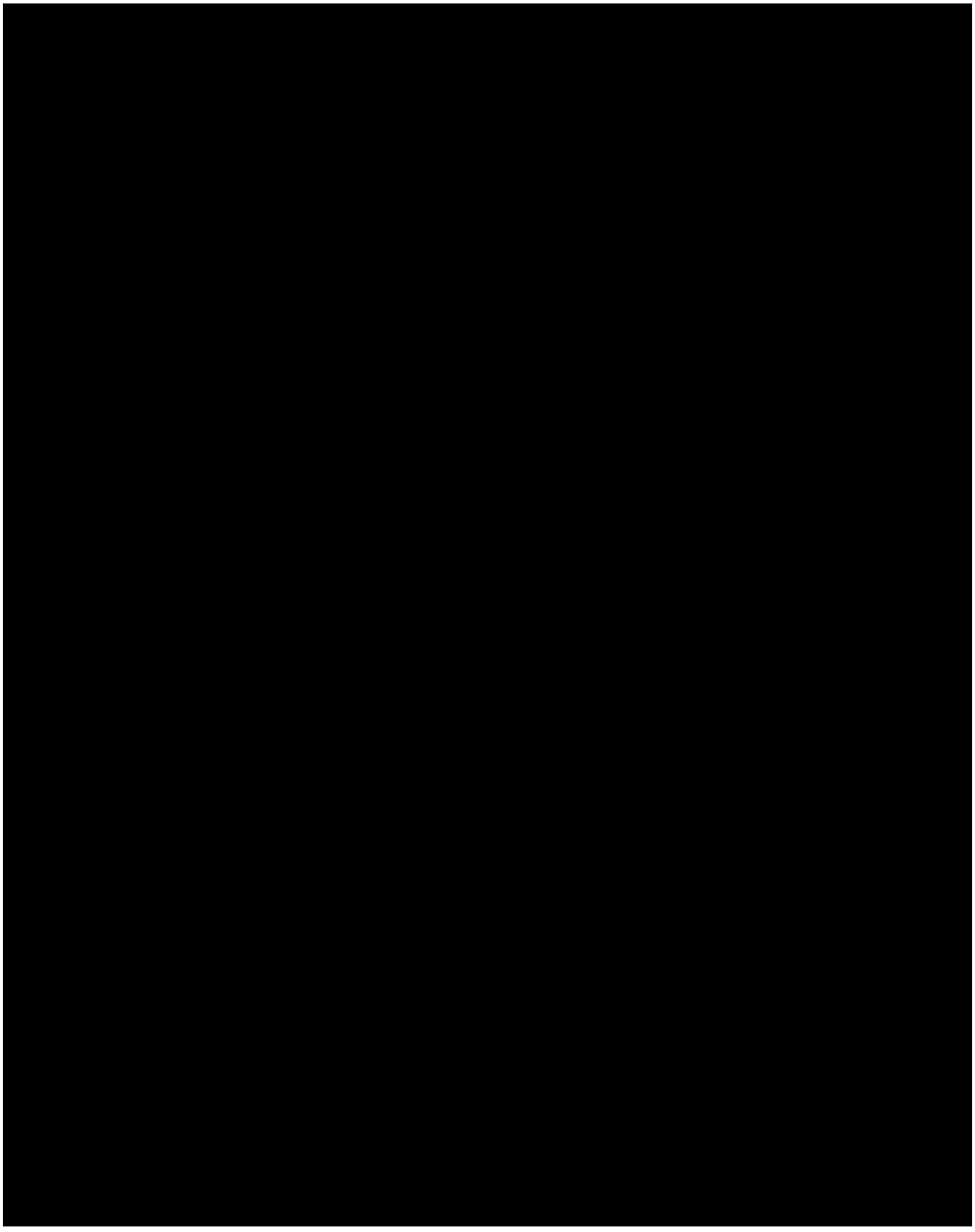

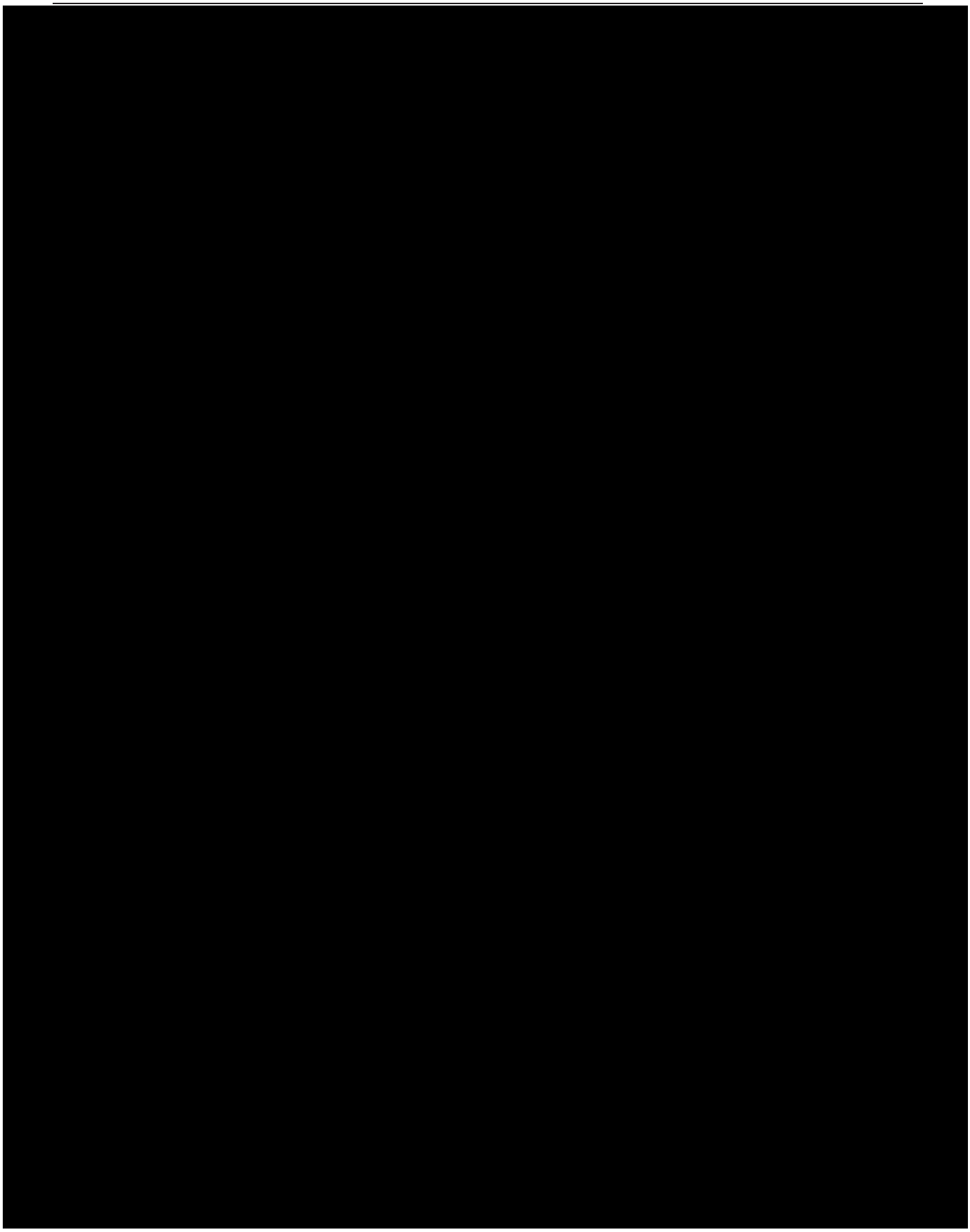

