CLINICAL STUDY PROTOCOL

A Phase II, Prospective, Randomized, Double-Blind, Multi-center, Placebo-Controlled Trial of DaxibotulinumtoxinA for Injection for the Management of Plantar Fasciitis

Protocol Number: 1820201

IND Number: IND 128510

National Clinical Trial Identified Number: NCT03825315

Sponsor: Revance Therapeutics, Inc
7555 Gateway Boulevard
Newark, California 94560, USA
Telephone: (510) 742-3400

Protocol Version: 4.0

Protocol Date: 15 July 2019

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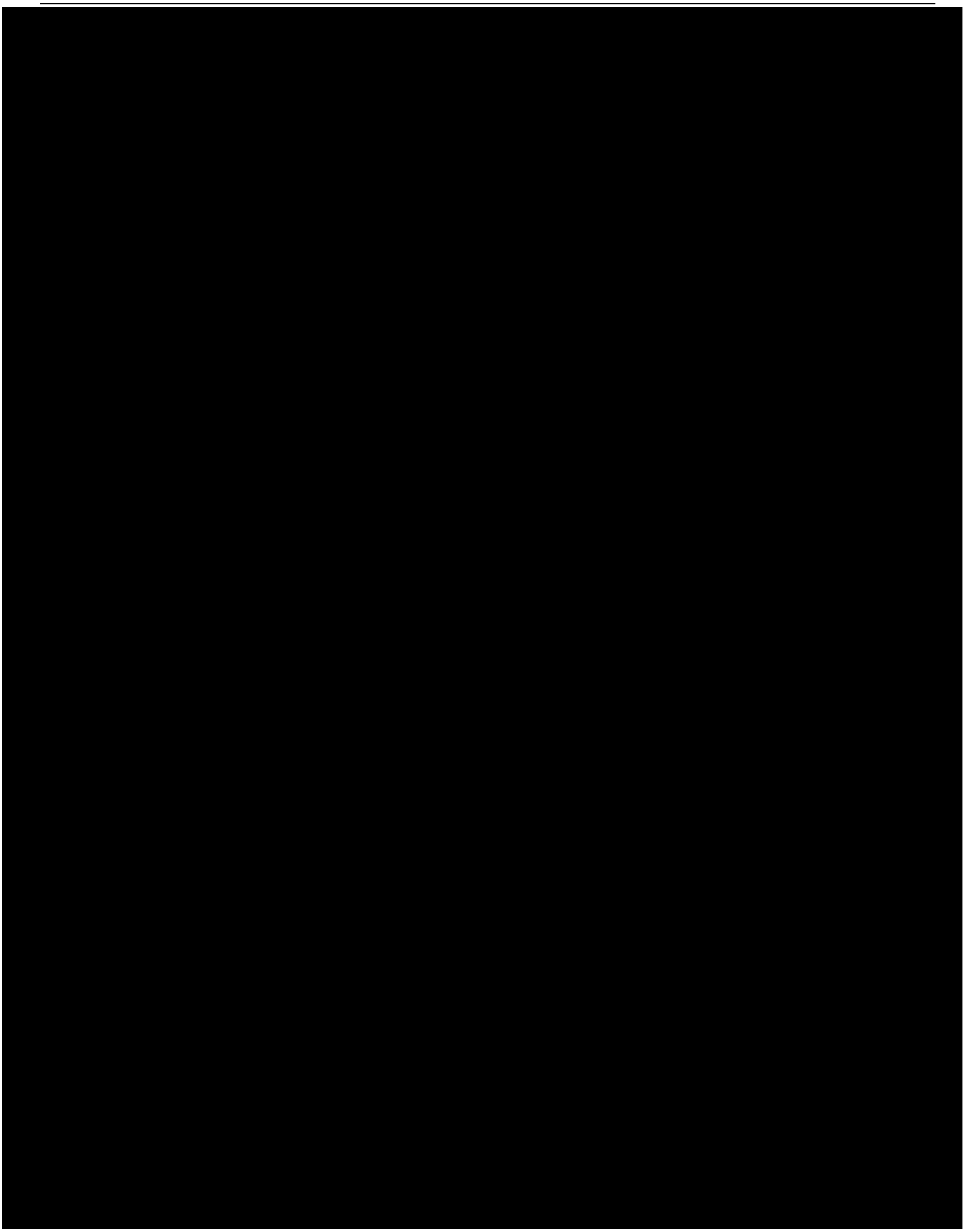

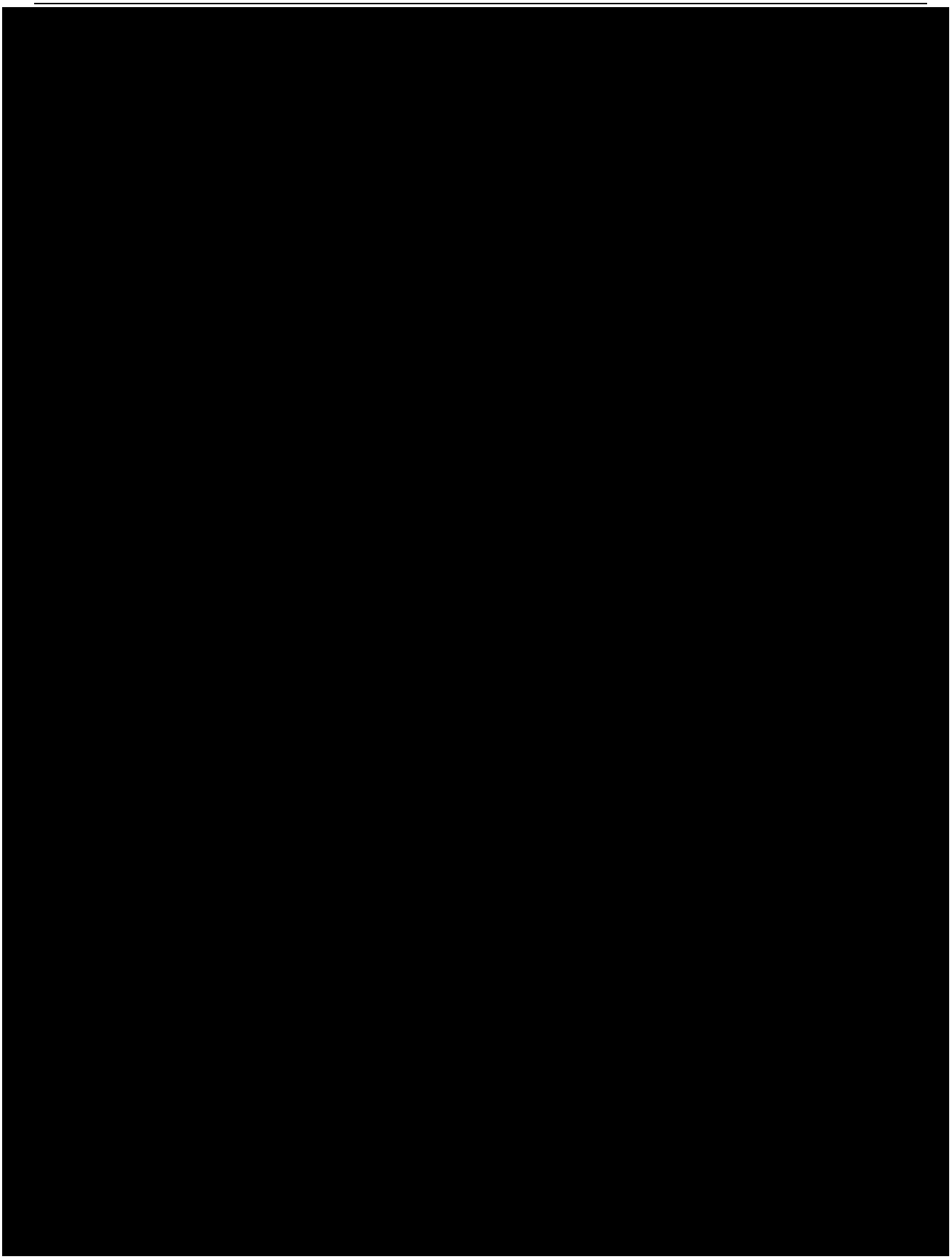

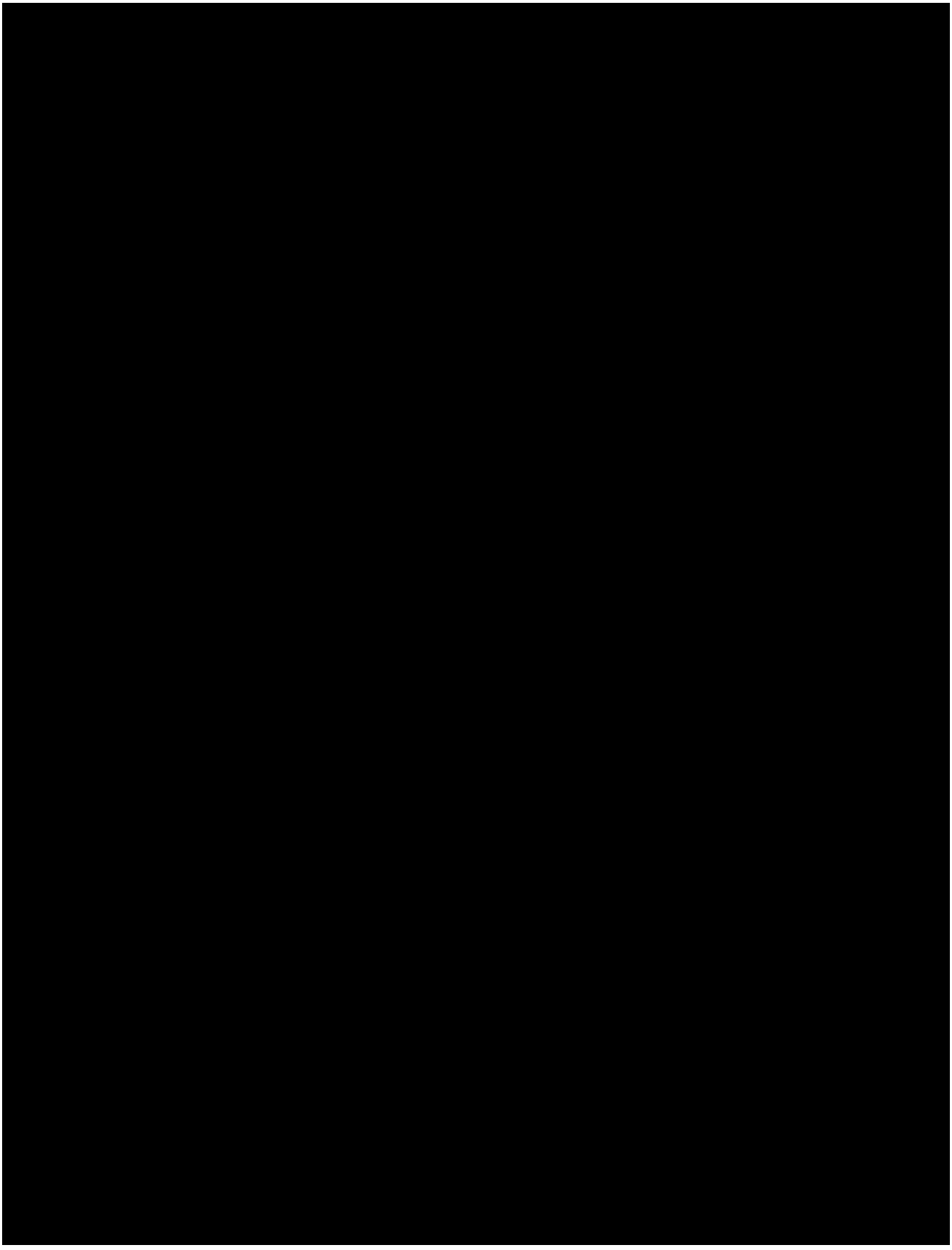

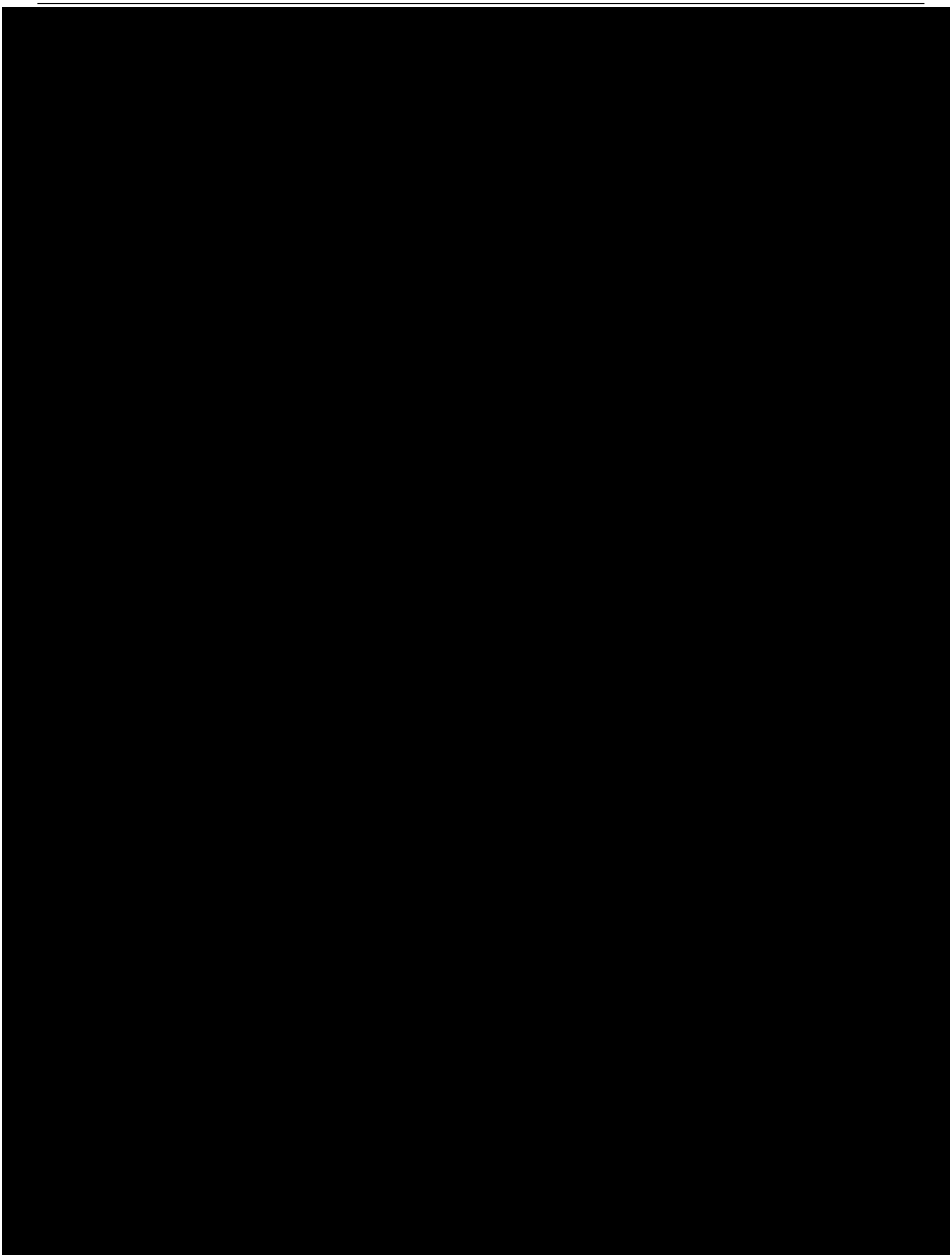

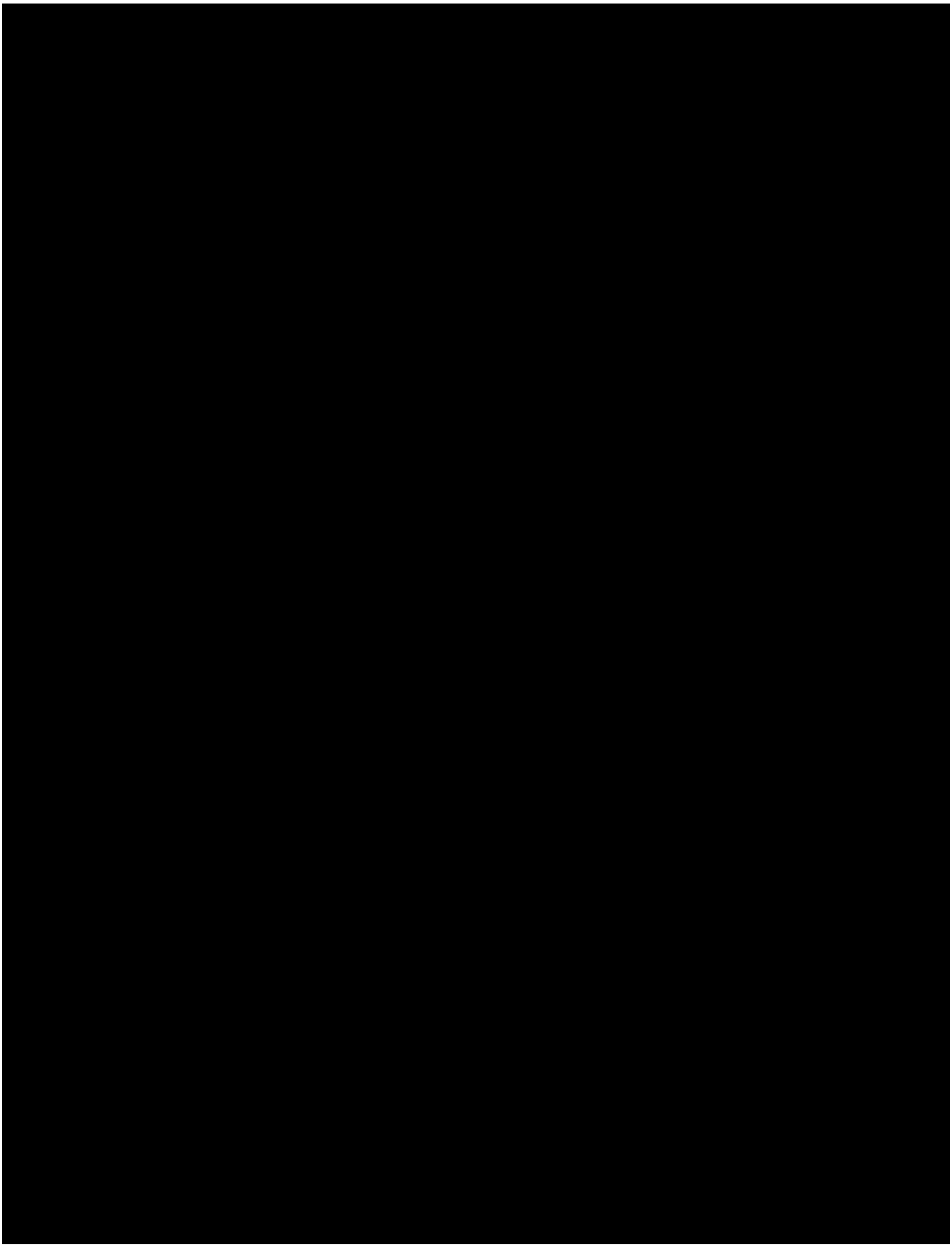

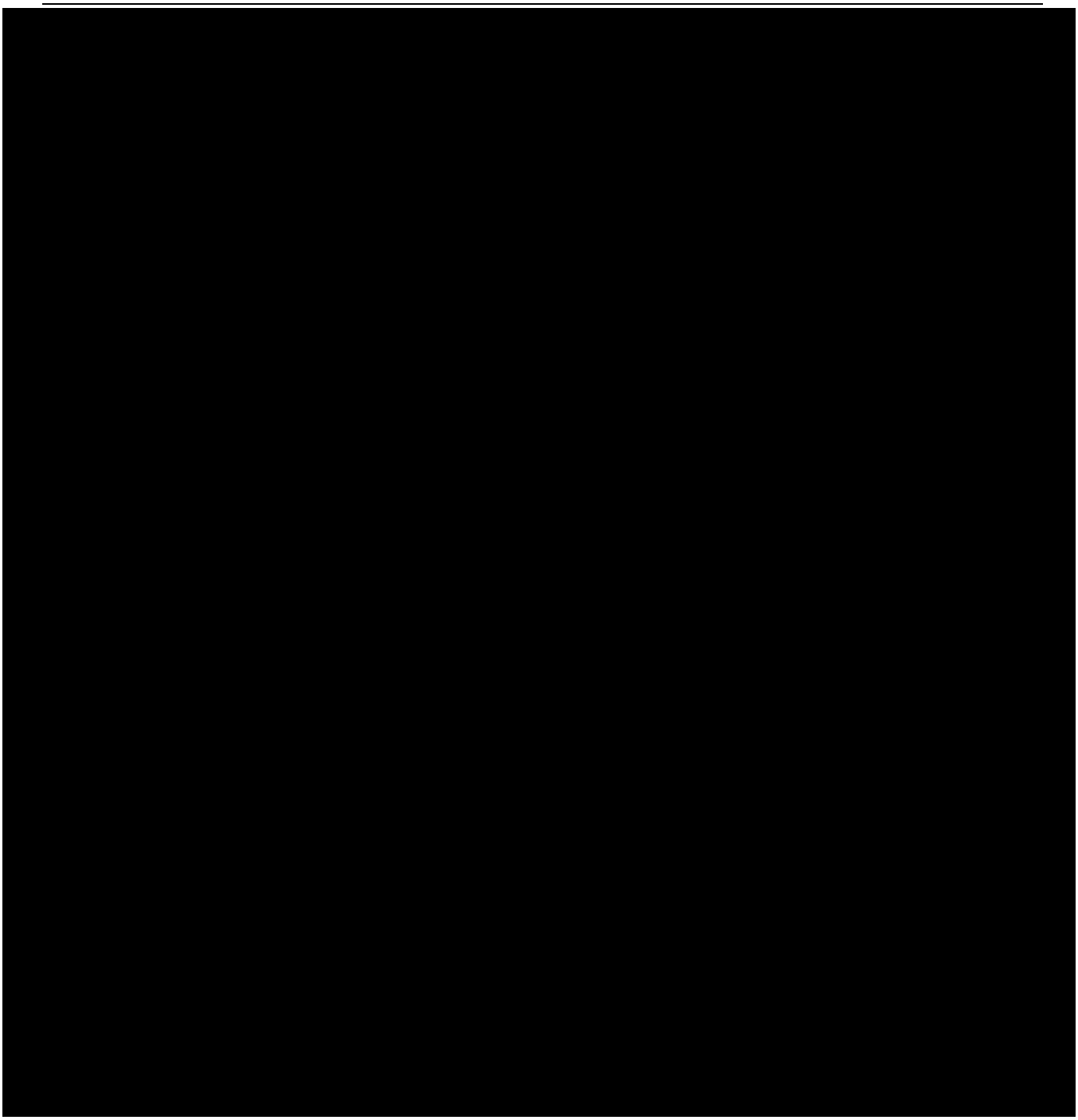

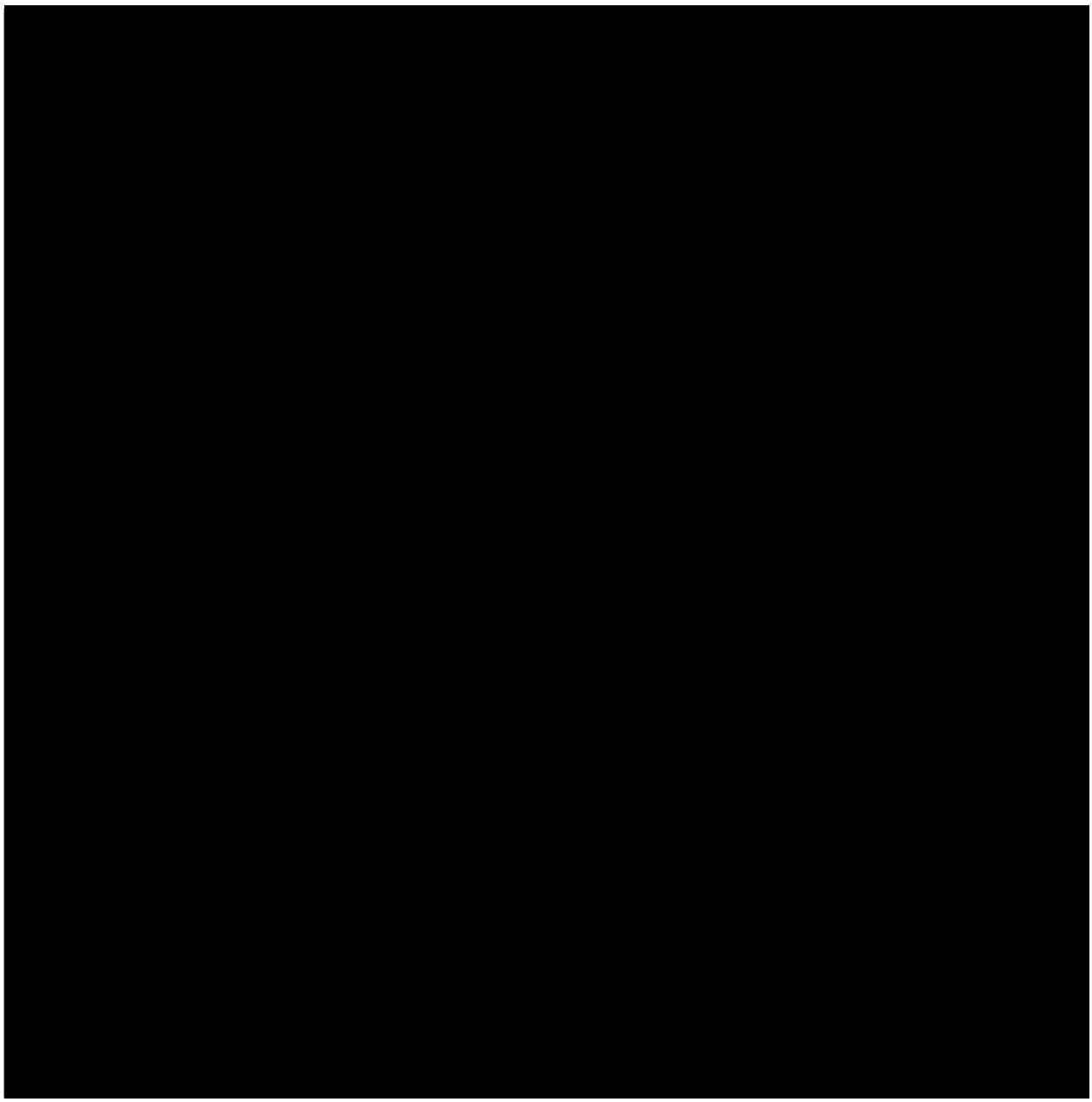

INVESTIGATOR'S AGREEMENT

I have carefully read the protocol entitled: "*A Phase II, Prospective, Randomized, Double-Blind, Multi-center, Placebo-Controlled Trial of DaxibotulinumtoxinA for Injection for the Management of Plantar Fasciitis*" and, I will provide copies of the protocol, any subsequent protocol amendments, and access to all information provided by the sponsor/CRO to the site staff under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational drug and the study protocol.

I agree to conduct this clinical study according to the attached protocol, in compliance with all applicable laws and regulations, and in accordance with the ethical principles stipulated in the Declaration of Helsinki.

_____	_____
Investigator Signature	**Date**
_____	
Printed Name	
_____	
Institution Name	
_____	
Address	
_____	_____
City, State, Postal Code, Country	**Phone Number**

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3 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ANCOVA	Analysis of covariance
BMI	Body Mass Index
BoNT	Botulinum toxin
BoNTA	Botulinum toxin type A
CD	Cervical dystonia
CI	Confidence interval
CRF	Case Report Form
CRO	Clinical Research Organization
CGIC	Clinical Global Impression of Change
CS	Clinically significant
C-SSRS	Columbia – Suicide Severity Rating Scale
DAXI	DaxibotulinumtoxinA, previously referred to as RTT150
DAXI for injection	DaxibotulinumtoxinA for injection, previously referred to as RT002
DMC	Data Monitoring Committee
ECG	Electrocardiogram
EOS	End of study
ePRO	Electronic Patient Reported Outcome
ET	Early termination
FAAM	Foot and Ankle Ability Measure
FDA	Food and Drug Administration (United States)
FFI	Foot Function Index
GCP	Good Clinical Practices
GLMM	Generalized Linear Mixed Model
ICH	International Council On Harmonisation
IEC	Independent Ethics Committee
IM	Intramuscular(ly)
IND	Investigational New Drug
IP	Investigational product
IRB	Institutional Review Board
IRT	Interactive Response Technology

Abbreviation	Definition
ISF	Investigator Site File
ITT	Intent-to-treat
kg	Kilograms
kDa	Kilodalton
NPRS	Numeric Pain Rating Scale
Onabot	OnabotulinumtoxinA
PF	Plantar fasciitis
PGIC	Patient Global Impression of Change
PI	Principal investigator
PP	Per protocol
PPT	Pressure Pain Threshold
PT	Prothrombin time
QT	Measure of time between start of the q wave and the end of the t wave in the heart's electrical conduction
QTcF	Corrected QT interval using Fridericia's correction formula
Revance	Revance Therapeutics, Inc.
RICE	rest, ice, compression, and elevation
RT002	Previous company name for drug product daxibotulinumtoxinA for injection
RTP004	Revance novel excipient
RTT150	Previous company name for drug substance, daxibotulinumtoxinA
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SIV	Site Initiation Visit
SOA	Schedule of Assessments
SOP	Standard operating procedure
SPT	Serum pregnancy test
TdP	Torsades de Pointes
TEAE	Treatment-emergent adverse event
TMF	Trial Master File
TSQ	Treatment Satisfaction Questionnaire
TWSTRS	Toronto Western Spasmodic Torticollis Rating Scale
U	Units (botulinum toxin)
UP	Unanticipated problem

Abbreviation	Definition
UPT	Urine pregnancy test
US	United States
VAS	Visual Analogue Scale
WOCBP	Women of child bearing potential

4 STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the International Council On Harmonisation Good Clinical Practice (ICH GCP) and applicable United States (US) Code of Federal Regulations (CFR) Terms and Conditions of Award. The Principal Investigator (PI) will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to subjects. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained prior to subject enrollment. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from subjects who provided consent, using a previously approved consent form.

5 PROTOCOL SUMMARY

5.1 SYNOPSIS

Title: A Phase II, Prospective, Randomized, Double-Blind, Multi-center, Placebo-Controlled Trial of DaxibotulinumtoxinA for Injection for the Management of Plantar Fasciitis

Study Description: This is a randomized, double-blind, placebo-controlled, multi-center study of two doses of daxibotulinumtoxinA (DAXI) for injection in adult subjects with unilateral plantar fasciitis (PF).

Approximately 150 subjects recruited from approximately 20 investigator sites in the US will be randomized [redacted]

PIs, site staff (excluding unblinded dose preparers), subjects, and [redacted]

The primary efficacy endpoint is the change from baseline in the Numeric Pain Rating Scale (NPRS) score at Week 8.

In case of no improvement, defined as no change or worsening of the NPRS score from baseline, Week 8 will serve as the early completion visit for the subject (i.e., the "early study completer"). Subjects who experience any treatment benefit (any decrease from baseline on NPRS score) will continue in the study. NPRS scores will be collected by subjects daily in an ePRO diary. Algometry, Clinical Global Impression of Change (CGIC), and Patient-reported Outcomes (PROs; i.e., Foot Function Index [FFI], Foot and Ankle Ability Measure [FAAM], Patient Global Impression of Change [PGIC] and Treatment Satisfaction Questionnaire [TSQ]) will be performed at prespecified time points during the study, as efficacy evaluations. Safety will be assessed based on adverse events (AEs), clinical laboratory parameters, vital signs, 12-lead electrocardiograms (ECGs), [redacted] physical examination, and the Columbia – Suicide Severity Rating Scale (C-SSRS).

Trial Objective:

- To compare the efficacy and safety of two doses of DAXI for injection versus placebo for managing plantar fasciitis

Endpoints:

Primary Efficacy Endpoint:

- Change from baseline in the NPRS score, which is recorded within 15 minutes after stepping out of bed in the morning and averaged over 5 days (defined as 4 days prior to study visit and on the study visit day), at Week 8

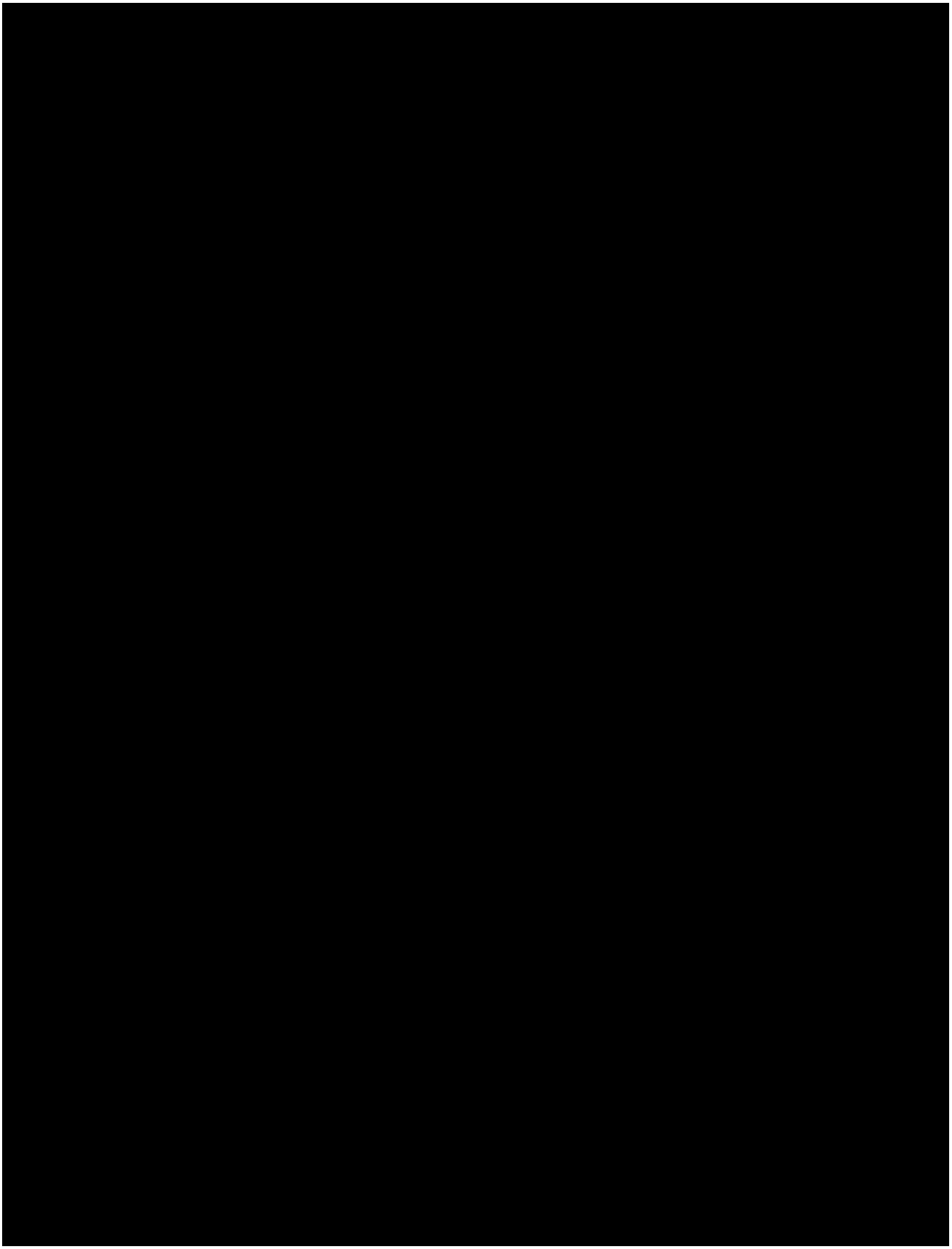
[redacted]

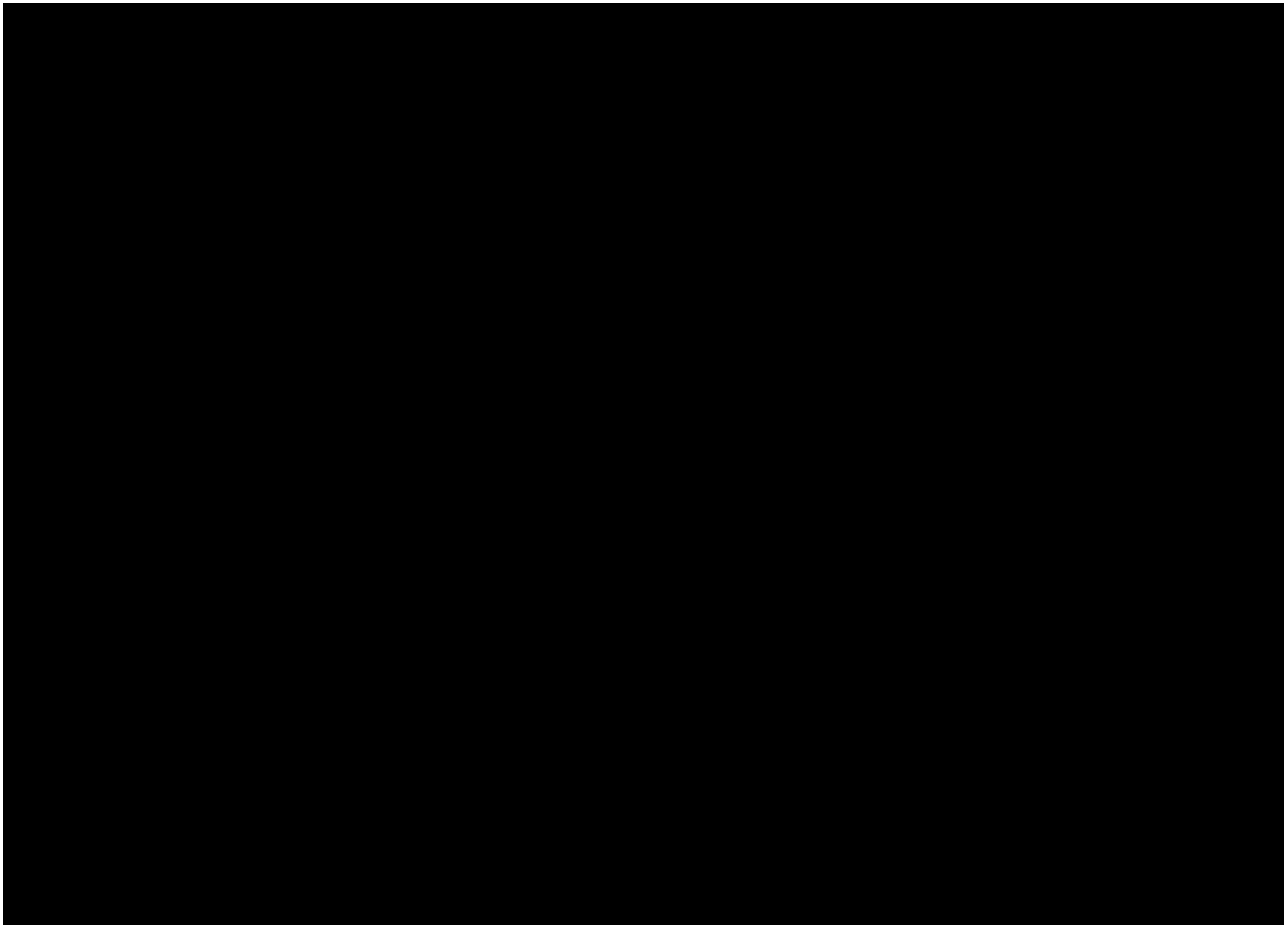
Safety Endpoints

- Frequency, severity and relationship to study drug of treatment-emergent adverse events during the first 8 weeks post treatment and the overall study duration
- Frequency, severity and relationship to study drug of treatment-emergent serious adverse events during the first 8 weeks post treatment and the overall study duration