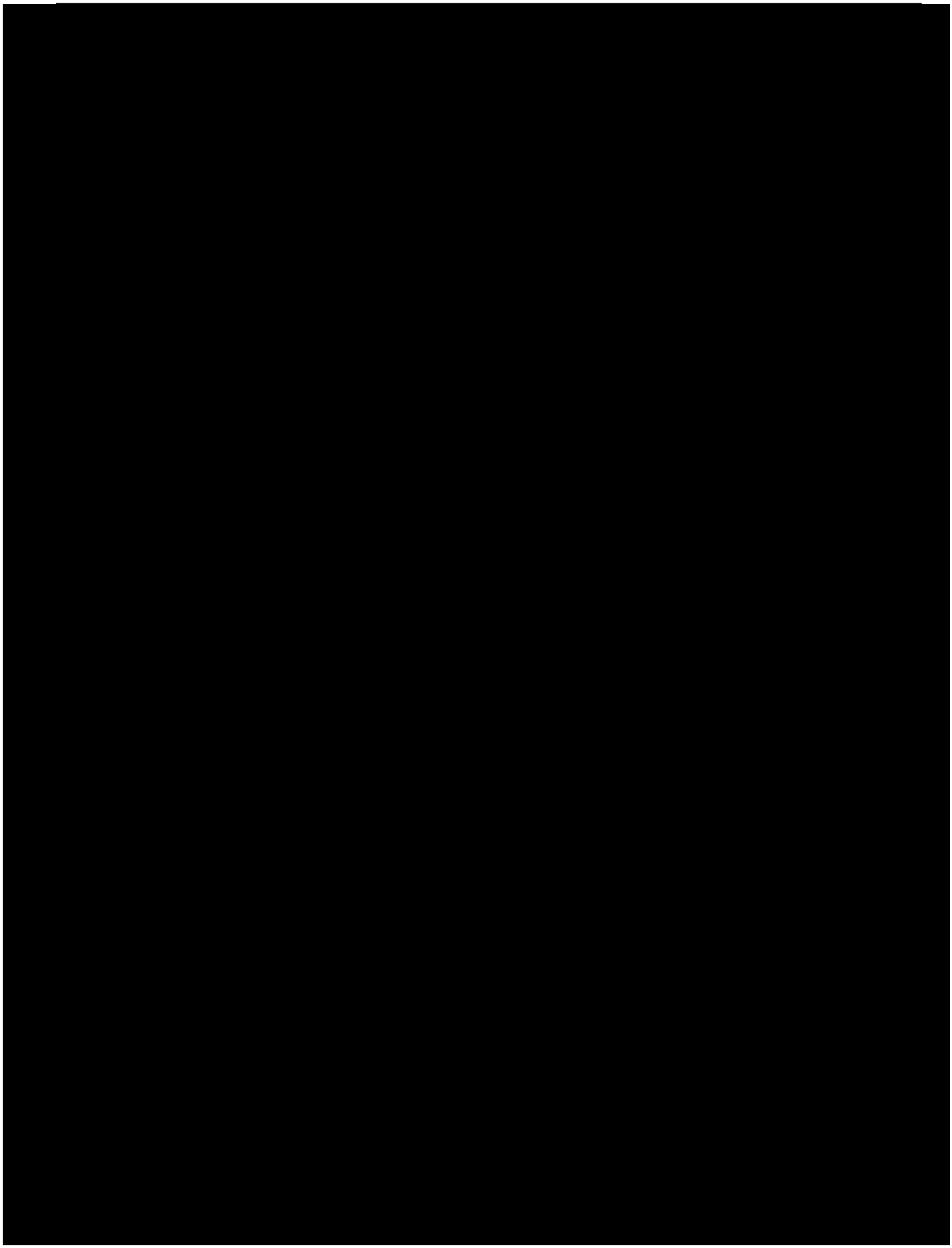

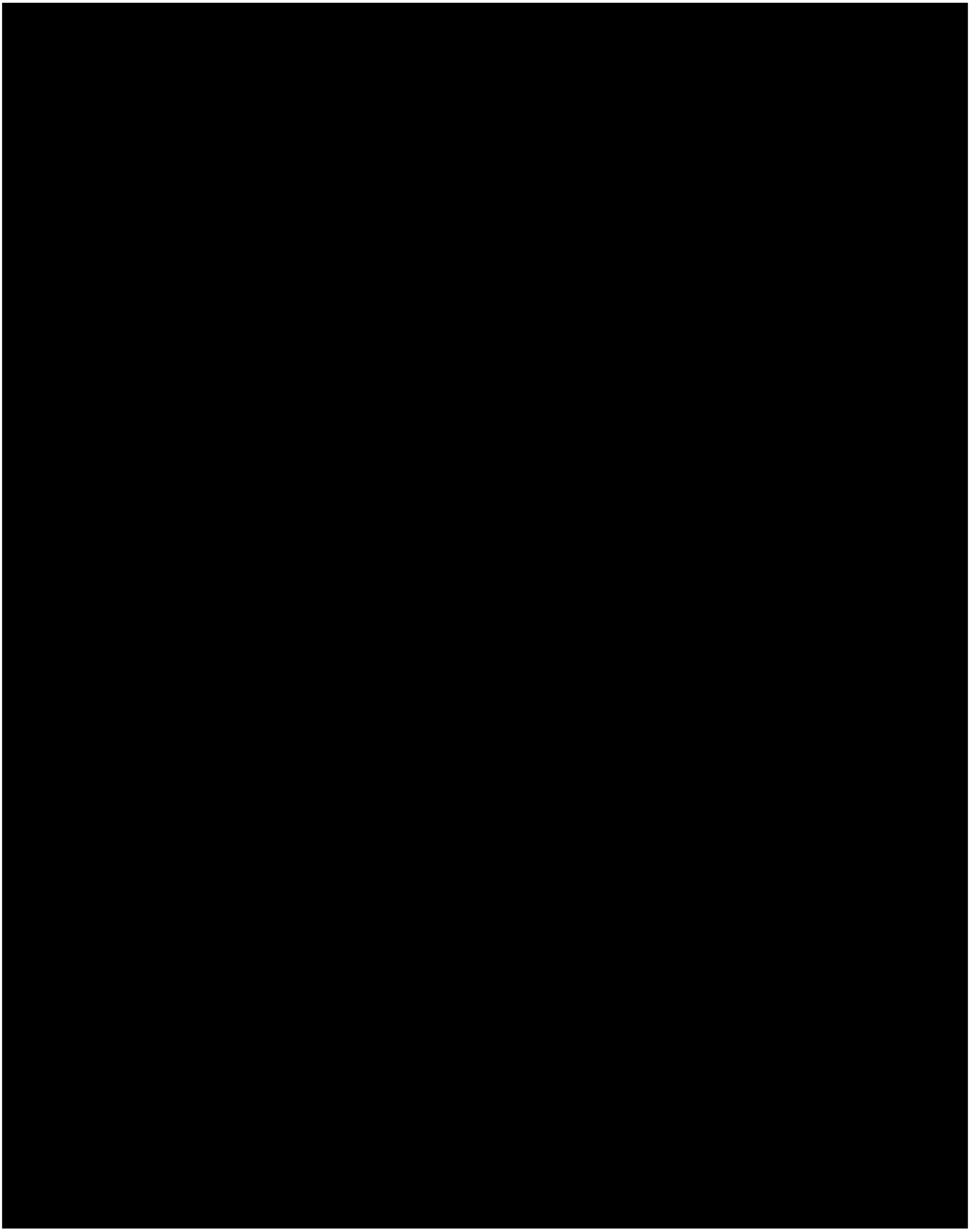