Study Population:	Subjects aged 18-65, inclusive, with unilateral PF for ≥ 3 months and ≤ 15 months, have failed conservative treatment, and have an NPRS score of ≥ 5 and ≤ 9, and have not previously received botulinum toxin therapy in the lower extremities or feet.
Phase:	2
Description of Sites/Facilities Enrolling Subjects:	Approximately 20 sites in the US will participate in the study. Approximately 150 subjects will be randomized.
Description of Study	[redacted]
Study Duration:	Approximately 21 months
Subject Duration:	The study duration for each subject is approximately 7 months (up to 14 days for screening, 7 days [+3] for run-in, Treatment Day 1, and up to 24 weeks for follow-up).
Sample Size Justification:	The sample size calculations are based on the minimal clinically important difference of 2 points for NPRS (*Farrar, 2001; Michener, 2011*). [redacted]

[redacted]





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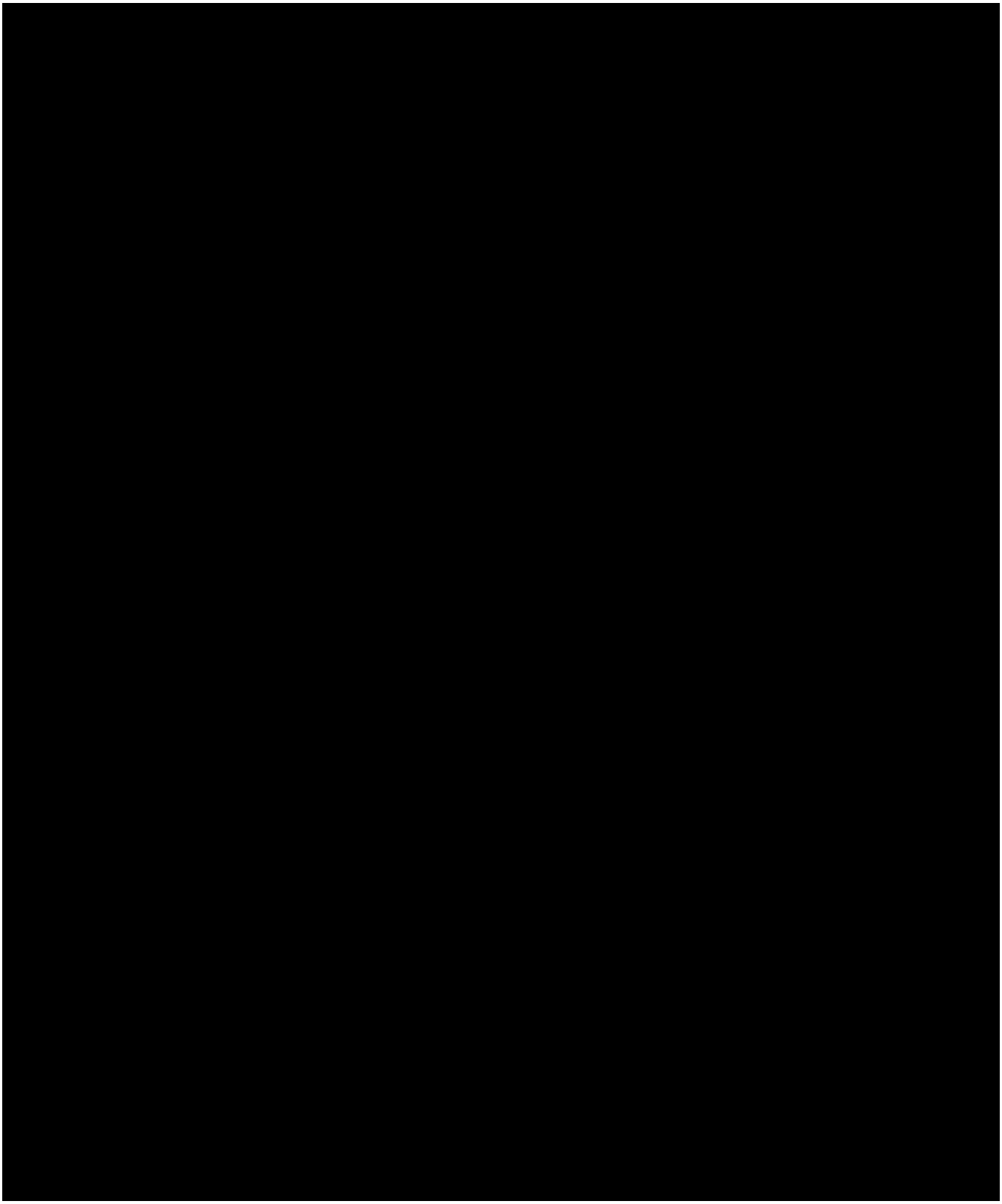
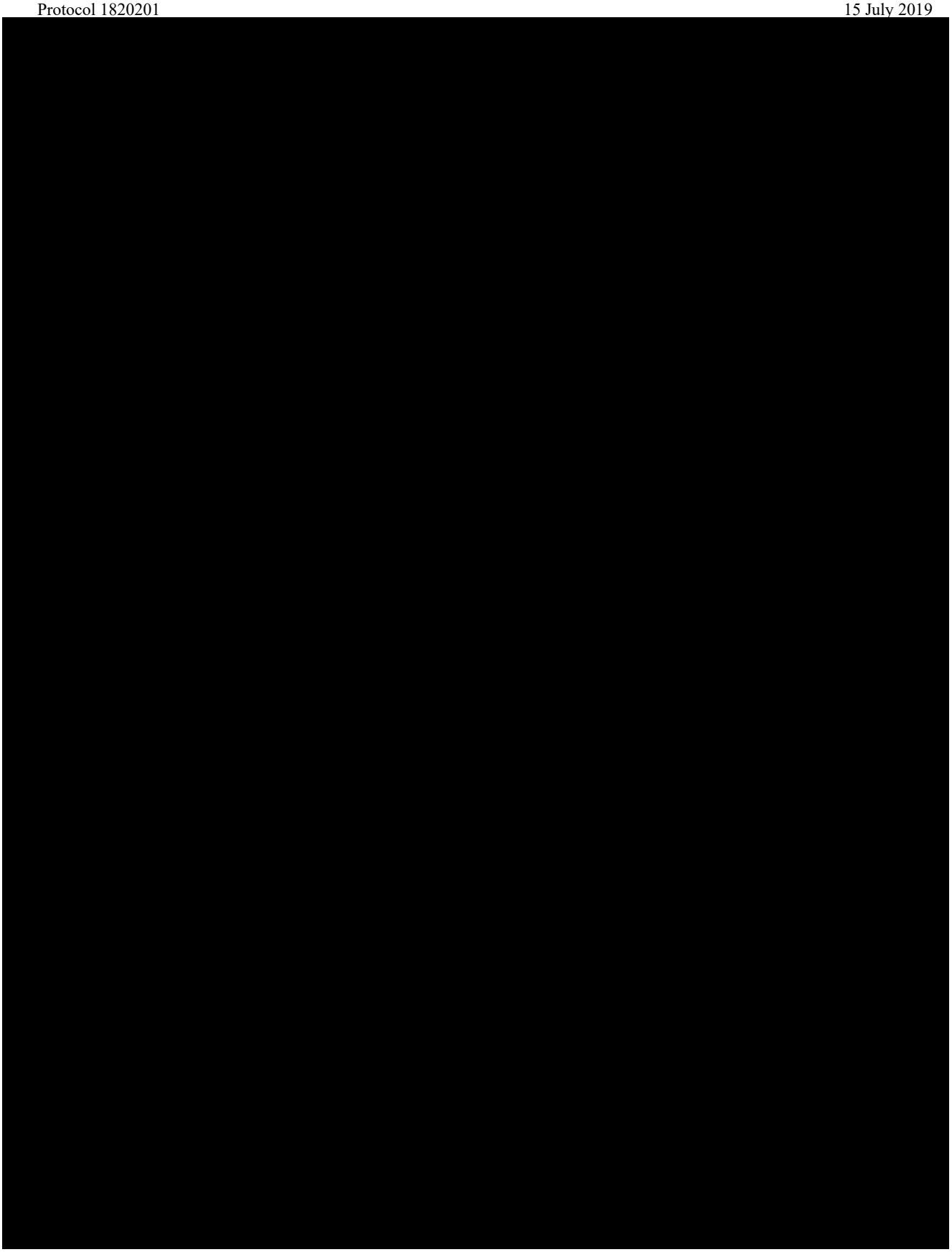
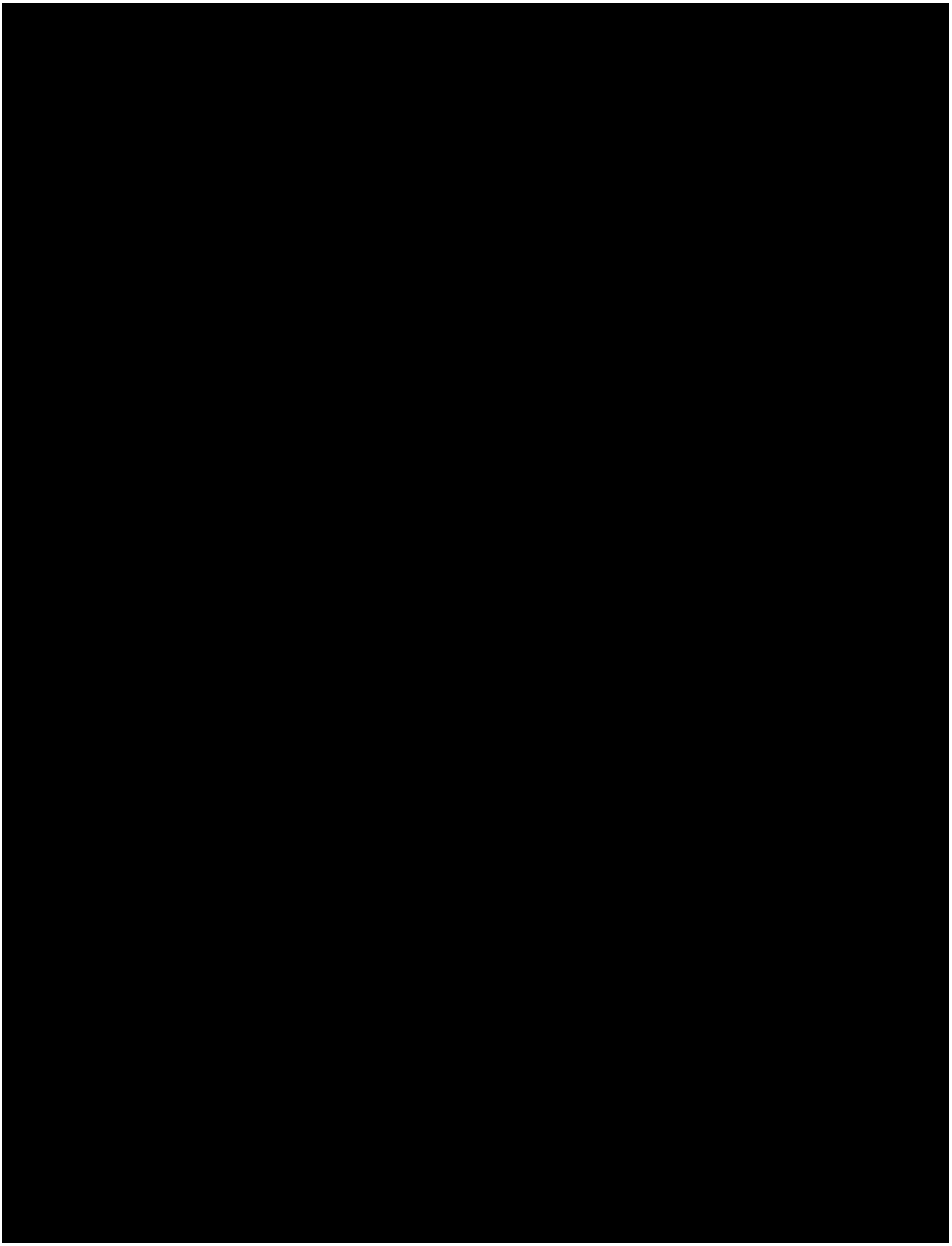
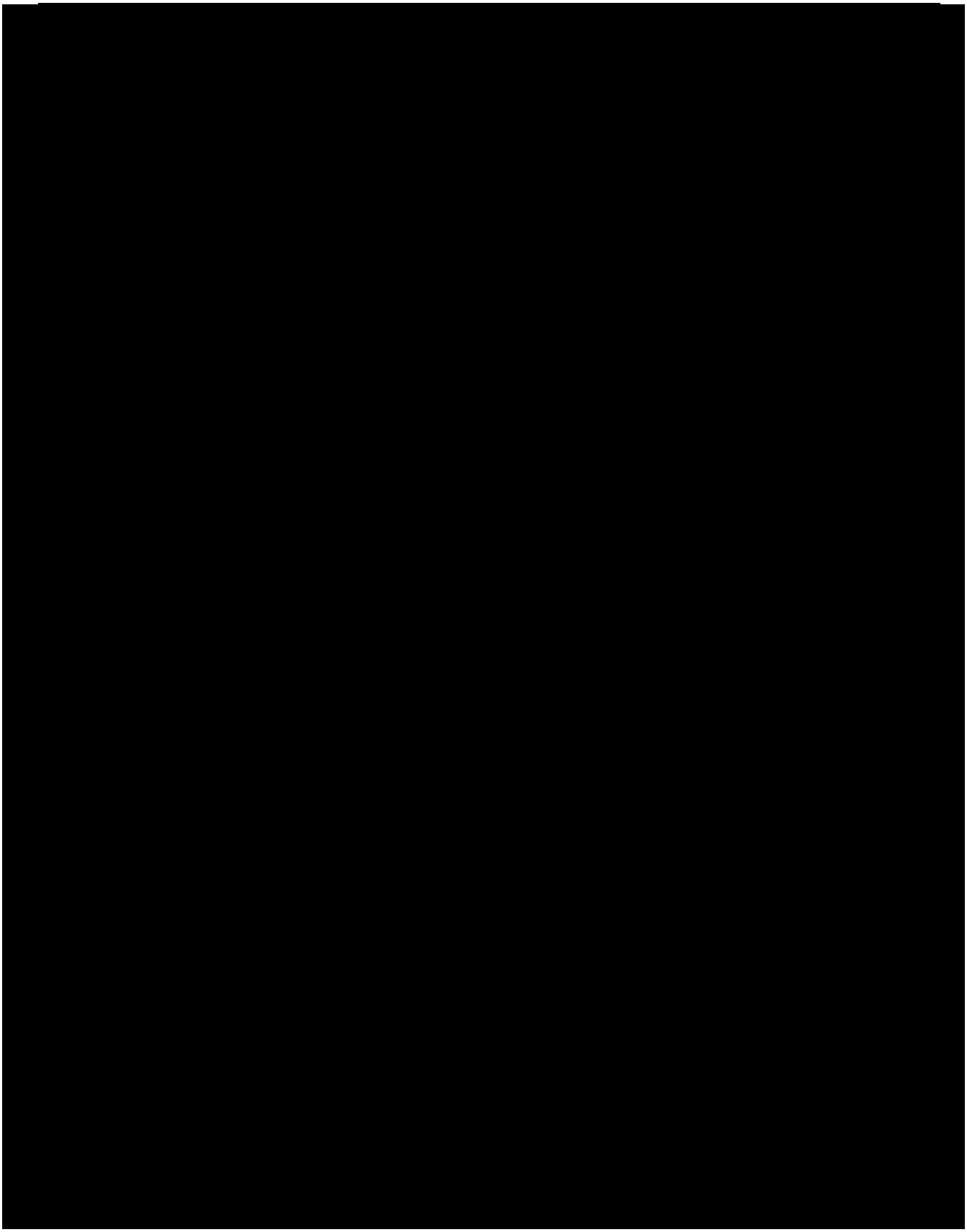
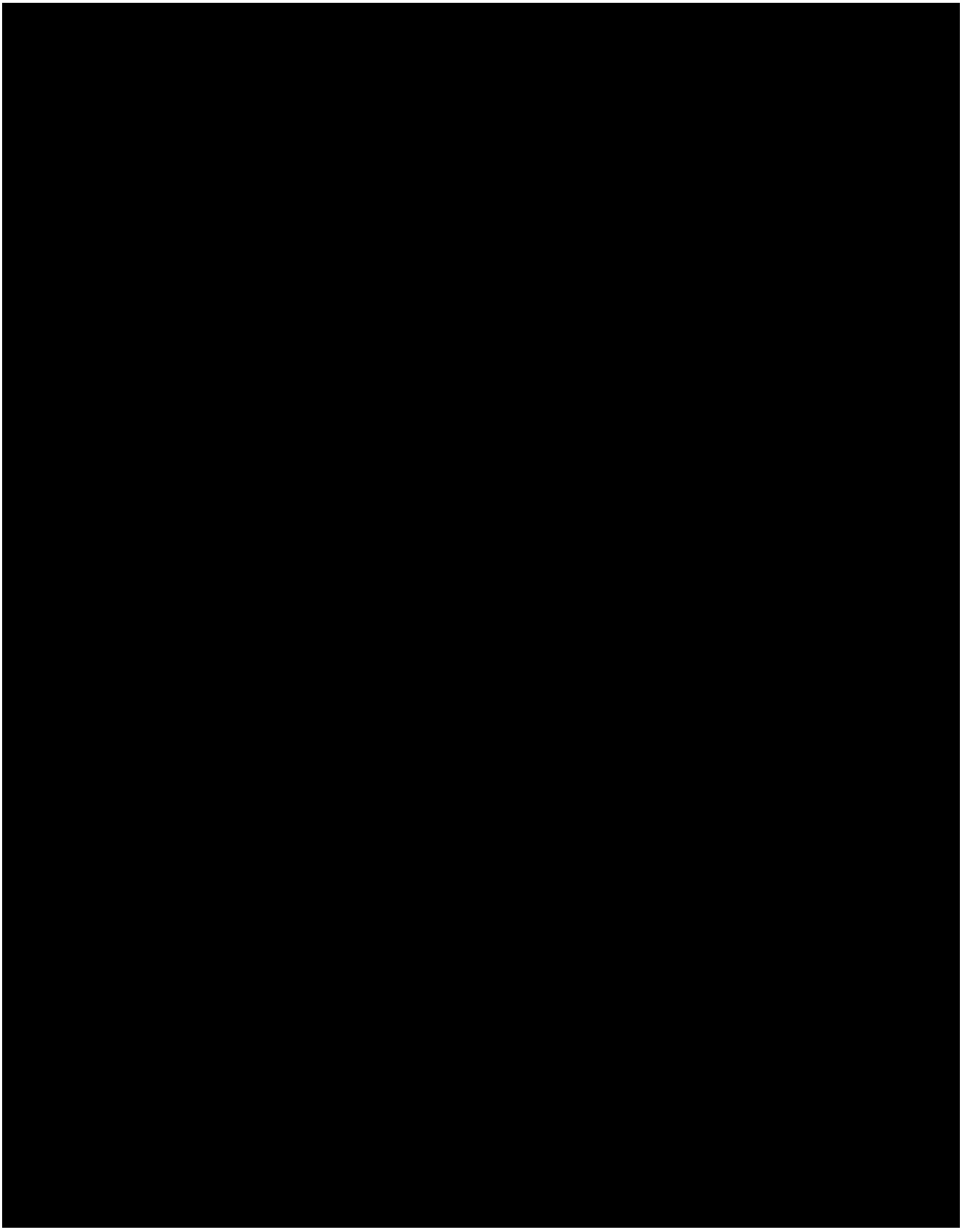
6 INTRODUCTION

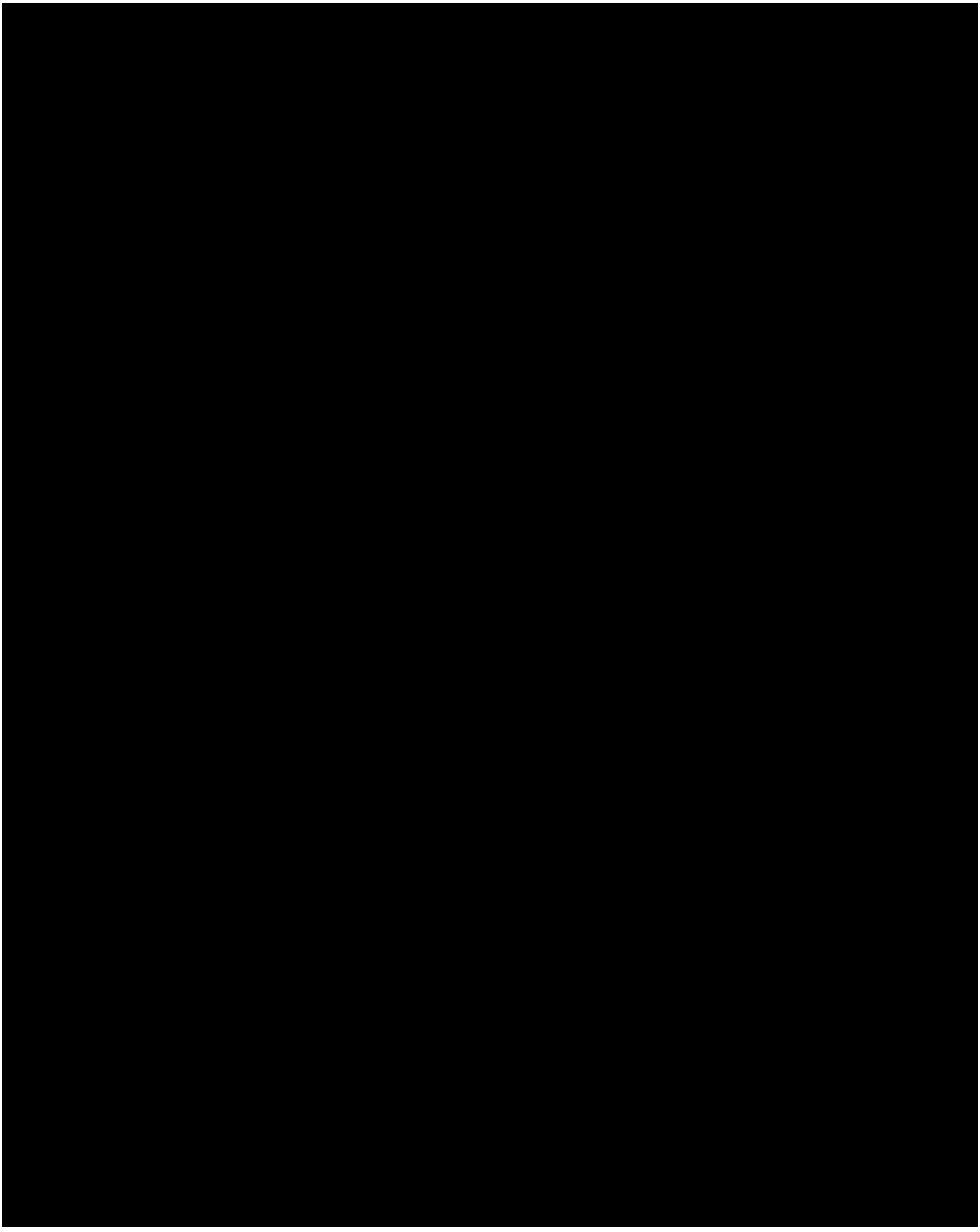












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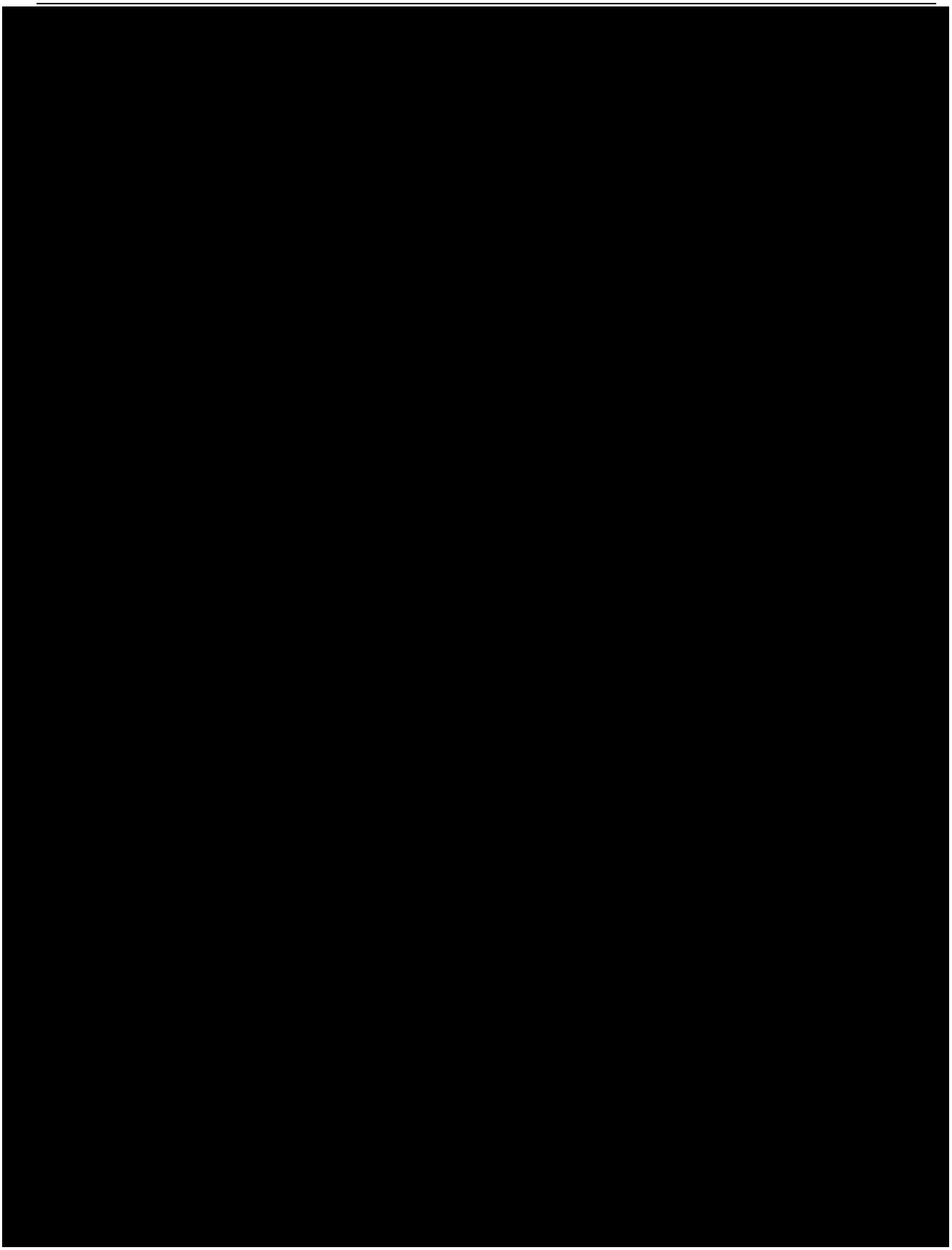
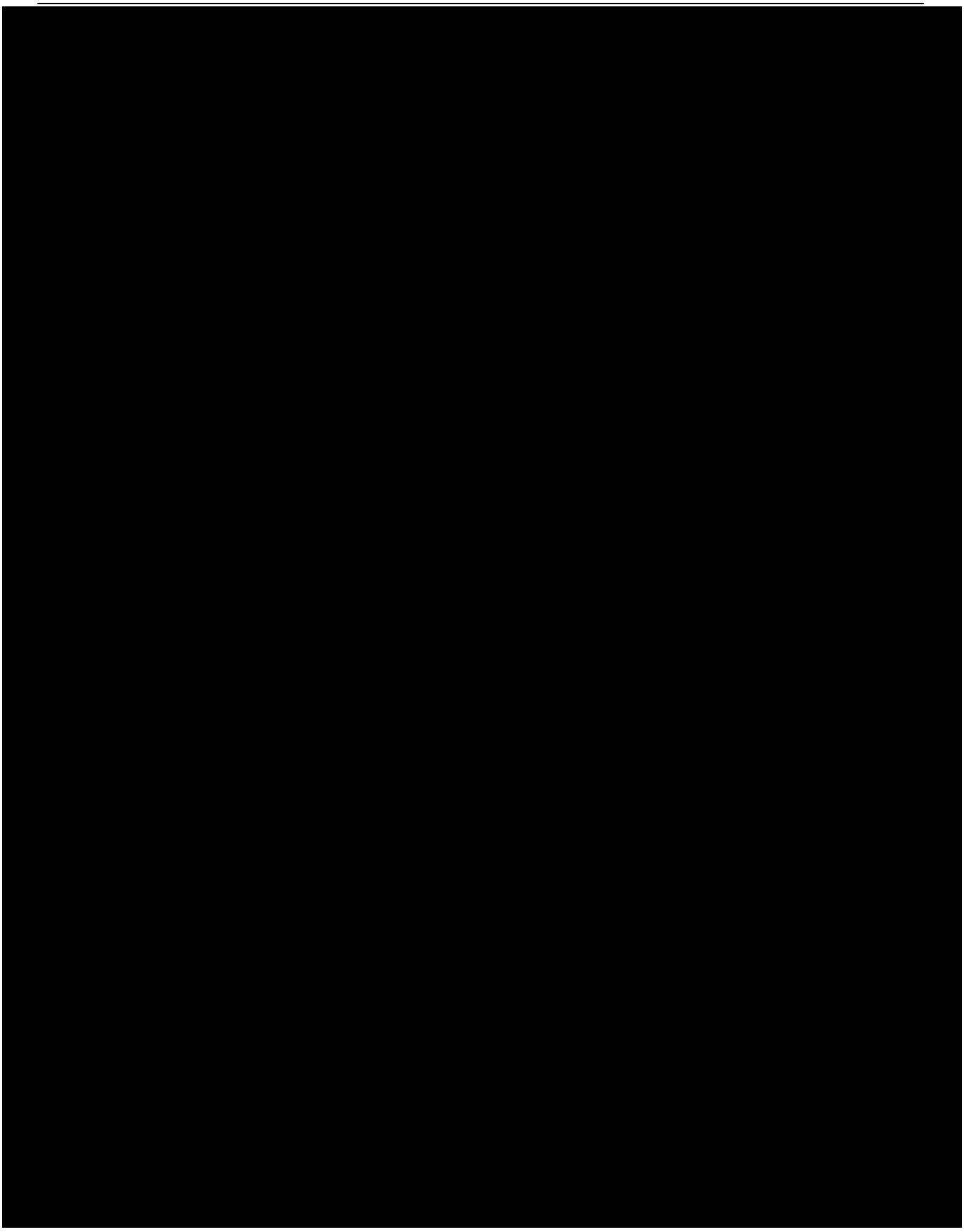
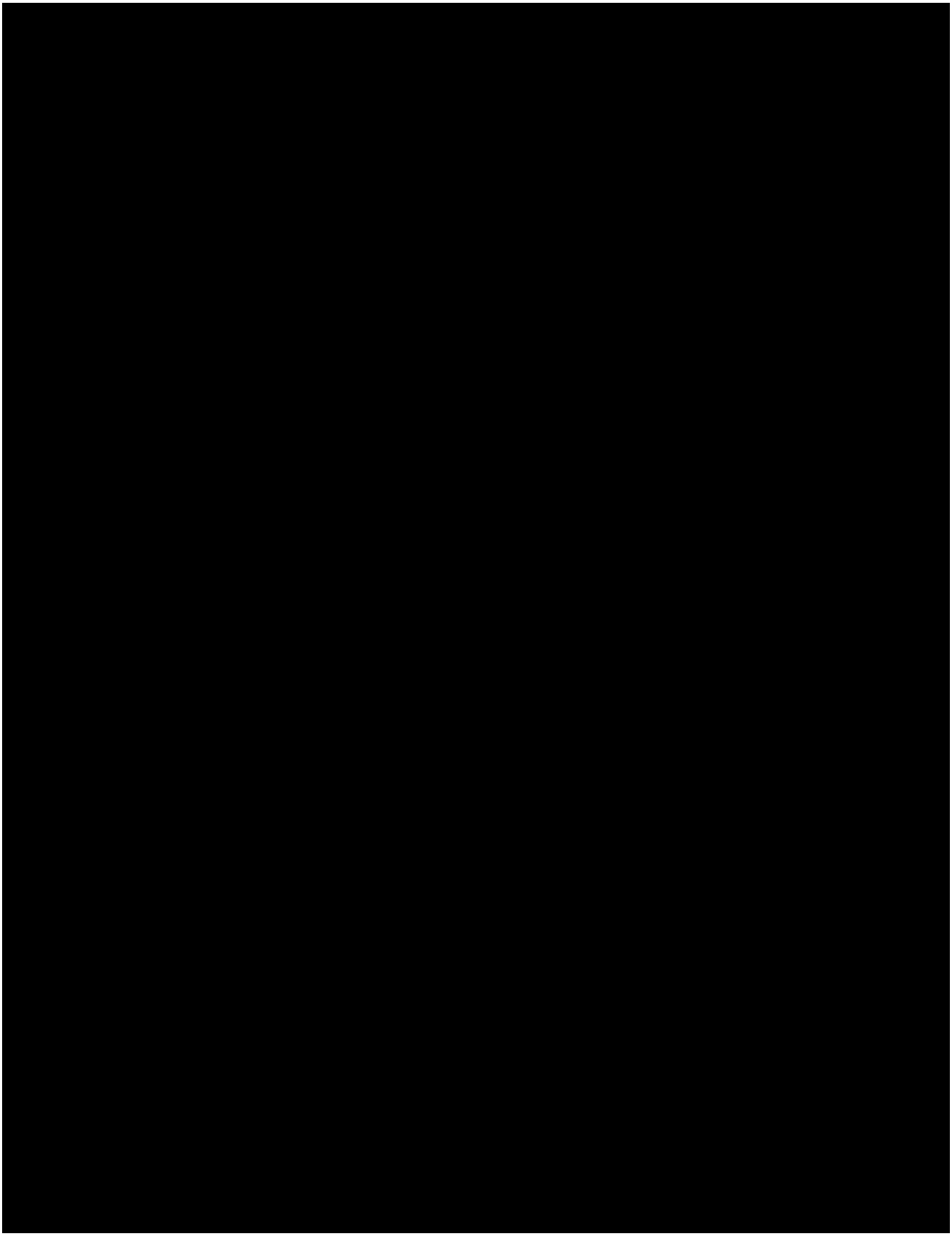
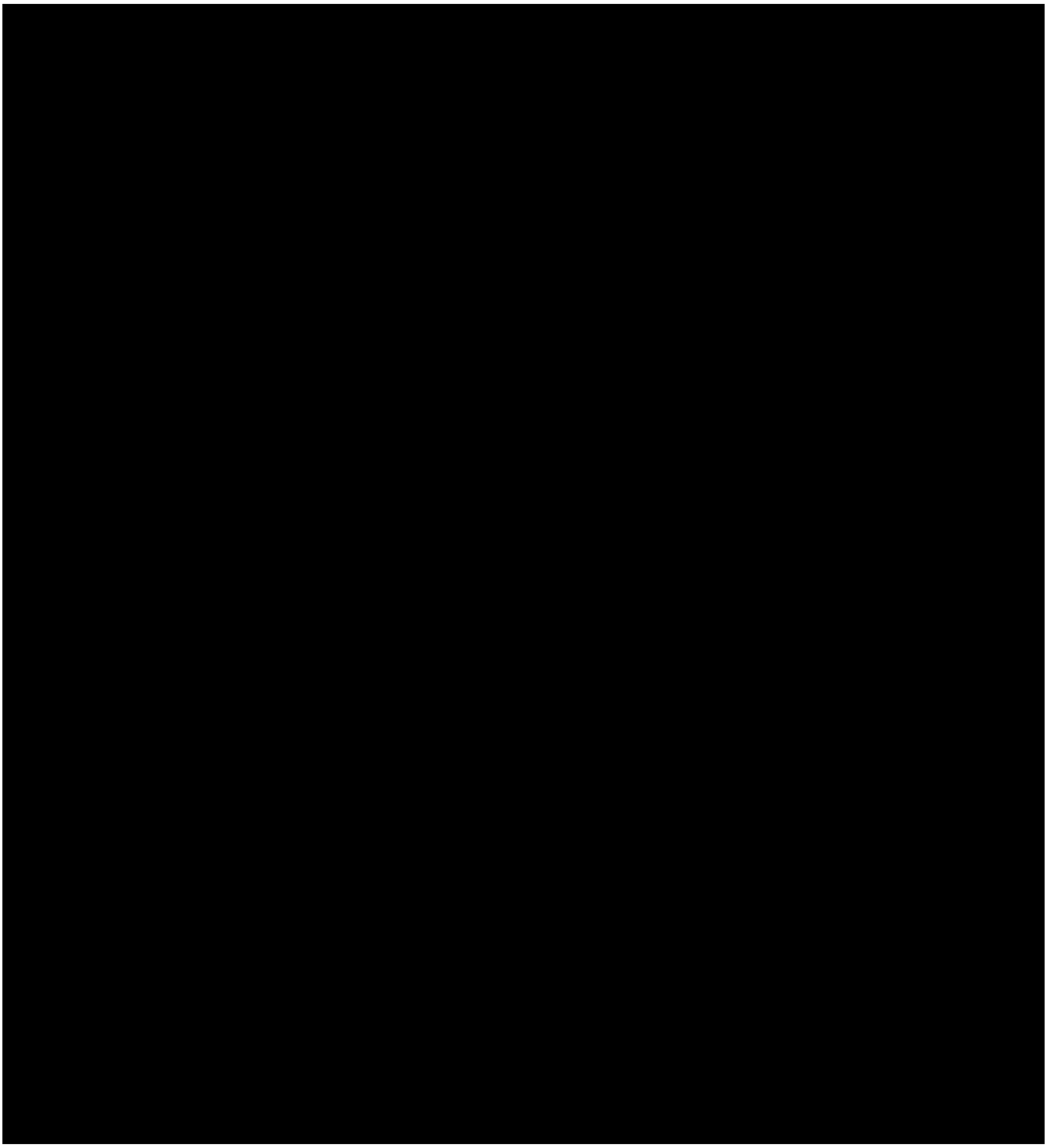
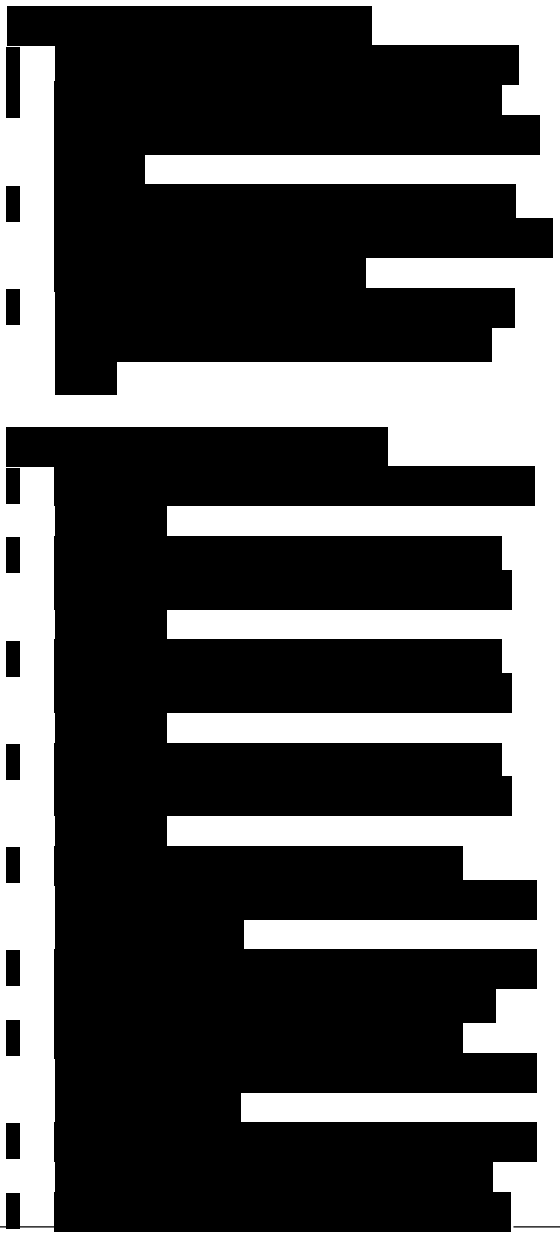