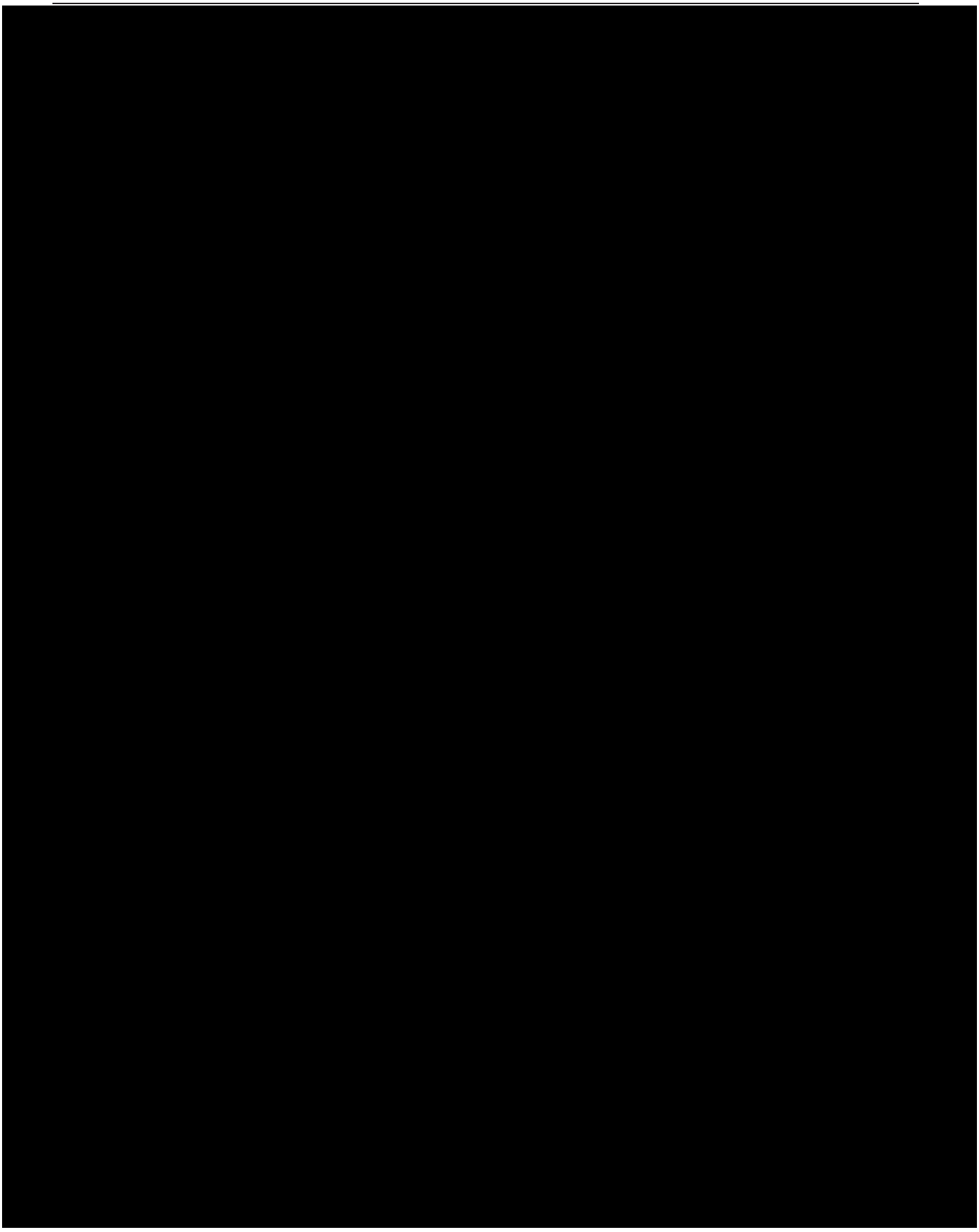

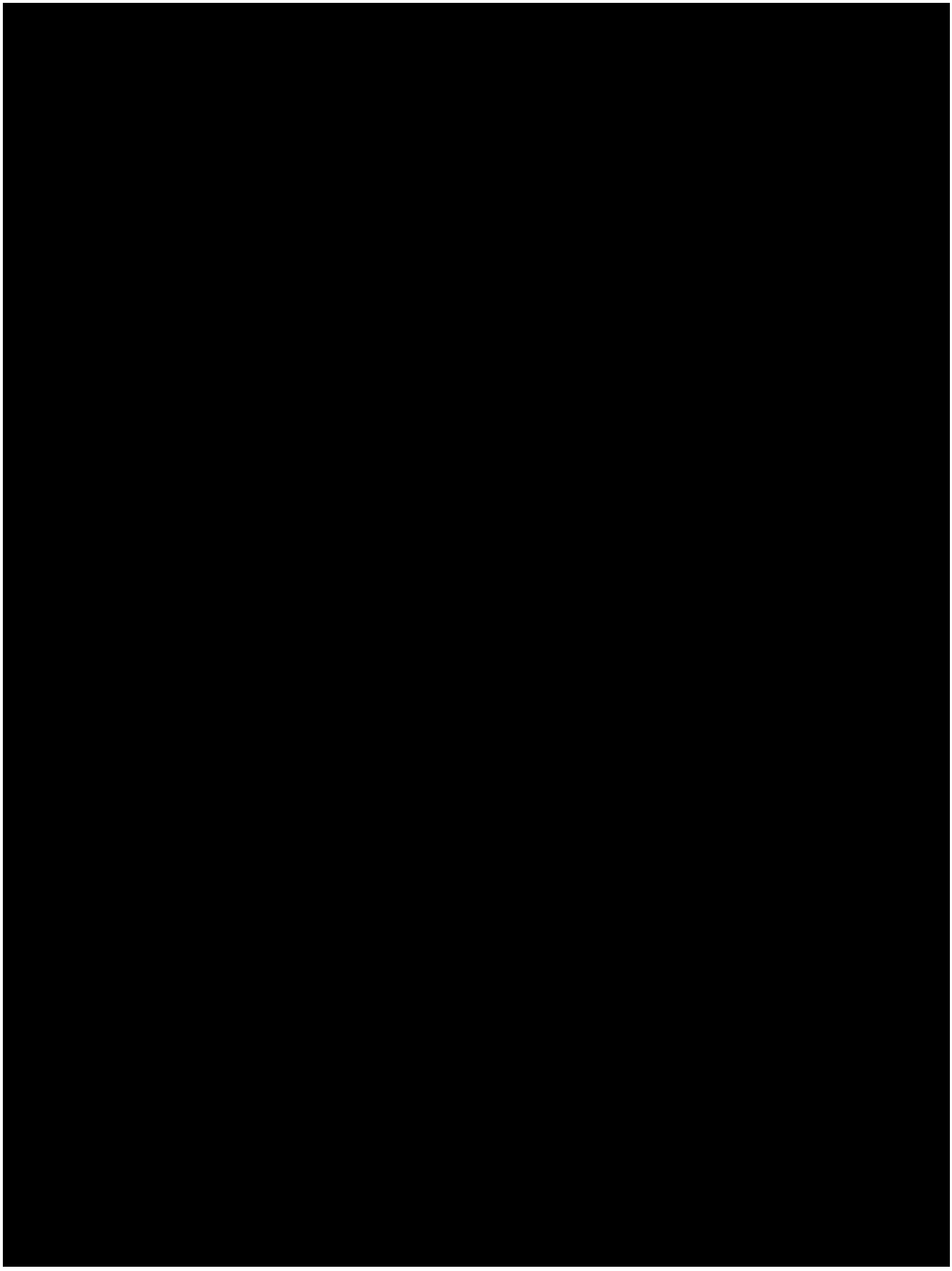