7 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Trial		
To compare the efficacy and safety of two doses of DAXI for injection versus placebo for managing plantar fasciitis	Primary Efficacy Endpoint: • Change from baseline/treatment in NPRS score as recorded within 15 minutes of taking first step when getting out of bed in the morning (average over 5 days, defined as 4 days prior to study visit and on the study visit day) at Week 8. 	Clinically relevant outcome measure for this indication.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	[redacted] Safety Endpoints: • Frequency, severity and relationship to study drug of treatment-emergent adverse events during the first 8 weeks post treatment and the overall study duration • Frequency, severity and relationship to study drug of treatment-emergent serious adverse events during the first 8 weeks post treatment and the overall study duration	

8 STUDY DESIGN

8.1 OVERALL DESIGN

This is a Phase 2, randomized, double-blind, placebo-controlled, multicenter study of two doses of DAXI for injection in adult subjects with unilateral PF.

Approximately 150 subjects, recruited from approximately 20 investigator sites in the US will be randomized [redacted]

Imaging (e.g., x-ray or sonography) of the foot will be used to rule out concomitant disease conditions. [redacted]

[redacted]

[redacted]

The primary efficacy endpoint is the change from baseline in NPRS score (average over 5 days, defined as 4 days prior to study visit and on study visit day) at Week 8. Daily NPRS scores will be recorded in an ePRO diary within the first 15 minutes after the first steps out of bed in the morning.

In cases of no improvement, Week 8 will serve as the early completion visit for the subject (i.e., the "early study completer"). Subjects who experience any treatment benefit, defined as any decrease in NPRS score from baseline, will continue to be observed up until Week 24 (see Section 8.7 for additional detail). The NPRS score will be recorded daily in an ePRO diary by the subject, as the primary efficacy evaluation. At site visits, algometry (to determine PPT), FFI, FAAM, CGIC, PGIC, and TSQ will be performed at prespecified time points during the study.

Safety assessments are AE monitoring [redacted], clinical laboratory tests (hematology, prothrombin time, chemistry, and urinalysis), pregnancy tests for WOCBP, [redacted], physical examinations, vital signs, 12 lead ECGs, C-SSRS, injection site evaluations, and concomitant medications. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

8.5 DURATION OF TRIAL

The study duration for each subject is approximately 7 months (up to 14 days for screening, 7 days [+3] for run-in, and up to 24 weeks for follow-up after the Day 1 treatment visit).

[redacted]

[redacted]

8.7 END OF STUDY DEFINITION

Study completion may occur at Week 8 ("early study completers" who have no treatment benefit based on NPRS) or at Week 24 ("study completers"):

Week 8 Early Study Completers:

- No Treatment Benefit:
    - Subjects who do not demonstrate improvement at Week 8, where improvement is defined as any decrease from baseline on NPRS score
    - A subject may also complete the study at Week 8 based on the investigator's clinical judgment of no clinical improvement following treatment, regardless of whether the subject showed a treatment benefit based on the NPRS score evaluation described above.

Week 24 Study Completers:

- Treatment Benefit: Subjects who demonstrate improvement at Week 8, defined as any decrease from baseline on NPRS score, should continue in the study for follow-up until Week 24 and will be considered "complete" following the conclusion of their Week 24 visit.

For subjects who choose to discontinue from the study prior to these timepoints for any reason, every effort should be made to complete the Week 24/ET visit.

9 STUDY POPULATION

9.1 INCLUSION CRITERIA

All subjects must meet the following inclusion criteria at screen or if indicated at screening and baseline:

1. Able to understand the nature of the study and protocol requirements and provide written informed consent and including authorization to release health information.
2. Male or female subjects 18 to 65 years of age inclusive with diagnosis of unilateral PF.
3. Upon physical exam, unilateral presence of pain upon palpation over medial calcaneal tuberosity.
4. Persistent heel pain at the insertion of the plantar fascia in the posterior-inferior medial calcaneal tuberosity for 3 months or more, but not to exceed 15 months

[redacted]

[redacted]

9.2 EXCLUSION CRITERIA

Subjects will not be enrolled if they meet any of the following exclusion criteria at screening:

1. Non-ambulatory
2. BMI > 32.5 kg/m^2
3. Pain anywhere else in the foot, elicited upon palpation or ongoing, other than at the insertion of the plantar fascia on calcaneus.
4. Previous injection of botulinum toxin in the lower extremities or feet.
5. More than one steroid injection for the treatment of current PF in the affected foot or administered within 3 months prior to screening.
6. Study foot has been previously treated with tissue engineered materials.
7. History of radiation on plantar surface of foot.
8. History of a partial or full thickness tear or surgery of the plantar fascia.

[redacted]

9.3 LIFESTYLE CONSIDERATIONS

[redacted]

9.4 SCREEN FAILURES

Screen failures are subjects from whom written informed consent has been obtained, but who do not meet all eligibility requirements per protocol. Screen failed subjects will be excluded from study participation, however, they may be considered for one-time re-screening in consultation with the sponsor/CRO.

9.5 RE-SCREENINGS

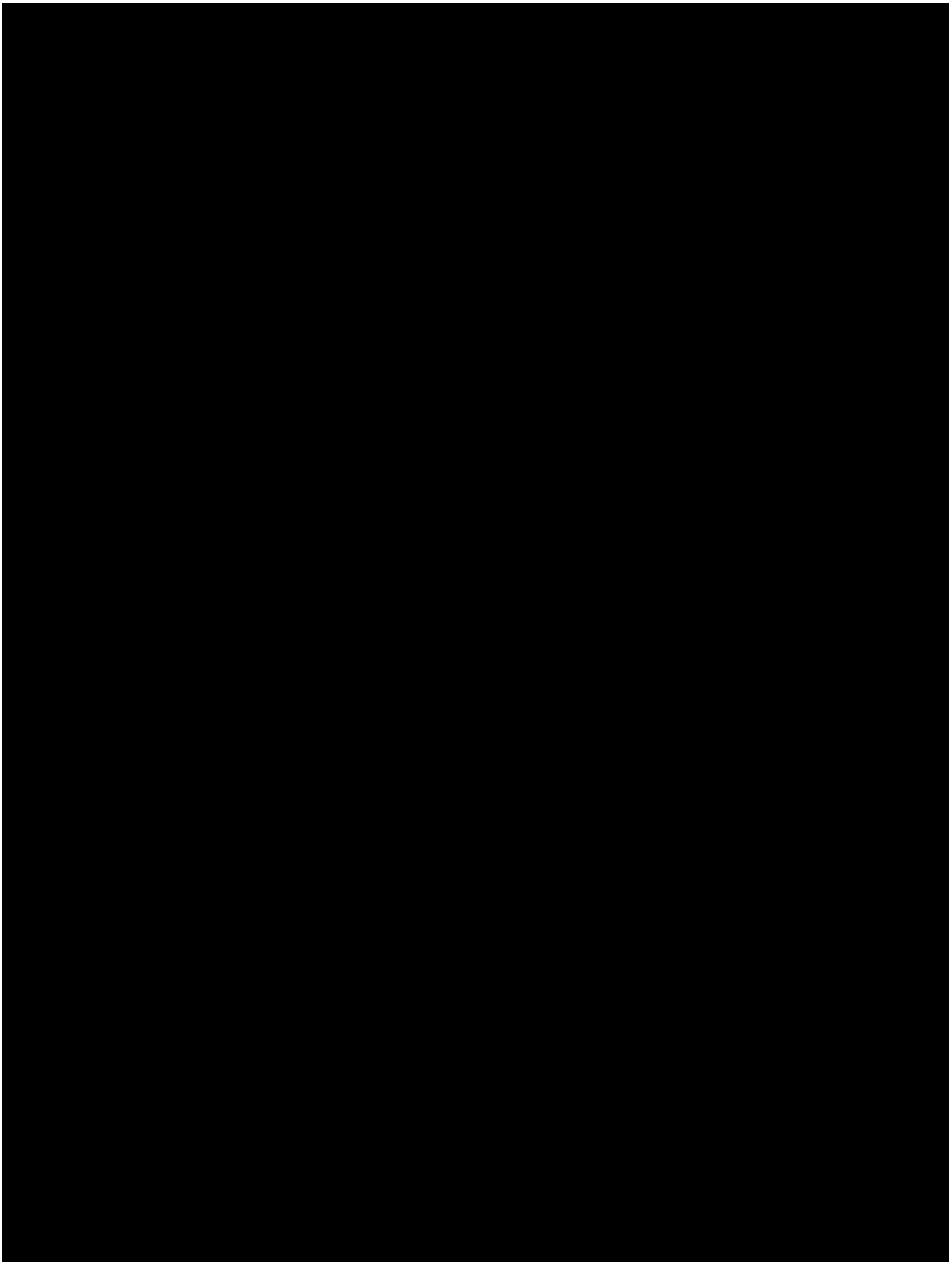
Screen failed (those that do not meet all eligibility requirements per protocol) may be considered for one-time re-screening in consultation with the sponsor/CRO. For re-screening, subjects will be assigned a new subject number in the study and must fulfill all eligibility requirements per protocol.

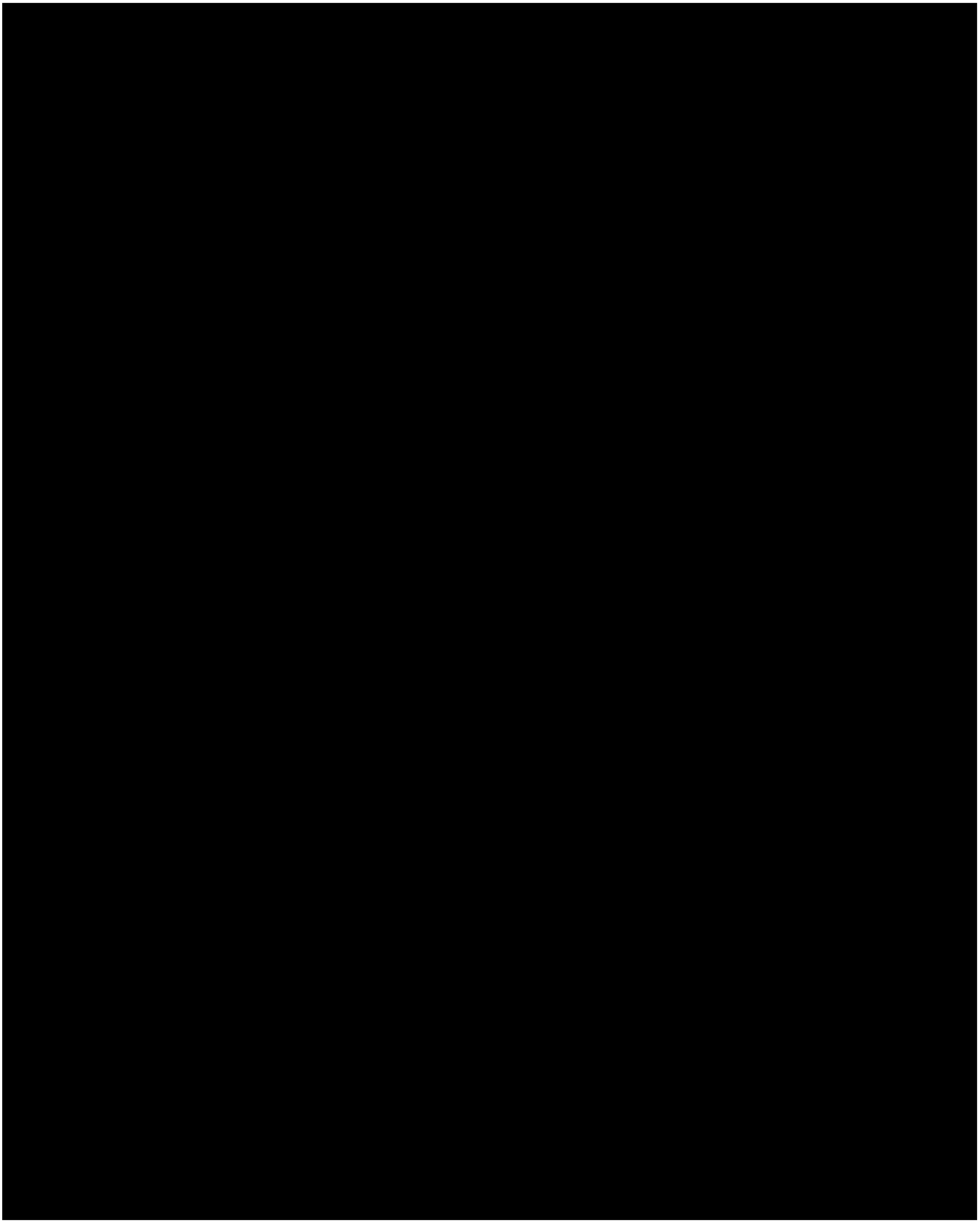
Subjects that underwent imaging of their foot during their initial screening visit will not be required to repeat this assessment.

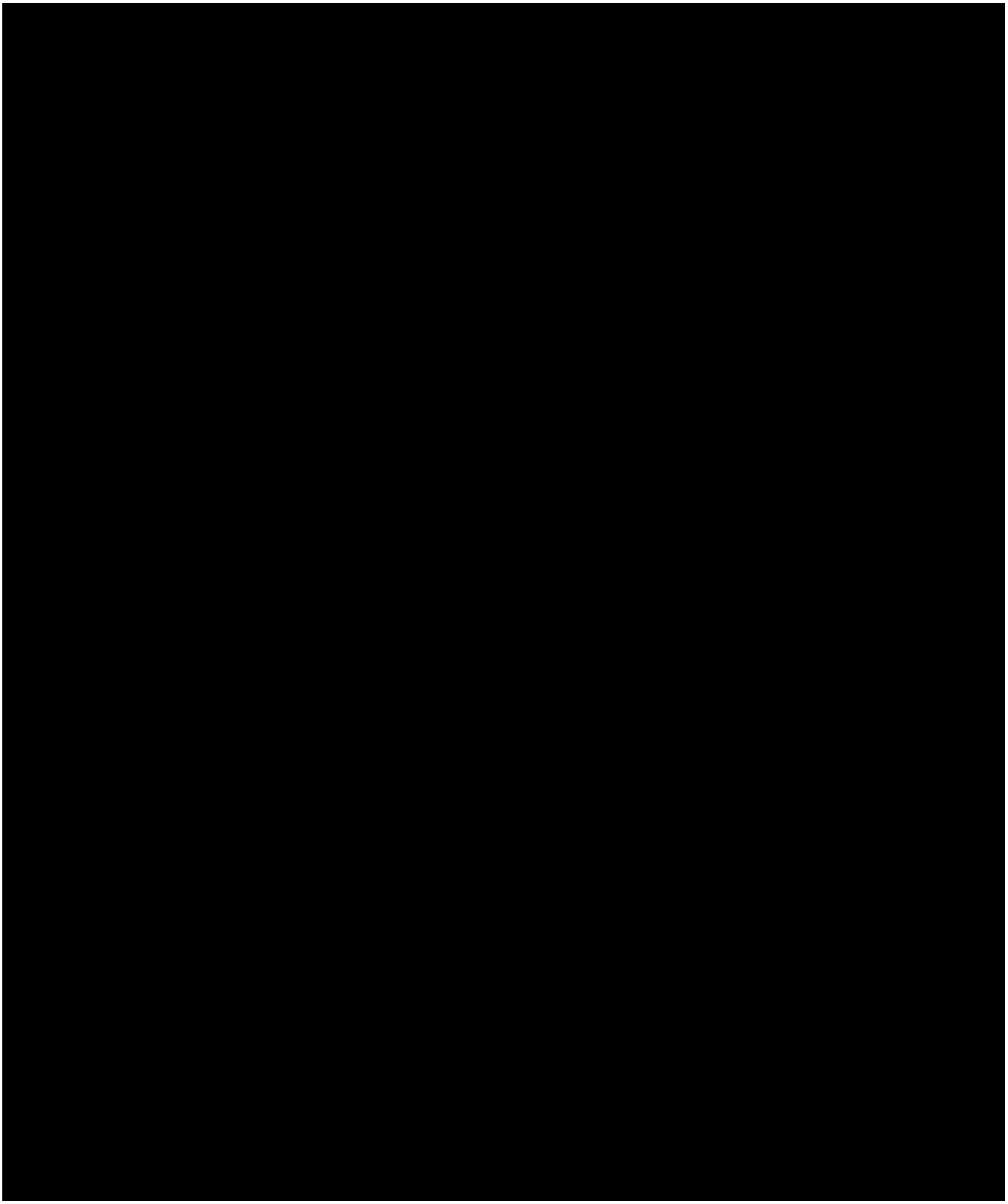
Subjects that screen fail for a second time will not be permitted to re-screen further.