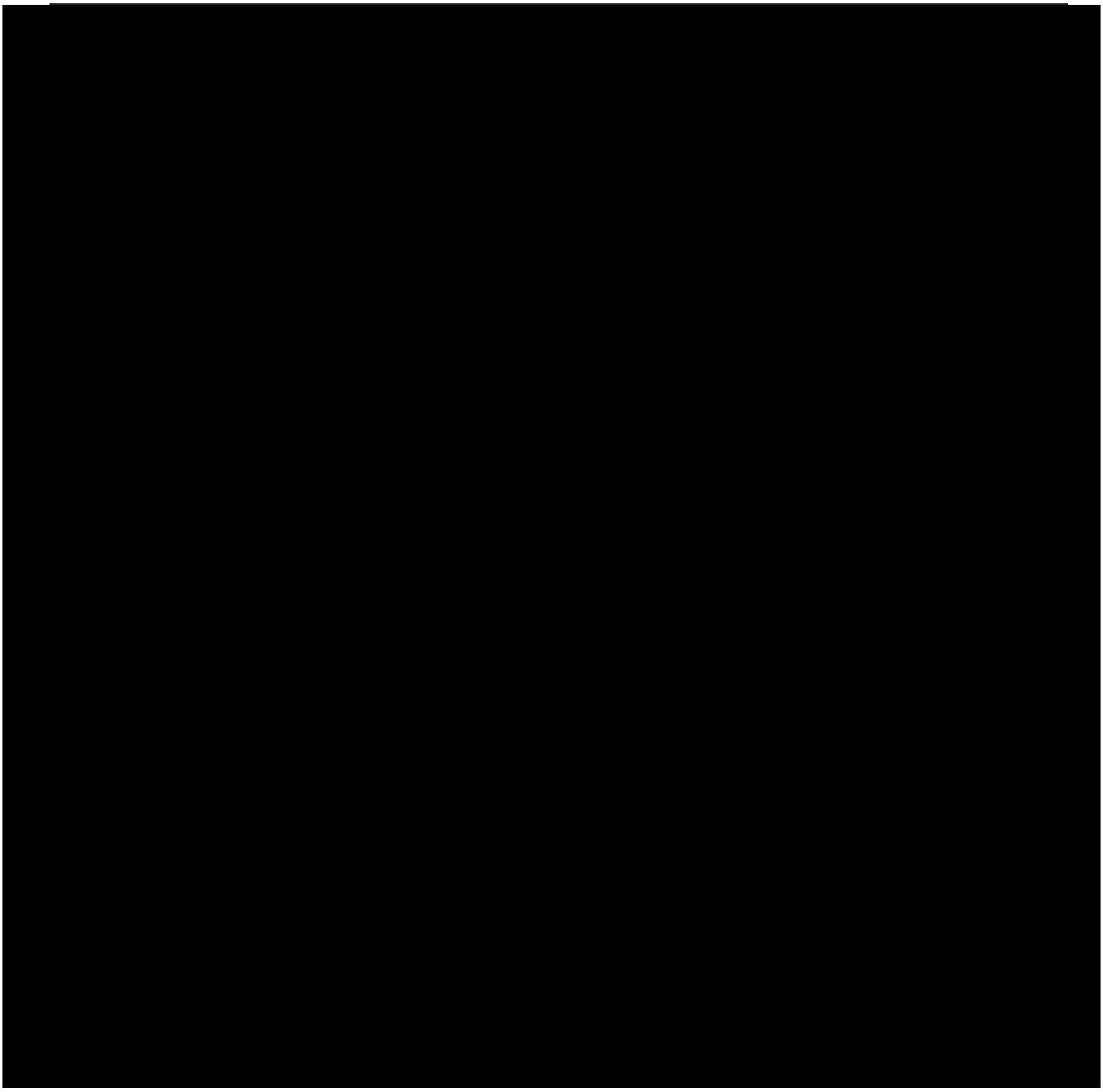

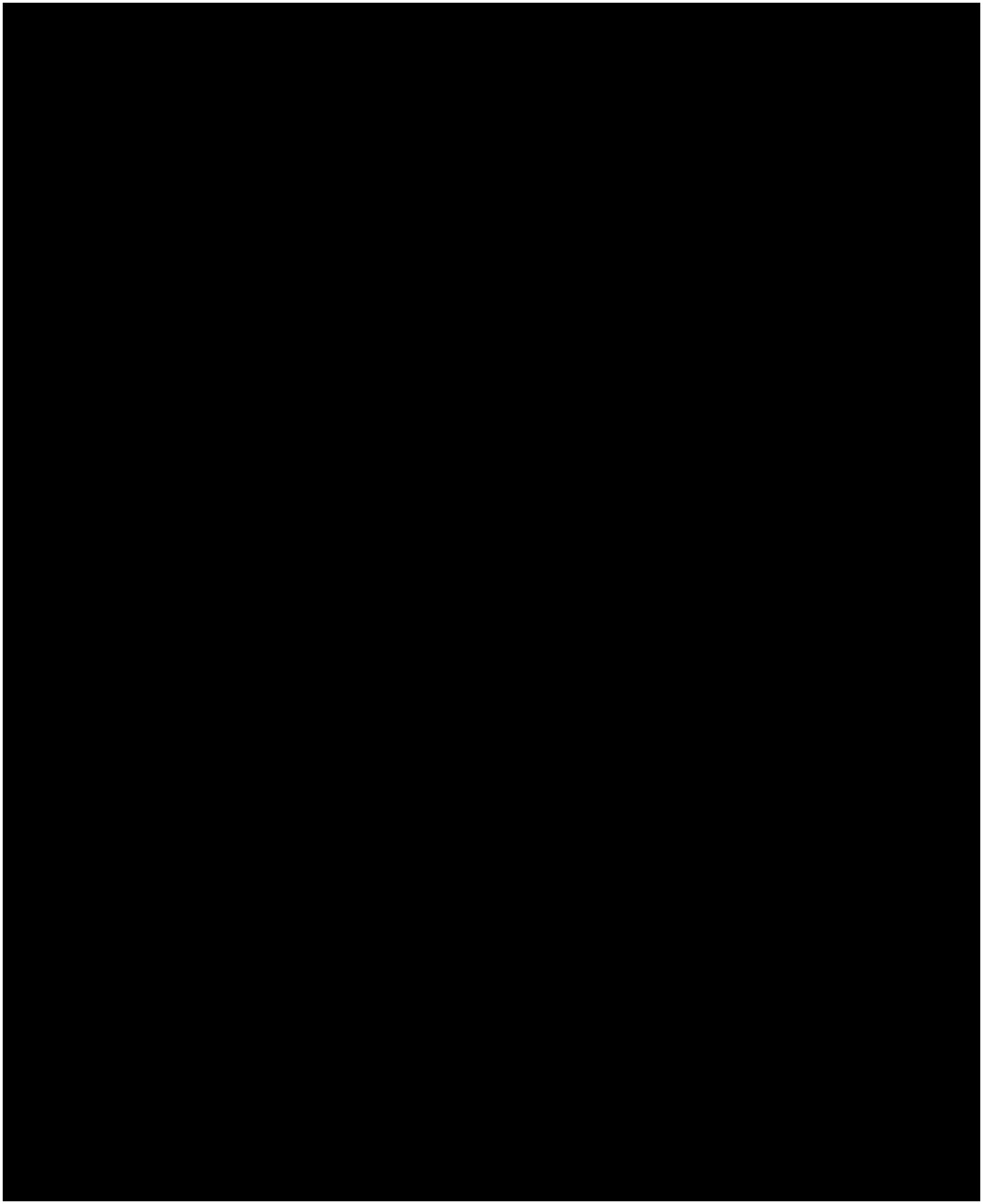

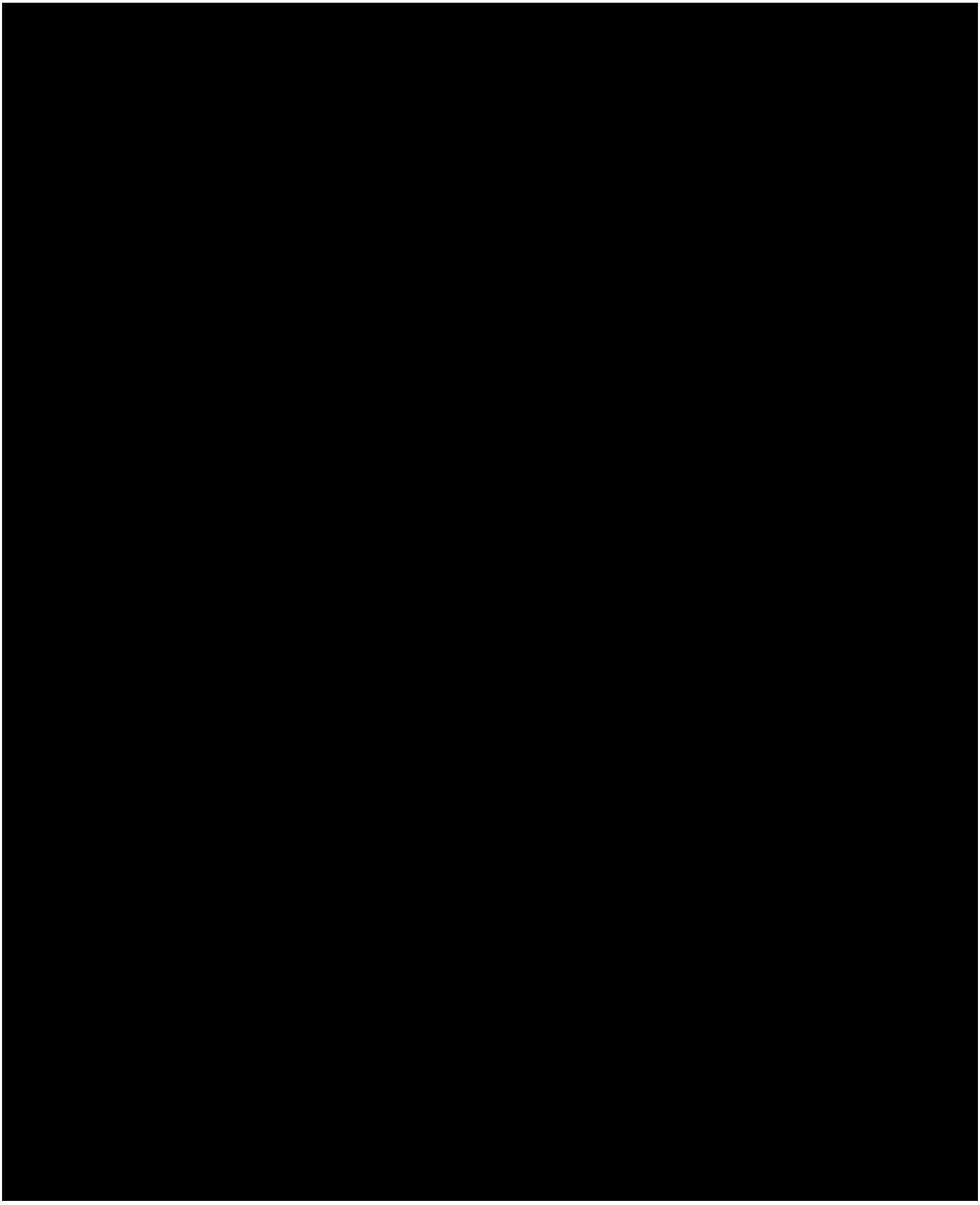

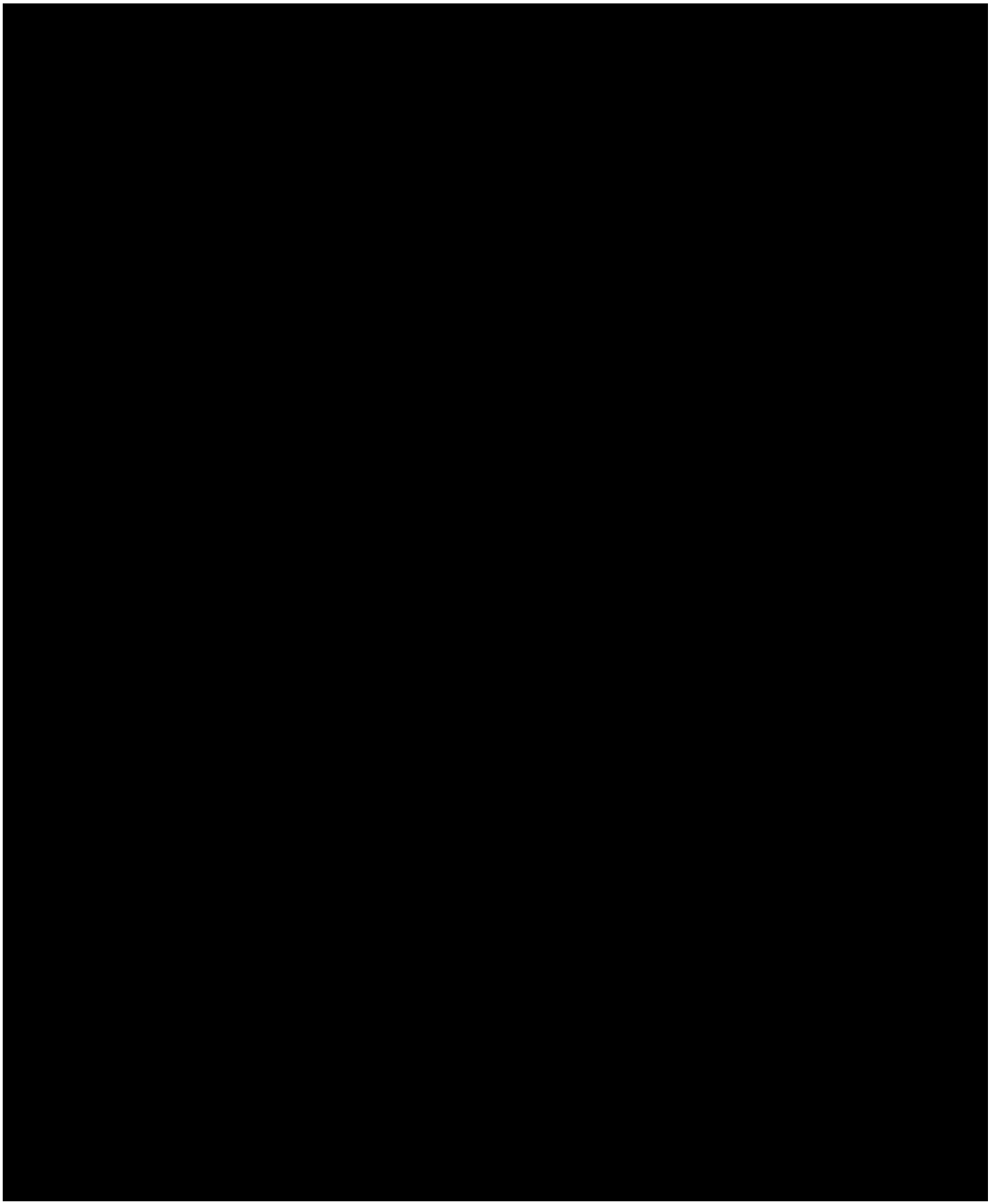