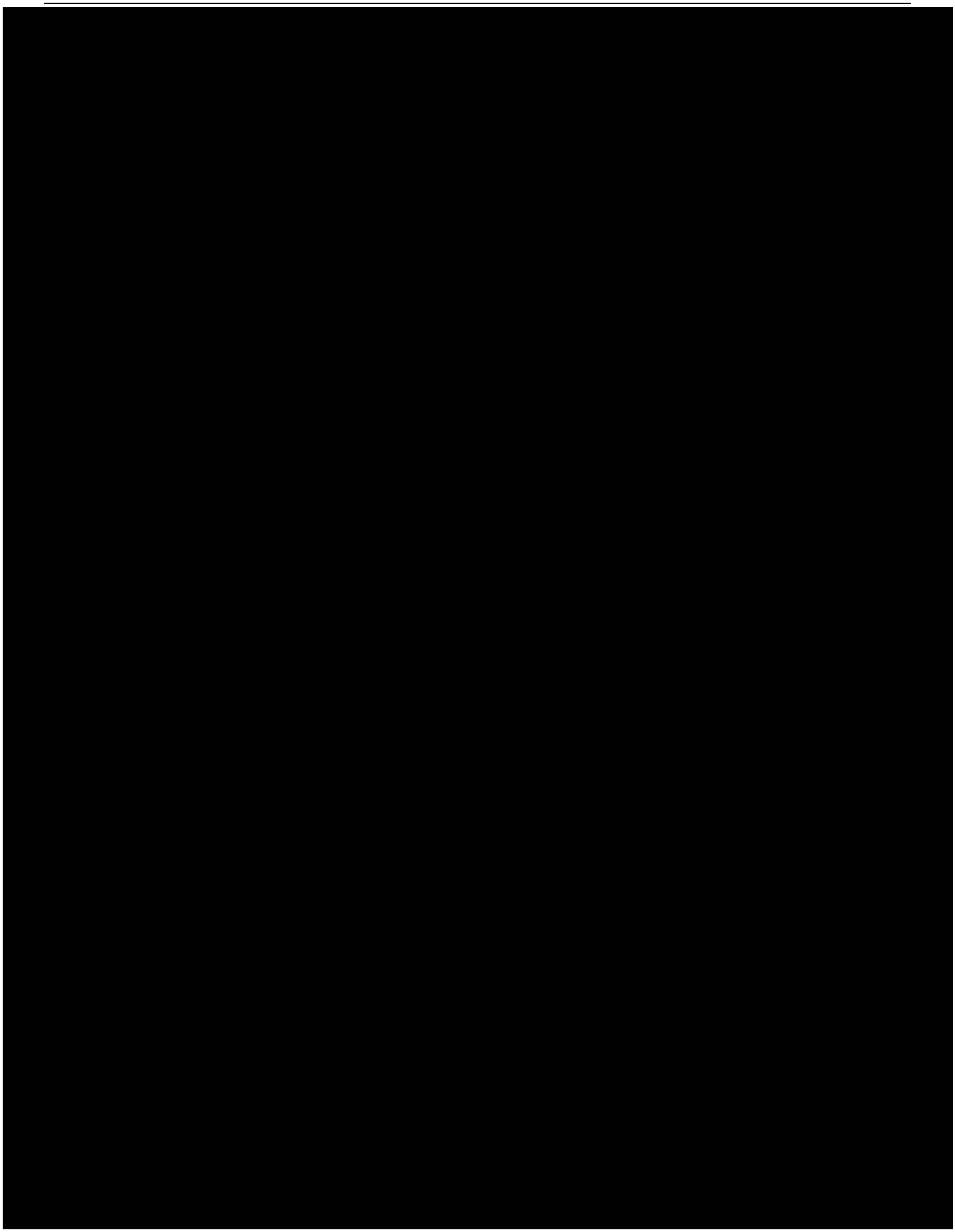
9.6 STRATEGIES FOR RECRUITMENT AND RETENTION

The recruitment and retention plan for this study will be provided separately.









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10.6 CONCOMITANT THERAPY

Concomitant medications are any prescription or over-the-counter preparations used by subjects during participation in the study. Use of concomitant medications will be recorded on the Concomitant Medications CRF beginning at Screening through Week 24/ET. The dose and dosing regimen of all prescription and non-prescription therapies and medications, including herbs, vitamins, or other nutritional supplements administered will be documented.

Use of prohibited medications/treatments as described in Section 9.3.1 will be considered as a protocol deviation.

10.6.1 RESCUE MEDICINE

At the Week 8 visit, the following 2 categories of subjects will be identified to the sites:

- subjects having no improvement from baseline on NPRS scores (see Section 8.7)
- subjects having improvement from baseline of <20% based on NPRS scores

Prior to Week 8, the protocol does not allow for any type of rescue medication for the treatment of PF. At Week 8, for subjects with <20% reduction from baseline in their NPRS score at Week 8, physician-prescribed physical therapy will be permitted upon subject request.

Subjects may withdraw from the study at any time if medication is required to address the subject's symptoms associated with PF (in addition to other reasons a subject may have for early discontinuation).

11 STUDY INTERVENTION DISCONTINUATION AND SUBJECT DISCONTINUATION/WITHDRAWAL

11.1 DISCONTINUATION OF STUDY INTERVENTION

Study subjects will receive a one-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. Refer to Early Discontinuation/Withdrawal Procedures, Section 11.2, for more details.

11.2 EARLY DISCONTINUATION/WITHDRAWAL PROCEDURES

A subject may voluntarily withdraw from study participation at any time. If the subject withdraws consent and discontinues from the trial, the PI will attempt to determine the reason for discontinuation and record the reason in the subject's study records and on the 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 Week 24) and whenever possible, the subject should be asked to return to the investigator site to complete the assessments specified for Week 24/ET. Subjects who withdraw from the study will not be replaced. Early study completers, as defined in Section 8.7 will also complete the Week 24/ET CRF, at the time of study exit (ie, Week 8 visit).

If at any time during the trial, the PI determines that it is not in the best interest of the subject to continue, the subject will be discontinued from participation. The PI can discontinue a subject from study participation at any time if medically necessary or if the subject has failed to follow study procedures or to keep follow-up appointments. Appropriate documentation in the subject's study record and CRF regarding the reason for discontinuation must be completed. Prior to discontinuing a subject from study participation, the PI will discuss his/her intentions with the medical monitor or designee.

All subjects who fail to return to the investigator site 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 study. If a subject is unreachable by telephone after a minimum of 2 documented attempts (1 attempt on 2 different days), a registered letter will be sent requesting that contact be made with the PI.

The sponsor/CRO has the right to terminate or to stop the study at any time. Should this be necessary, both the sponsor/CRO and the PI will ensure that proper study discontinuation procedures are completed.

11.3 LOST TO FOLLOW-UP

A subject 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 investigator site staff.

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

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

- Before a subject is deemed lost to follow-up, the PI or designee will make every effort to regain contact with the subject (where possible, 2 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the blinded ISF.

- Should the subject 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.

12 STUDY ASSESSMENTS AND PROCEDURES

12.1 STUDY ASSESSMENTS

All clinical laboratory assessments will be conducted by a central lab.

12.1.1 SCREENING VISIT

Subjects presenting with heel pain will be examined to verify a diagnosis of PF. Once verified, subjects with PF will be screened to determine if they meet the study eligibility criteria and informed of all requirements for study participation. Subject informed consent and applicable privacy authorization must be obtained prior to conducting screening procedures. Refer to Section 5.3 Schedule of Assessments, for activities to be performed.

After the informed consent is obtained, the following procedures will be completed:

- Demographics, complete medical/surgical history, and physical examination
- Foot and ankle examination of both feet (including range or motion and motor strength)
- Collect vital signs (blood pressure [BP], pulse, temperature, respiration rate), weight, and height
- Collect blood samples for clinical laboratory (chemistry, hematology, urinalysis), [redacted]
- C-SSRS (Baseline Version)
- Collect ECG
- Collect foot imaging (X-rays or sonography) if not done within the last 6 months; if performed within the last 6 months, the image must be available for evaluation by the investigator at the time of screening to determine eligibility
- Collect concomitant medications/therapies
- Dispense ePRO diary and train the subject on its use for capturing NPRS scores every morning within 15 minutes after getting out of bed for the day. The subject must bring this diary to the clinic at each subsequent follow up visit.
- FFI

Results from clinical laboratory tests and cardiologist-interpreted ECG must be obtained, reviewed, and signed by the PI. Any abnormal results must be determined to be not clinically significant by the PI prior to randomization. Any WOCBP having a positive pregnancy test pre-treatment will not be enrolled in the study.

12.1.2 RUN-IN PERIOD

The NPRS will be completed through an ePRO diary entry by the subject, measured within 15 minutes of stepping out the bed in the morning for the course of the run-in period. Subjects will not be required to return to the investigator site at this time.

12.1.3 DAY 1 TREATMENT VISIT

The following procedures will be completed **pre-treatment**:

- Confirm subject eligibility.
- Medical history and physical examination
- [redacted]
- Collect vital signs (BP, pulse, temperature, respiration rate) and weight
- C-SSRS (since last visit)
- [redacted]

After study eligibility is confirmed, as defined by the eligibility criteria in Sections 9.1 and 9.2, the [redacted]

12.1.4 FOLLOW-UP VISITS

Subjects will be evaluated 8 times following Day 1 Treatment Visit completion at Weeks 1, 2, 4, 8, 12, 16, 20 and 24/ET. The following procedures will be completed at each follow-up visit unless otherwise specified:

- [redacted]
- [redacted]
- [redacted]
- Collect vital signs (BP, pulse, temperature, respiration rate) and weight
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Collect concomitant medications/therapies and AE(s)

Variation from Scheduled Visit Days

To allow for scheduling flexibility, limited variation will be permitted from the specified time of each visit as in table shown below.

Allowed Variation from Scheduled Visit Days

Scheduled Visit	Allowed Variation
Weeks 1 and 2	± 2 days
Weeks 4, 8, 12, 16, 20 and 24	± 3 days

12.2 EFFICACY ASSESSMENTS

The timing of all efficacy assessments is as described in the Schedule of Assessments in Section 5.3.

Numeric Pain Rating Scale (NPRS): (*Ferreira-Valente, 2011; McCaffery, 1989; Jensen, 2015; Dworkin, 2005***)** The NPRS is a segmented numeric version of the visual analog scale (VAS) in which a respondent selects a whole number (0–10 integers) that best reflects the intensity of his/her pain. The common format is a horizontal bar or line. Similar to the VAS, the NPRS is anchored by terms describing pain severity extremes. **See APPENDIX B**

FFI (Foot Function Index): The FFI (*Budiman-Mak, 1991*) was developed to measure the impact of foot pathology on function in terms of pain, disability and activity restriction and is a self-administered index consisting of 23 items divided into 3 sub-scales. Both total and sub-scale scores are produced. The FFI can be applied to the effect of PF on foot function. Foot function and pain levels directly can be correlated with treatment outcomes in the Revance Phase 2 study. See **APPENDIX C**

FAAM (Foot and Ankle Ability Measure): The FAAM was developed to comprehensively assess physical performance among individuals with leg, and ankle musculoskeletal disorders (*Martin, 2005*). The FAAM can be applied to performance as relates to PF. See **APPENDIX D**

CGIC (Clinical Global Impression of Change): The CGIC is a questionnaire that captures the clinician's overall impression of the subject's response to study treatment. The clinician's selected response maps to a 7-point scale: -3 (very much worse), 0 (about the same), to +3 (very much better). *(Guy, 1976).* See **APPENDIX E**.

PGIC (Patient Global Impression of Change): The PGIC is a questionnaire that captures the subject's overall impression of their response to study treatment. The subject's selected response maps to a 7-point scale: -3 (very much worse), 0 (about the same), to +3 (very much better). *(Farrar, 2001).* See **APPENDIX F.**

TSQ (Treatment Satisfaction Questionnaire): The TSQ is self-administered instrument that measures the subject's overall satisfaction with his or her study treatment (*Revicki, 2004*). See **APPENDIX G**.

Algometry: Pressure algometers are designed to measure deep pressure pain thresholds or tenderness resistance. When a particular site of the body is pressed with a rubber disk having an area of 1 cm^2, the device displays the pressure (*Park, 2011*). PPT will be measured by algometry beginning pre-treatment on Day 1 and at each subsequent clinic visit at Weeks 1, 2, 4, 8, 12, 16, 20, and 24/ET. The PI will identify the point of maximum tenderness and mark the spot, position the digital pressure algometer and

press against until the subjects reports pain (note; this is the minimal amount of pain, not pressure). The pressure pain threshold is measured 3 times, with at least 1 minute between each evaluation, and the peak reading when pain is first reported recorded in kg/cm^2 for each test.

12.3 SAFETY ASSESSMENTS

The timing of all safety assessments is as described in the Schedule of Assessments in Section 5.3.

12.3.1 ADVERSE EVENTS

12.3.1.1 ASSESSMENT OF ADVERSE EVENTS

AEs will be graded as mild, moderate, or severe as defined in Section 12.3.1.2.3 of this protocol.

Section 12.3.1.2.5 outlines the procedures for recording and reporting AEs.

AEs will be reported by the sponsor in accordance with "21CRF part 312.32 and Guidance for Industry and Investigators: Safety Reporting Requirements." The PI will report any SAEs to the IRB.

[redacted]

12.3.1.2 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

12.3.1.2.1 DEFINITION OF ADVERSE EVENTS (AE)

For this protocol, an 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 IP and until the end of study participation that may not necessarily have a causal relationship to the administration of the IP. 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 IP, whether or not considered related to the IP. A treatment-emergent AE 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 IP use will also be considered an AE.

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 IP 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.

12.3.1.2.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An 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 PI and/or sponsor/CRO, 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 IP 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 of the outcomes listed above (i.e., is a significant or important medical event)

12.3.1.2.3 CLASSIFICATION OF AN ADVERSE EVENT

Severity of Event

The PI 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 definitions:

- **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 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 trial; treatment or other intervention usually needed

Relationship to Study Intervention

Relationship of an AE to IP will be assessed by the PI as follows:

- **Definite:** There is a clinically plausible time sequence between the onset of the AE and the administration of IP; when the event responds to withdrawal of IP and/or recurs with re-administration of IP
- **Probable:** There is a clinically plausible time sequence between the onset of the AE and the administration of IP; 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 IP and a cause cannot be ruled out
- **Unrelated:** There is not a temporal or causal relationship to IP administration

Expectedness

The medical monitor and sponsor/CRO will be responsible for determining whether an 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.

12.3.1.2.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of investigator site staff during study visits and interviews of a subject presenting for medical care, or upon review by the blinded monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate 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. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the subject is screened will be considered as medical history and not reported as an AE. However, if the subject's condition deteriorates at any time following injection at their Day 1 Treatment visit 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 PI or investigator site staff will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the PI or investigator site staff will inquire about the occurrence

of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

12.3.1.2.5 ADVERSE EVENT REPORTING

The PI will assess subject post-treatment and at each subsequent study visit for the occurrence of AEs. 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.

In addition, PIs and/or investigator site staff must report an SAE to the sponsor/CRO within **24 hours** of their awareness of the event according to the procedure outlined below. All fatal or life-threatening SAEs should be telephoned to the sponsor/CRO or the authorized representative as soon as the PI learns of the event.

12.3.1.2.6 SERIOUS ADVERSE EVENT REPORTING

It is the responsibility of the PI to report all SAE occurrences to the sponsor/CRO authorized representative within **24 hours** of their awareness of the event:

- Complete and return an SAE Form with all information known to date; including the PI's assessment of causality.
- If the event is fatal or life-threatening, telephone sponsor/CRO or the authorized representative as soon as the PI learns of the event.
- Obtain and maintain all pertinent medical records (discharge summary, autopsy report, etc.) and medical judgments of investigator site staff who assisted in subject's treatment and follow-up.
- Provide follow-up information to the sponsor/CRO or the authorized representative.

All SAEs will be followed until satisfactory resolution or until the PI deems the event to be chronic or the subject is stable. Other supporting documentation of the event may be requested by the Data Coordinating Center/sponsor/CRO and should be provided as soon as possible.

The 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 investigator sites in an IND safety report, of potential serious risks from clinical studies (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/IEC, and investigator sites will be notified of SAEs in accordance with applicable regulations and requirements (e.g., GCPs, ICH Guidelines, national regulations and local requirements).

The PI will collect information on SAEs until subject's health has returned to baseline, the SAE has stabilized, or remaining health issues have otherwise been explained.

12.3.1.2.7 REPORTING EVENTS TO SUBJECTS

The sponsor/CRO will disclose clinical study data to individuals, to investigator sites, and publicly (as aggregate summaries) in accordance with regulatory and local legal requirements.

Follow-up of Non-Serious Adverse Events

Non-serious AEs that are identified during the last scheduled study 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 24/ET visit should be followed to resolution or until determined by the PI to be stabilized. Repeat tests may be indicated to establish this.