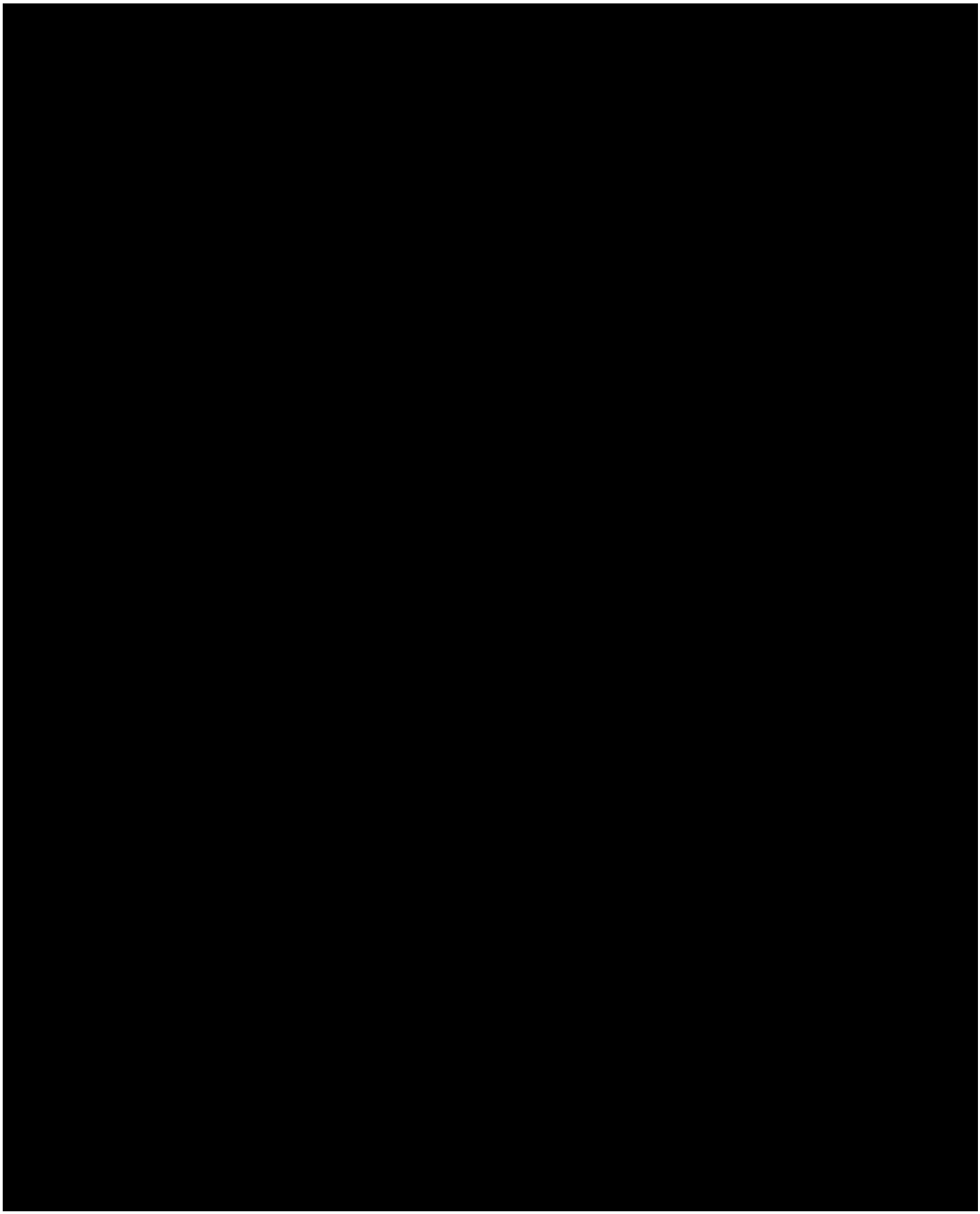

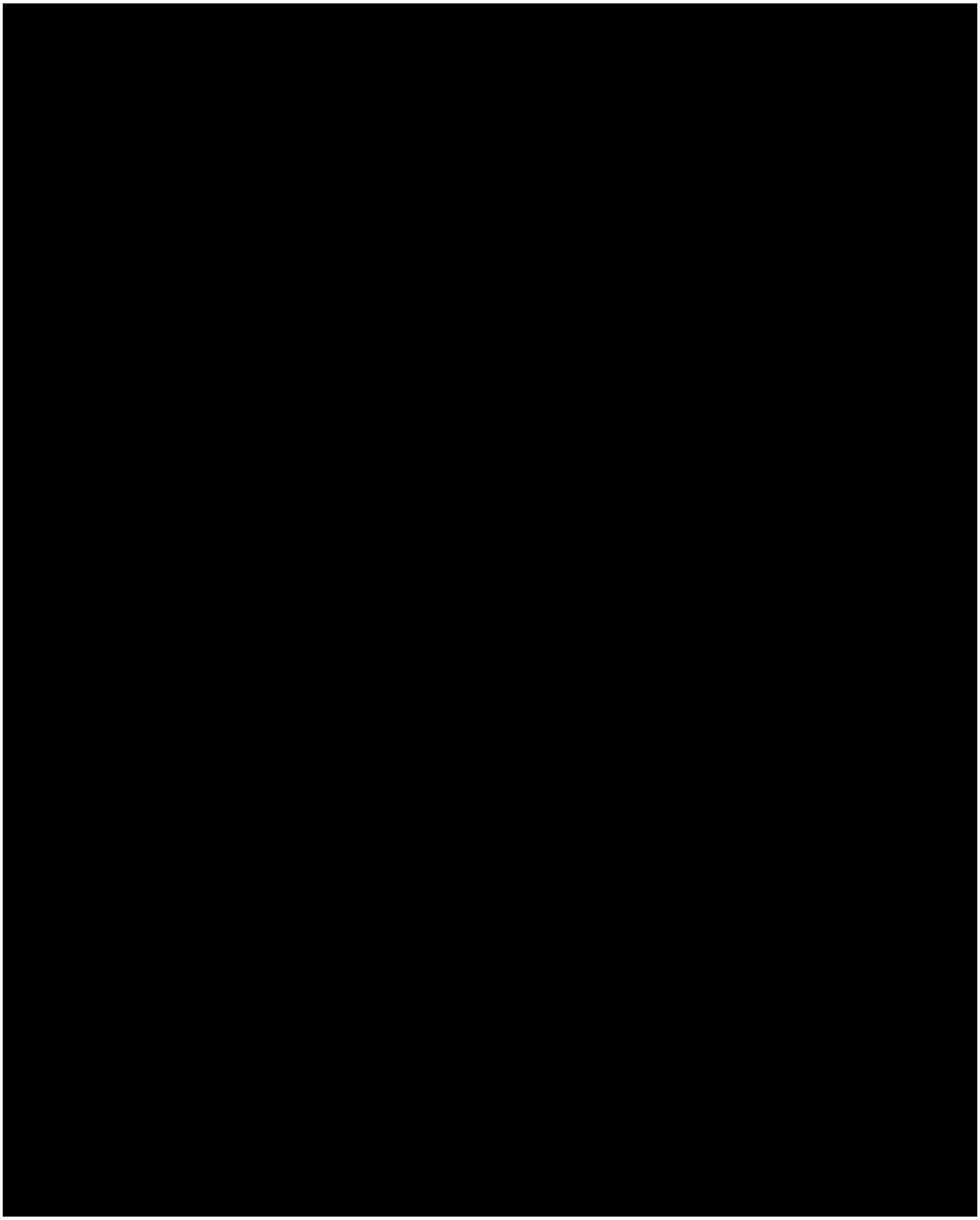

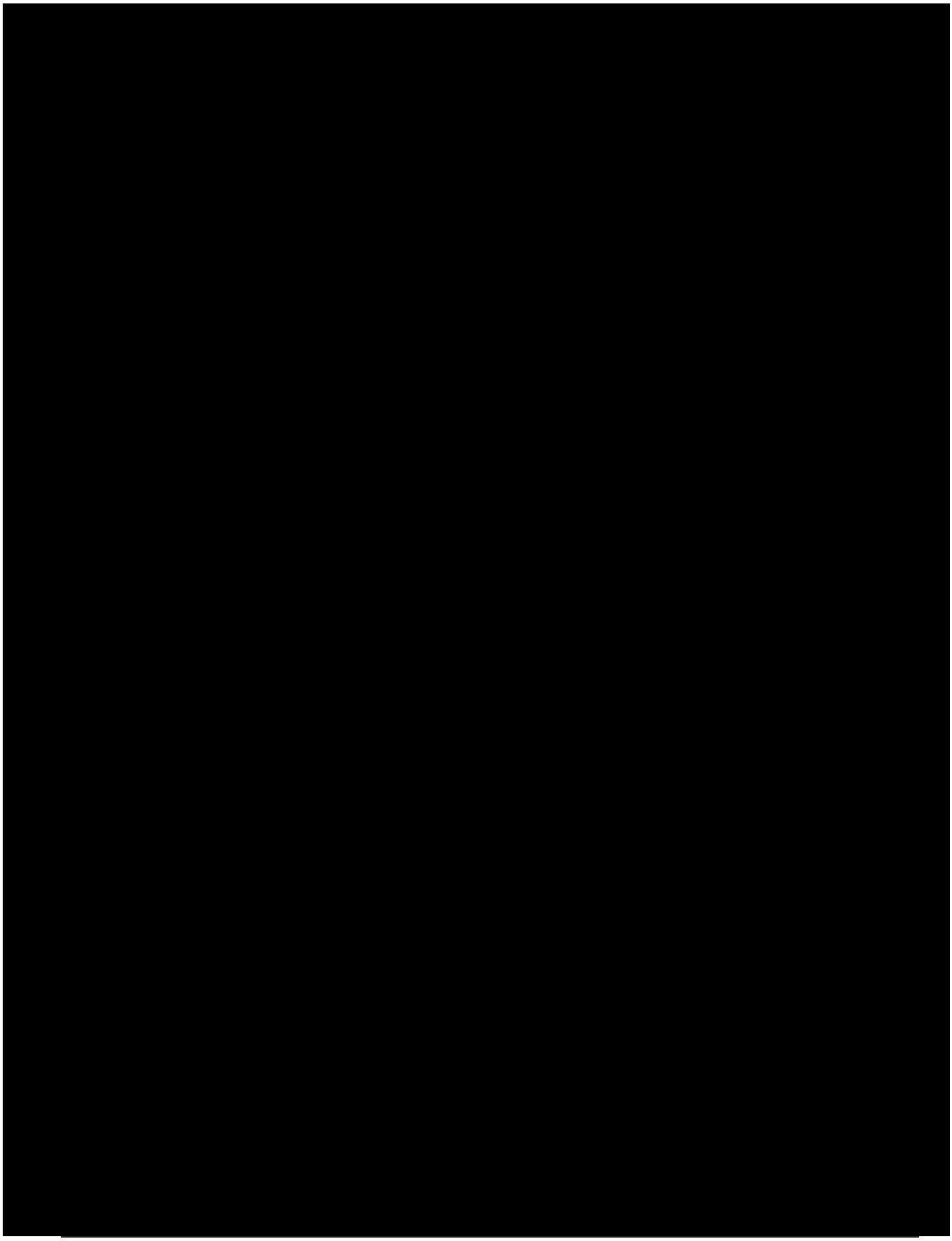