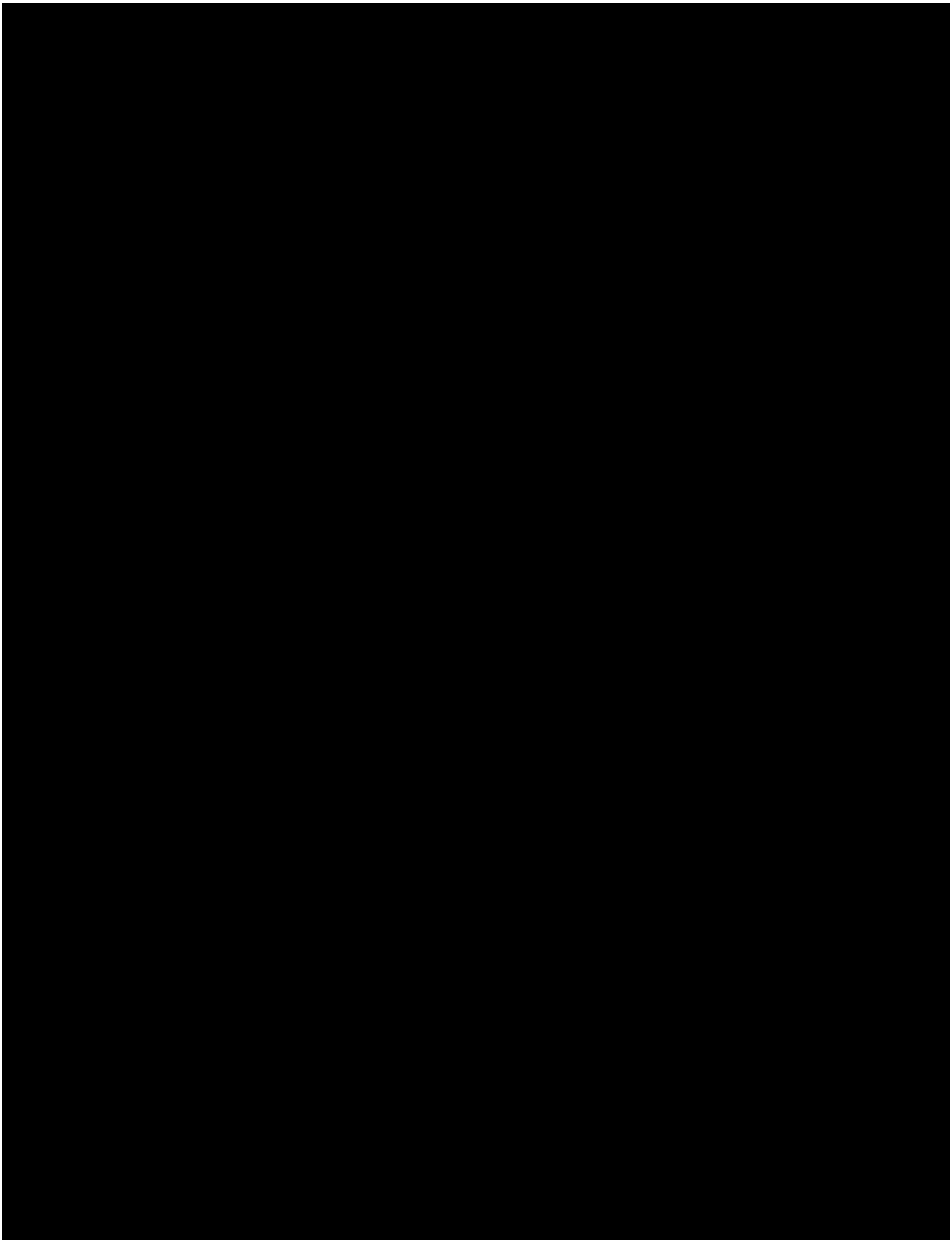
If a subject has any clinically significant, trial-related abnormalities at the end of the trial, the medical monitor should be notified, and every effort made by the PI to arrange follow up evaluations at appropriate intervals to document the course of the abnormalities.

Follow-up of Post Study 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 sponsor/CRO according to the reporting procedures outlined in Section 12.3.1.2.6. This may include unresolved previously reported SAEs, or new SAEs. The PI should follow the SAE until it resolves or is determined by the PI to be stable, or the subject is lost to follow-up. The PI should continue to report any significant follow-up information to the medical monitor, sponsor/CRO, and the IRB/IEC 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 PI does not expect any further improvement or worsening of the subject's condition.

Any new SAEs reported by the subject to the PI that occur after the last scheduled contact and are determined by the PI to be reasonably associated with the administration of IP should be reported to sponsor/CRO and the IRB/IEC.

[redacted]



[redacted]

12.3.2 CLINICAL LABORATORY TESTS

As outlined in the Clinical Laboratory Tests table below, non-fasting samples for hematology, chemistry, and urinalysis will be collected at Screening and at Weeks 8 and 24/ET. [redacted]

Blood and urine will be collected using applicable safety precautions and will be processed according to the clinical laboratory's instructions. [redacted]

Hematology	Chemistry	Urinalysis	Additional Tests
Hemoglobin Hematocrit Leukocyte count (total) Leukocyte count (differential) Red blood cell count Platelet count	Glucose Total bilirubin Alanine aminotransferase Aspartate aminotransferase Alkaline phosphatase Blood urea nitrogen Sodium Potassium Chloride Calcium Carbon Dioxide (Bicarbonate) Total Protein Creatinine	Specific gravity pH Glucose Protein Blood Bilirubin Ketones	[redacted] PT/INR

It is the PI's responsibility to review the results of all laboratory tests as they become available. For each laboratory test result outside the reference range, the PI 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 PI must ascertain if this is an abnormal and clinically significant change pre-treatment for that individual subject. The PI may repeat the laboratory test or request additional tests to verify the results of the original laboratory test. The PI 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. Toxicity grading for laboratory results is standardized using the FDA's "Guidance for Industry: Toxicity Grading Scale for Health Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" dated September 2007. 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 12.3.1.2.3 for further information.

[redacted]

12.3.3 12-LEAD ELECTROCARDIOGRAMS (ECGS)

At screening, re-screening (if applicable), and at Weeks 8 and Week 24/ET, a single standard supine 12-lead ECG will be obtained after a subject has rested quietly for at least 5 minutes. The ECG data will be submitted to a central reader for measurement. Instructions for the collection, transmission, and archiving of the ECG data are outlined in the ECG central reader manual. The analyzed ECG data will be reviewed and signed by the PI.

12.3.4 INJECTION SITE EVALUATION

The injection site evaluation will be a global evaluation of the injection site.

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		

12.3.5 HYPERSENSITIVITY EVALUATION

The following skin reactions may indicate hypersensitivity during injection site evaluation:

- Erythema
- Wheal(s)

- Pruritus
- Warmth at the injection site

An additional blood draw should be performed in order to address immediate hypersensitivity concerns. Revance recommends that at least 2 of the 4 above-listed symptoms should be present to make this clinical diagnosis. The investigator should also use his/her clinical judgment in addition to the aforementioned guidelines.

12.3.6 PHYSICAL EXAMINATIONS

Physical examination will include neurological examination; the PE will include examination of the face, general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, heart, lungs, abdomen, lymph nodes, and extremities. Urogenital exam need only be completed if clinically indicated. At post-treatment visits, the physical examination may be abbreviated, as deemed medically appropriate at the discretion of the PI; the neurological examination must be conducted at a minimum. Significant physical examination findings that are present prior to IP administration are to be included on the Medical History page.

Significant physical examination findings which meet the definition of an AE will be recorded on the AE page post-treatment.

12.3.7 FOOT AND ANKLE EXAMINATION

Examination for the foot will be conducted, including ankle, toe, and subtalar range of motion, foot motor strength, location of pain, and examination of the heel fat pad and Tinel's sign. The presence of toe deformities, bunions, ulcers, and/or sores will be documented. The feet will be examined for signs of swelling, pitting edema, infection, or vascular abnormalities (refer to APPENDIX A).

12.3.8 HEIGHT, WEIGHT, VITAL SIGNS

Height, weight, and vital signs (i.e., body temperature, respiration rate, sitting radial pulse rate, and sitting systolic and diastolic BP) will be obtained. Height will only be collected at the Screening visit.

12.3.9 COLUMBIA-SUICIDE SEVERITY RATING SCALE

The C-SSRS monitors changes in suicidal thinking and behavior over time, in order to determine risk (*Posner, 2011*; **APPENDIX H**). The following four constructs are measured: the severity of ideation, the intensity of ideation, behavior, and lethality.

The C-SSRS will be used to assess suicidal ideations and behaviors. The C-SSRS results for each subject should be reviewed by the PI at each visit. If at any time the C-SSRS results for a given subject reveal potential suicidality, then the PI should assess the clinical significance of such results. If a clinically significant risk of suicidality is identified for a subject, then the PI should discontinue the subject and implement appropriate treatment.

12.3.10 REPORTING OF PREGNANCY

During the trial, all WOCBP should be instructed to contact the investigator site immediately (within 24 hours) if they suspect they might be pregnant (e.g., missed or late menstrual cycle). The PI must immediately notify sponsor/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 investigator 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 study.

12.3.11 PREGNANCY TESTING

All WOCBP will have a SPT at the Screening, Week 8 and 24/ET visits and a UPT at the Day 1 Treatment Visit pre-treatment. If any result is positive prior to treatment, the subject will not be allowed to participate. The results of the UPTs for WOCBP will be evaluated at the investigator site.

WOCBP must use an effective method of birth control during the course of the trial, such as the oral contraceptive pill, injection, implant, patch, vaginal ring, intrauterine coil, intrauterine device, tubal ligation, barrier method used WITH an additional form of contraception (e.g., sponge, spermicide or condom), abstinence, no heterosexual intercourse, or has a vasectomized partner. 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.

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

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

Prior to study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during participation in this clinical study and the potential risk factors for an unintentional pregnancy. The subject must sign the informed consent document stating that the above-mentioned risk factors and the consequences were discussed with her.

12.3.12 IMAGING

X-rays or sonography of the affected foot will be collected at Screening. This procedure is to be done at the investigator site. Records of the imaging are to be collected and kept with the subject's study information. In the event a subject has had imaging of the affected foot within the 6 months prior to Screening, the subject does not need to have imaging conducted as part of the Screening procedure if the image is available for evaluation by the investigator at the time of Screening to determine eligibility.

12.4 UNANTICIPATED ADVERSE EVENTS

12.4.1 DEFINITION OF UNANTICIPATED ADVERSE EVENTS

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to subjects 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 subject 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

The sponsor/CRO will comply with these criteria for reporting unanticipated AEs.

12.4.2 UNANTICIPATED ADVERSE EVENT REPORTING

The investigator site will report unanticipated AEs to the reviewing Institutional Review Board (IRB) and the sponsor/CRO. The unanticipated AE 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 AE;

- A description of any changes to the protocol by the sponsor/CRO or other corrective actions that have been taken or are proposed in response to the unanticipated AE.

- The sponsor/CRO will update the IB or provide Dear Doctor letter should these actions be deemed required.

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

- Unanticipated AEs that are fatal and life-threatening SAEs will be reported to the IRB and to the sponsor/CRO within seven (7) days of the PI becoming aware of the event.

- Any other unanticipated AEs that are SAEs will be reported to the IRB and to the sponsor/CRO within 15 days of the PI becoming aware of the problem.

- All unanticipated AEs that non-serious AEs are not required to be reported to the IRB or to the sponsor/CRO.

- All unanticipated SAEs should be reported to appropriate institutional officials (as required by an

institution's written reporting procedures), the supporting agency head (or designee), and the OHRP if applicable.

- All SUSARs will be reported in compliance with the requirements of the respective Regulatory Authority.

12.4.3 REPORTING UNANTICIPATED ADVERSE EVENTS TO SUBJECTS

The sponsor/CRO will disclose clinical study data to individuals, to investigator sites, and publicly as aggregate summaries, in accordance to Regulatory and local legal requirements.

13 STATISTICAL CONSIDERATIONS

13.1 SAMPLE SIZE DETERMINATION

The sample size calculations are based on the minimal clinically important difference of 2 points for NPRS (*Farrar, 2001; Michener, 2011*). [redacted]

13.2 POPULATIONS FOR ANALYSES

Approximately 150 subjects, 18 to 65 years of age, will be randomized [redacted]

- **Intent-to-Treat (ITT) Population:** Efficacy analysis will be performed using the ITT population, which includes all subjects randomized who received study treatment, with treatment arms classified based on randomization assignment, regardless of the actual treatment received.

[redacted]

13.3 STATISTICAL ANALYSES

13.3.1 GENERAL CONSIDERATIONS

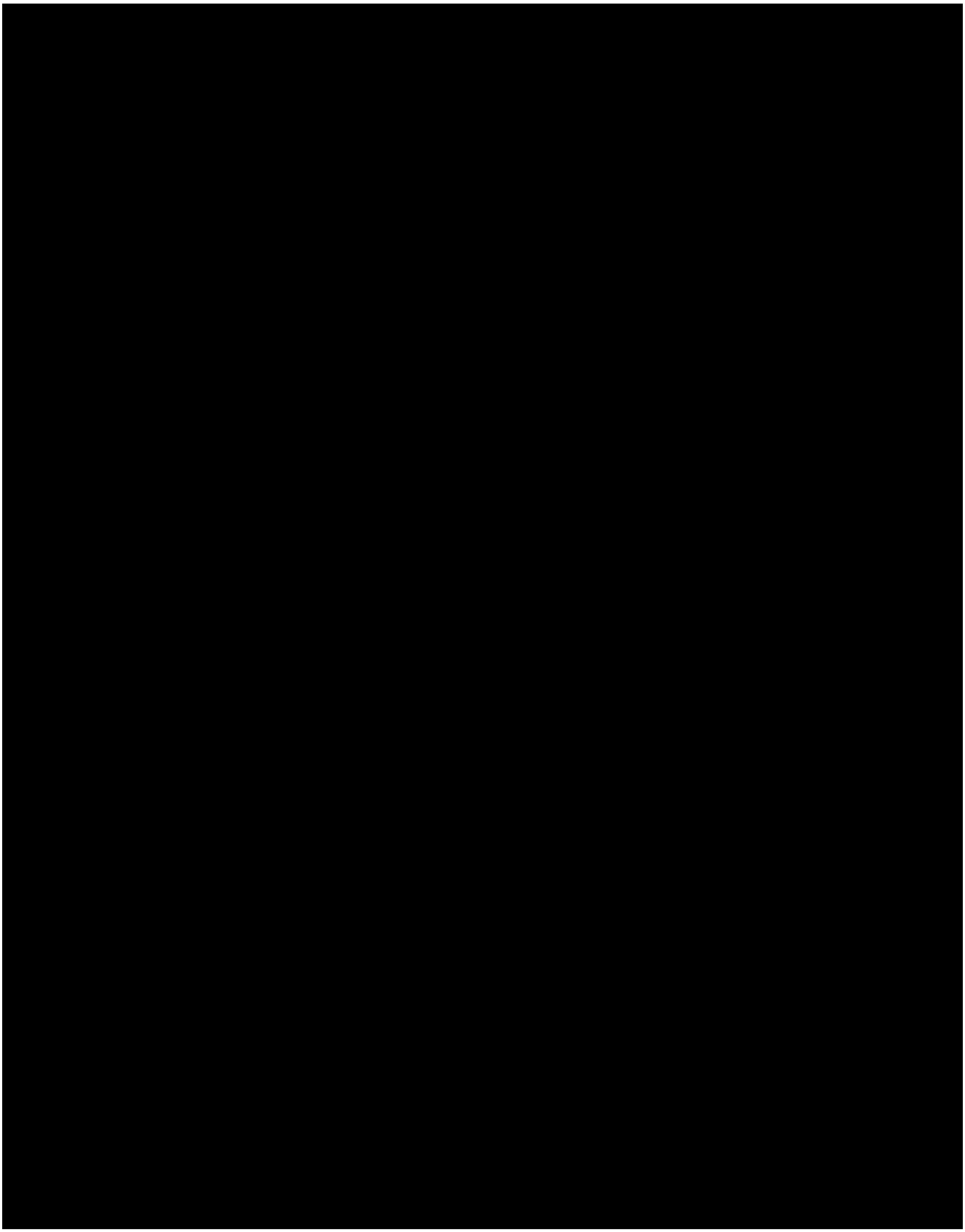
All evaluable efficacy data will be included in the analysis following the ITT principle.

13.3.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT

The primary endpoint is:

- Change from baseline in the NPRS score, which is recorded within 15 minutes after stepping out of bed in the morning and averaged over 5 days (defined as 4 days prior to the study visit and on the study visit day) at Week 8. For the primary analysis, missing data will be imputed by the multiple imputation approach. Analysis of covariance (ANCOVA) model will be used, including investigator site and treatment group as factors, and baseline NPRS score as a covariate.

  Analysis of the primary efficacy endpoint will be based on the ITT or treatment policy estimand and is fully defined in the Statistical Analysis Plan (SAP).



Laboratory results and vital sign data will be summarized by visit and treatment arm, using descriptive

[redacted]

13.3.11 SUB-GROUP ANALYSES

Sub-group analysis will be presented in the SAP, if appropriate.

13.3.12 TABULATION OF INDIVIDUAL SUBJECT DATA

Individual subject data will be listed by measure and time point at completion of the study.

14 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

14.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

14.1.1 INFORMED CONSENT PROCESS

14.1.1.1 INFORMED CONSENT AND AUTHORIZATION TO RELEASE HEALTH INFORMATION

Written informed consent will be obtained from all subjects before any study-related procedures (including any screening procedures) are performed. The PI 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 PI 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.

Investigator site-specific informed consent form templates must be forwarded to the sponsor/CRO for approval prior to submission to an IRB/Independent Ethics Committee (IEC) that is registered with the US Department of Health and Human Services (HHS) or applicable health authority. Each subject will sign the consent form that has been approved by the same IRB/IEC 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, as well as the elements required by the ICH GCP guideline, and applicable federal and local regulatory requirements. The consent form must also include a statement that the sponsor/CRO, 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 PI (or a qualified designee) and it is felt that the subject understands the implications and risks of participating in the trial, the IRB/IEC approved consent document shall be signed and dated by both the subject and the person obtaining consent (PI or designee), and by any other parties required by the IRB/IEC or other regulatory authorities. The subject will be given a copy of the signed informed consent document with the original maintained in the blinded ISF by the PI. All of the above activities must be completed before any study related procedures are conducted (including any screening study procedures).

14.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

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. Consent forms will be IRB-approved and the subject will be asked to read and review the document. The PI will explain the research study to the subject and answer any questions that may arise. A verbal explanation will be provided in terms suited to the subject's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research subjects. Subjects will have the opportunity to carefully review the written consent form and ask questions prior to signing. The subject should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The subject will sign the informed consent document prior to any procedures being done specifically for the study. Subjects must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the subjects for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the subject undergoes any study-specific procedures. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

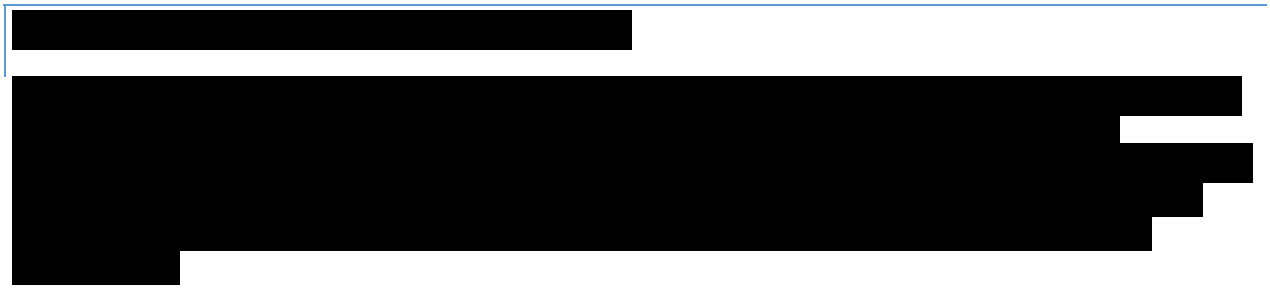
14.1.1.3 STUDY DISCONTINUATION AND CLOSURE.

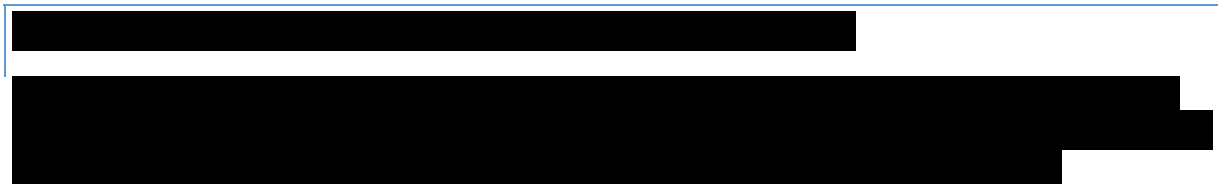
This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to subjects, investigator sites, the IND sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform subjects, the IRB, and sponsor/CRO and will provide the reason(s) for the termination or suspension. Subjects will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor/CRO, IRB and/or FDA.