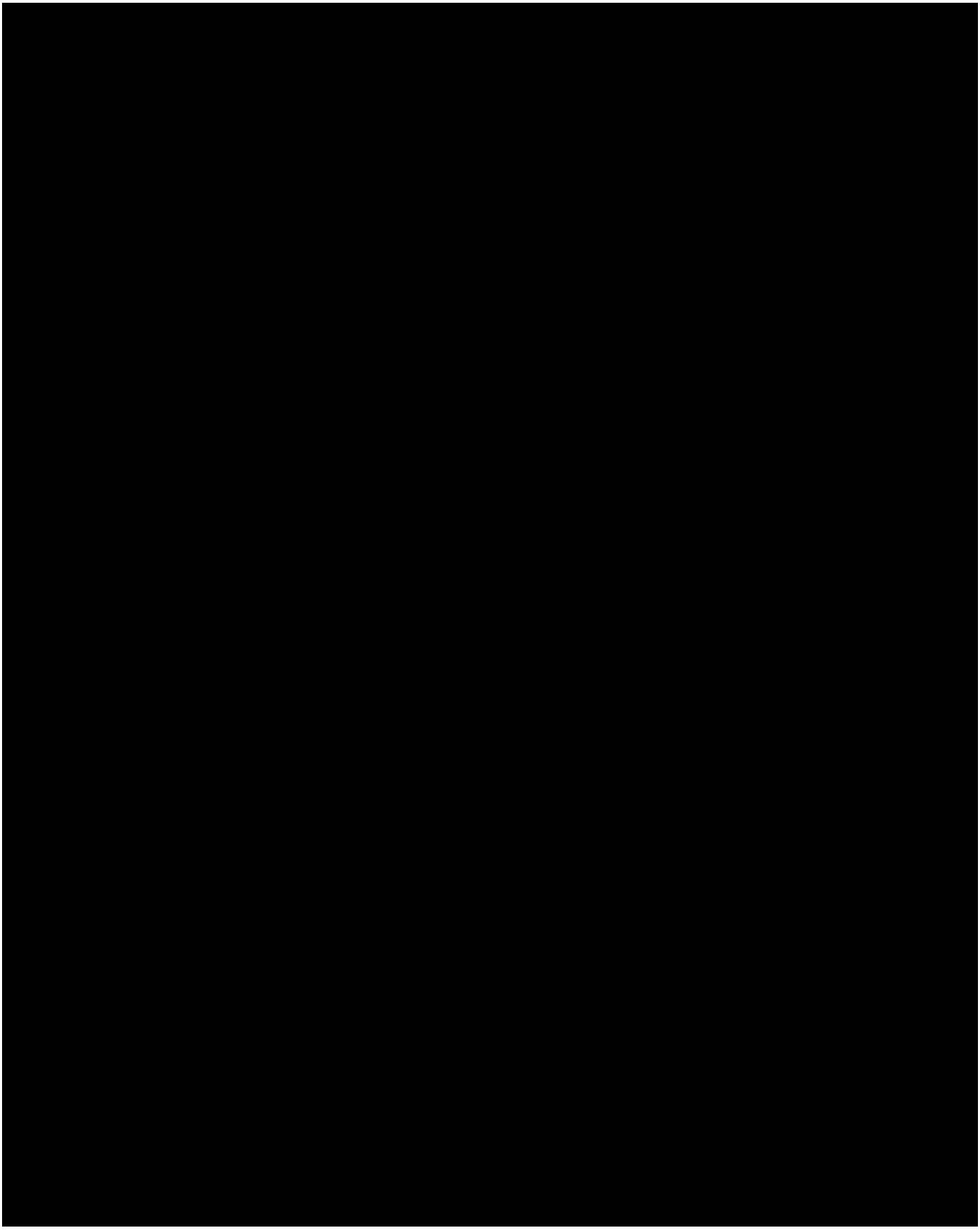

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