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14.1.5 SAFETY MONITORING/DATA MANAGEMENT

An Independent Data Monitoring Committee (DMC) will be appointed to review safety data during the study. Details of the composition and scope of the committee's mandate will be presented in a DMC charter document. The DMC will evaluate all safety data available at timepoints specified in the charter and will make appropriate recommendations.

14.1.6 MONITORING, COMPLIANCE, AND QUALITY

All aspects of the study will be monitored by the sponsor/CRO according to GCP and SOPs for compliance with applicable government regulations, (i.e., Informed Consent Regulations and Institutional Review Board regulations).

14.1.7.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

14.1.7.1.1 DATA COLLECTION

For this trial, all protocol-specified data recorded in the source documents will be entered on the CRFs from the source documents. Subject assessments will be completed by the individual subjects directly on the corresponding CRFs. In addition to signature confirmation that a subject meets the study eligibility criteria, upon each subject's completion of the trial, the PI 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 the sponsor/CRO'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 PI 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 un-interpretable data will be resolved with the PI or Study Coordinator. Data queries will be sent to the investigator site. Investigator site staff will be responsible for providing resolutions to the data queries and for correcting the CRFs, as appropriate.

The PI must keep written or electronic source documents for every subject participating in the clinical study. Source documentation must include subject demographic and medical information including but not limited to:

- Date of birth
- Sex
- Race
- Ethnicity
- Medical history
- Comorbid conditions
- Concomitant therapies/medication
- Study visit dates
- Performed examinations, evaluations, and clinical findings
- IP 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 initials, study number, and the date of the evaluation.

The data recorded during the course of the study will be documented in the CRF and/or the trial-specific forms. Before or at study termination, all data must be forwarded to the sponsor/CRO. The data will then be recorded, evaluated, and stored in anonymous 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 PI will ensure that the study documents forwarded to the sponsor/CRO, and any other documents, contain no mention of subject names.

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

Regulatory authorities, the IRB/IEC and/or the sponsor/CRO's Quality Assurance group (or designee) may request access to all source documents, CRFs, and other study documentation for on-site audit or inspection. The PI must guarantee direct access to these documents. CRFs will be kept by the sponsor/CRO 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/CRO after descriptive and statistical analyses and reports have been generated and are complete.

14.1.7.1.2 FILE MANAGEMENT AT THE INVESTIGATOR SITE

It is the responsibility of the PI to ensure that their blinded and unblinded ISF is maintained in accordance with ICH Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance, Section 8 – Essential Documents for the Conduct of a Clinical Trial. Documentation is subject to inspection by the sponsor and relevant regulatory agencies.

14.1.7.2 RECORDS RETENTION AT THE INVESTIGATOR SITE

It is a sponsor/CRO requirement that all PIs participating in clinical studies maintain detailed clinical data for 1 of the following periods:

- Country-specific requirements, or
- A period of at least 2 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 2 years after the sponsor/CRO notifies the PI that the data will not be submitted for review by any Regulatory Authority

14.1.7.3 TREATMENT OF MISSING DATA

Some data elements will be missing in this study due to subjects who withdraw from the study, subjects who are lost to follow-up, or subjects who do not complete all study visits. The completion status of each subject will be documented (e.g., completed protocol, withdrew from study, lost to follow-up, etc.). All reasonable efforts will be made by the investigator site staff to maintain contact with the subjects during their participation in the study. The study coordinator will attempt to contact any subjects who are lost to follow-up. For subjects who are unwilling to return to clinic for follow-up, the study coordinator will attempt to contact them and to collect study data from them during a telephone call or by forms sent to them through the mail.

14.1.8 PROTOCOL DEVIATIONS

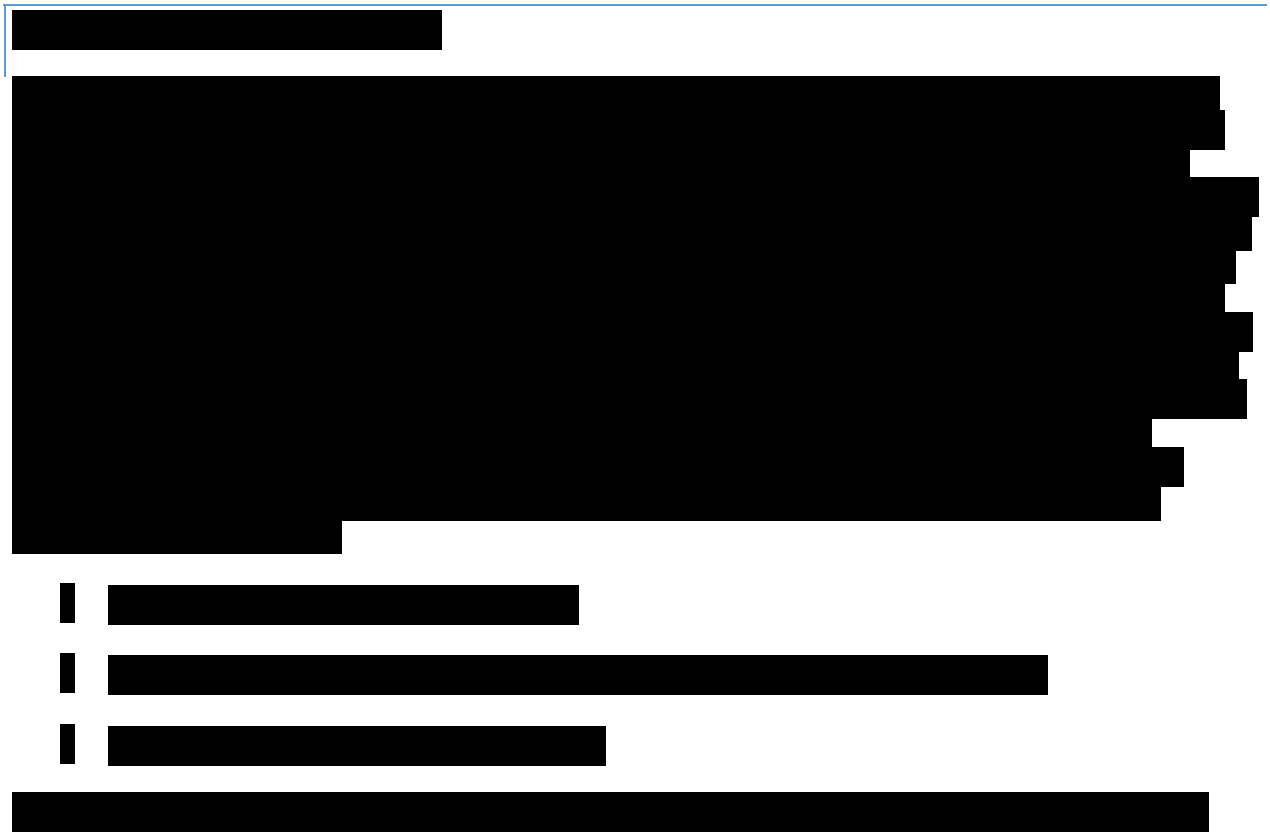
This study will be conducted as described in this protocol, except for an emergency situation in which the protection, safety, and well-being of the subject requires immediate intervention, based on the judgment of the PI (or a responsible, appropriately trained professional designated by the PI).

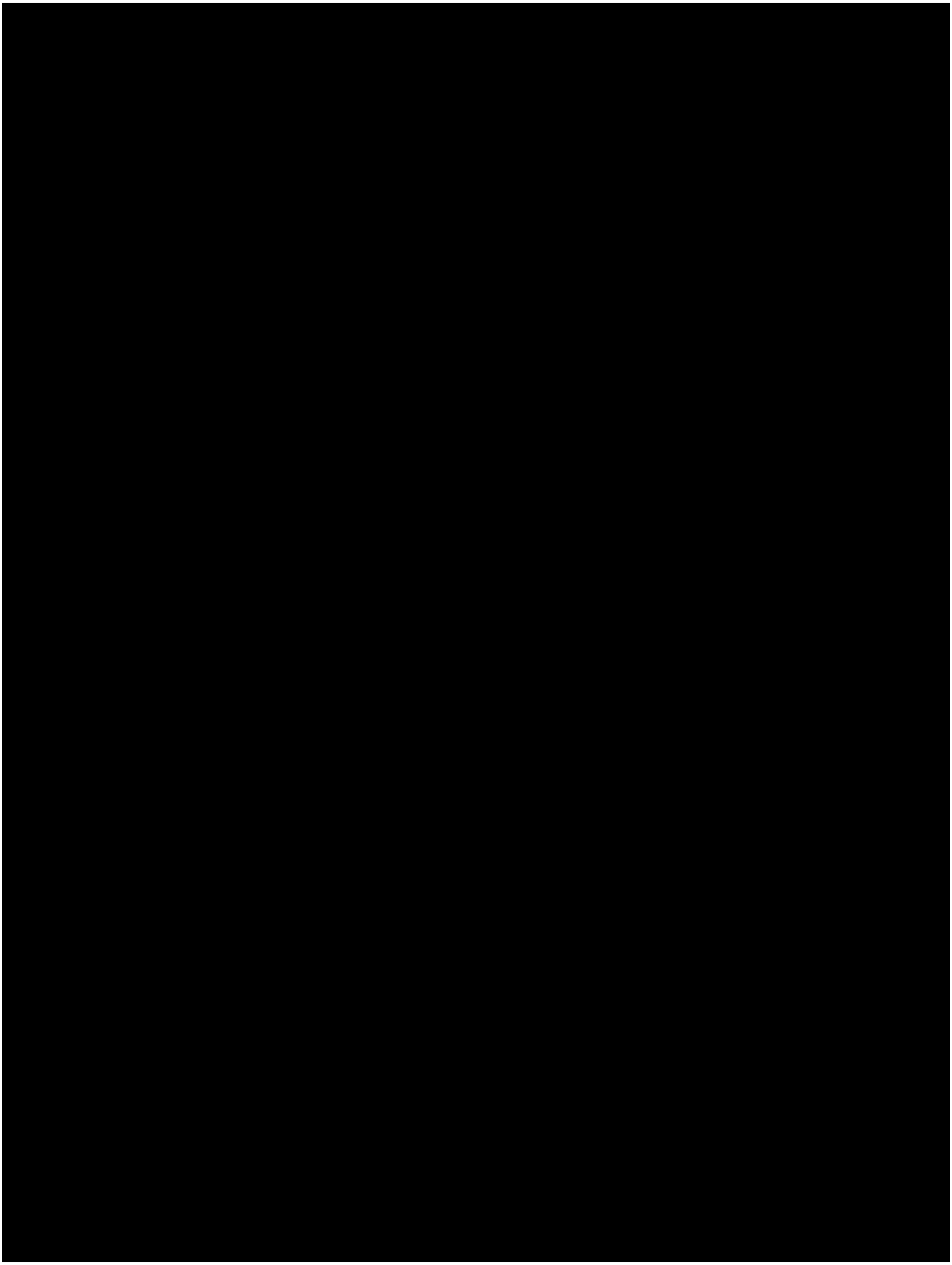
In the event of a significant deviation from the protocol due to an emergency, accident, or mistake, the PI or designee must contact the sponsor/CRO at the earliest possible time by telephone. This will allow an early joint decision regarding the subject's continuation in the study. This decision will be documented by the PI and the sponsor/CRO. It is the responsibility of the PI and/or designated investigator site personnel to report significant protocol deviations to the IRB/IEC per their institutional procedures.

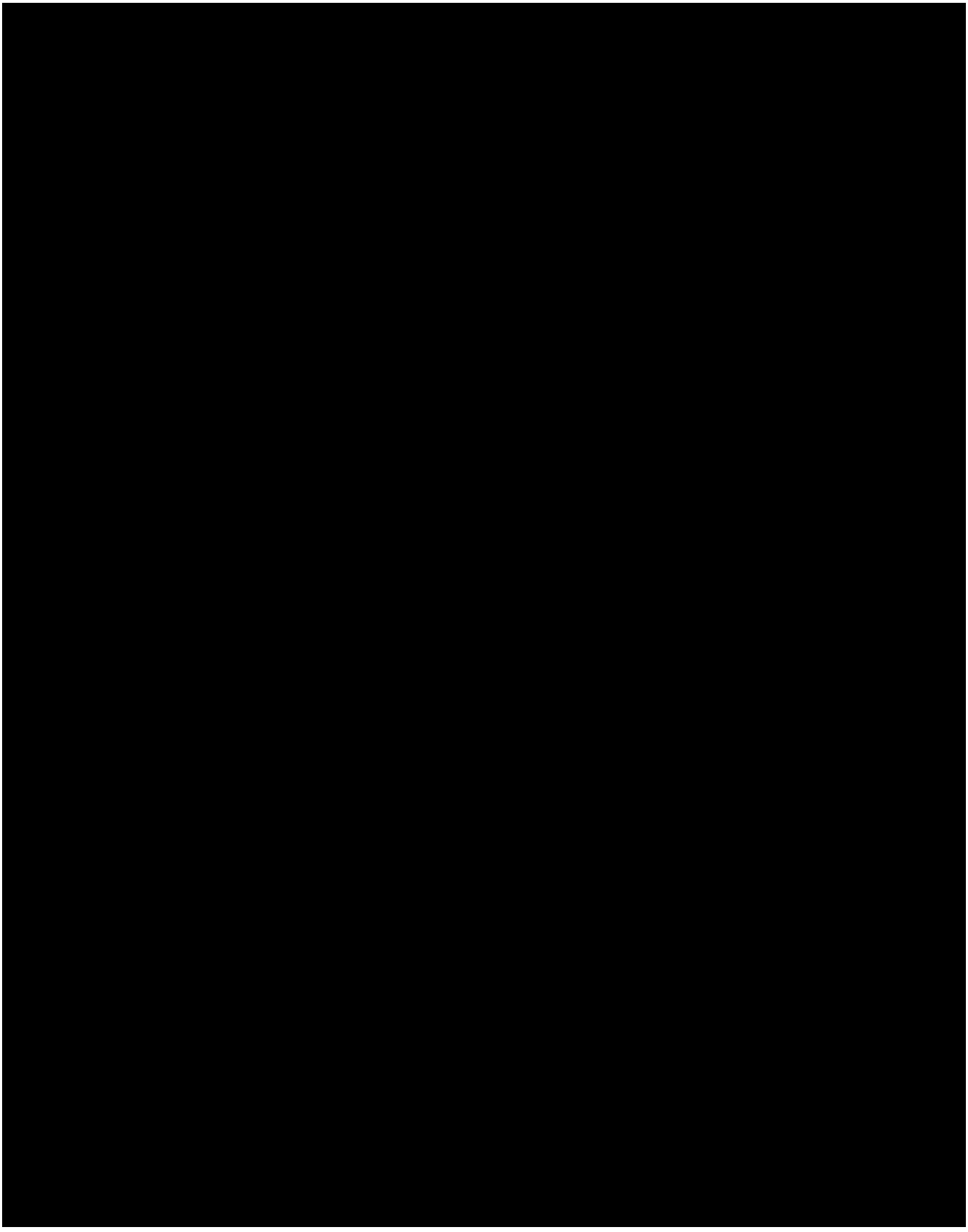
14.2 ADDITIONAL CONSIDERATIONS

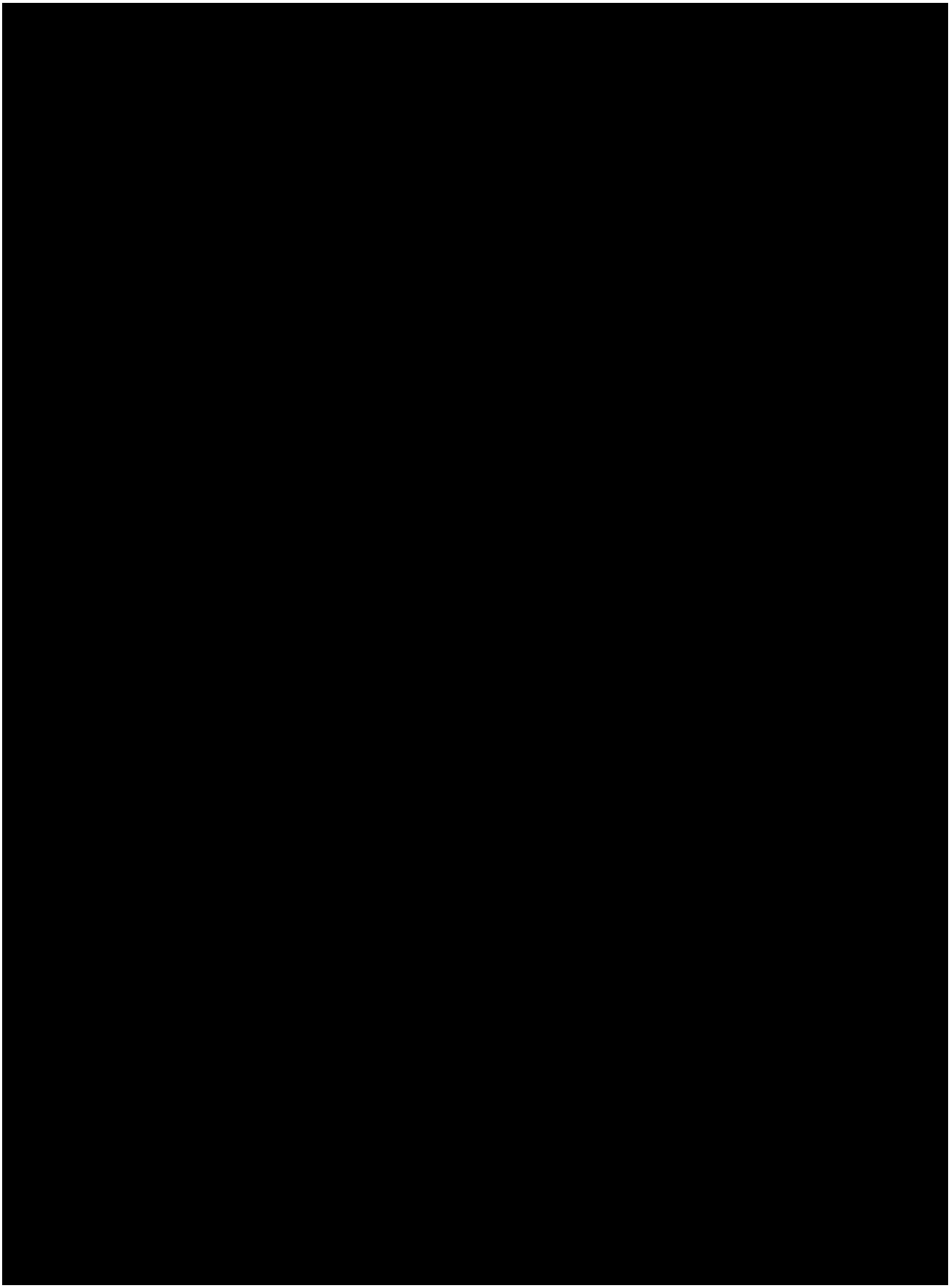
14.2.1 ETHICS AND RESPONSIBILITY

This study must be conducted in compliance with the protocol, the ICH Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance and the applicable regulatory requirements. PIs must submit all essential regulatory documentation, as required by local and national regulations (including approval of the protocol and informed consent form by an HHS-registered IRB/IEC) to the sponsor/CRO before IP will be shipped to the investigator site.









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