NCT03583359, redacted
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Clinical Study Protocol

Evaluation of Effectiveness and Safety of Radiesse (+) to Improve the Contour of Jawline by Adding Volume to the Jawline

Study protocol number: M900391004

Protocol amendment date: 20-JUL-2018 (replaces Version 3.0, 18-JUN-2018)

Development phase: Device Pre-Market - Pivotal study

Investigational product: Radiesse (+) Injectable Implant

Indication: Deep (subdermal and/or supraperiosteal) injection to improve the contour of jawline by adding volume to the jawline

Sponsor:
Merz North America, Inc.
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Authors:
Clinical Project Director: [redacted]
Medical Expert: [redacted]
Scientific Expert/Senior Medical Writer: [redacted]
Senior Biostatistician: [redacted]

Signature Page

This study will be conducted in compliance with the clinical study protocol, ICH-GCP principles, the Declaration of Helsinki, and regulatory authority requirements.

The following individual is responsible for the content of the clinical study protocol:

[redacted]

[redacted]
Signature

23 July 2018
Date

Statement of Compliance and Investigator Signature

I have thoroughly read and reviewed the clinical study protocol and assume responsibility for the proper conduct of the study and all investigational device testing at this site.

Having understood the requirements and conditions of the clinical study protocol, I agree to conduct the study in compliance with this protocol, any future amendments, and any other study conduct procedures provided by the sponsor. I will follow the principles of International Conference on Harmonization's Good Clinical Practice (ICH-GCP), all applicable regulatory authority requirements, and conditions of approval imposed by any reviewing or regulatory bodies when conducting this study. In addition, I agree to:

- Sign this clinical study protocol before the study formally starts.
- Wait until I have received approval from the appropriate Institutional Ethics Committee (IEC)/Institutional Review Board (IRB) before enrolling any subject in this study.
- Start the study only after all legal requirements in my country have been fulfilled.
- Obtain informed consent for all subjects prior to performing any study-related action.
- Permit study-related monitoring, audits, IEC/IRB review, and regulatory inspections and provide direct access to all study-related records, source documents, subject files, and case report forms for the sponsor, monitor, auditor, IEC/IRB, or regulatory authority upon request.
- Use all study materials only as specified in the clinical study protocol.
- Report to the responsible product safety officer, within 24 hours, any serious adverse event (SAE), and serious adverse device effect (SADE), whether considered related or not related to the investigational device.
- Provide to the sponsor, prior to initiating the study, my curriculum vitae, including details of relevant experience and an explanation of any prior terminated research (if applicable).
- Provide written disclosure of any financial interest, in accordance with 21 CFR Part 54, and promptly update this information if changes occur during or within one year after study completion.

Furthermore, I understand that:

- Changes to this protocol must be made in the form of an amendment that has the prior written approval of Merz and any applicable IEC/IRB or regulatory authority.
- The content of the clinical study protocol is confidential and proprietary to Merz.
- Any deviation from the clinical study protocol may lead to early termination of the study site.

Principal Investigator (print name)	***Date (dd-MMM-year)***	***Signature***

PROTOCOL SYNOPSIS

Protocol Title	Evaluation of Effectiveness and Safety of Radiesse (+) to Improve the Contour of Jawline by Adding Volume to the Jawline
Protocol Number	M900391004
Active Product	Radiesse (+)
Study Phase	Device Pre-Market - Pivotal study
Indication	Deep (subdermal and/or supraperiosteal) injection to improve the contour of jawline by adding volume to the jawline.
Number of Sites and Countries	This study will be conducted in the United States at up to 15 sites.
Number of Study Subjects	Approximately 180 subjects will be enrolled, with approximately 120 subjects in the treatment group and 60 subjects in the control/delayed-treatment group.
Objective(s)	Effectiveness • To demonstrate the effectiveness of Radiesse (+) following deep (subdermal and/or supraperiosteal) injection to improve the contour of jawline by adding volume to the jawline. Safety • Identification and description of adverse events (AEs) and serious adverse events (SAEs) during the course of the study. [redacted]
Key Endpoints	Primary • Comparison of the responder rate between the treatment group and the untreated control group at Week 12, according to the Merz Jawline Assessment Scale (MJAS) [redacted]. Treatment response is defined as ≥ 1-point improvement [redacted] Secondary • [redacted] FACE-Q satisfaction with lower face and jawline among treated subjects [redacted] as average percent change from baseline to Week 12. [redacted] • [redacted] Global Aesthetic Improvement Scale (GAIS) scores for treated subjects at Week 12, as completed by the treating investigator. [redacted] • [redacted] GAIS scores for treated subjects at Week 12, as completed by the subject. [redacted]

	[redacted] responder rates in the treatment group and the untreated control group at Week 12, according to the MJAS [redacted] Treatment response is defined as ≥ 1-point improvement compared to baseline. [redacted] Safety • [redacted] device- and/or injection-related AEs and SAEs observed during the study. [redacted]
Study Design Overview	This is a 60-week, prospective, multicenter, randomized, controlled, [redacted] pivotal clinical study to investigate the effectiveness and safety of Radiesse (+) to improve the contour of jawline by adding volume to the jawline. Approximately, 180 subjects with a grade of 2 or 3 on the MJAS will be enrolled into the study. [redacted] Enrolled subjects will be randomized (2:1 allocation ratio) to either receive treatment with Radiesse (+) or delayed treatment (i.e., untreated controls until primary endpoint assessment at Week 12 after which the controls are eligible for treatment and then followed for the remainder of the study). [redacted] Subjects who do not achieve a ≥ 1-point improvement on the MJAS [redacted] will be required to have a touch-up injection [redacted]. [redacted]

	[redacted] The primary effectiveness endpoint will be assessed 12 weeks post-treatment. Subjects randomized to the treatment group at baseline will have the option of a retreatment with Radiesse (+), upon agreement between the subject and the investigator, at Week 48 and will then be followed for an additional 12 weeks, for a total study duration of 60 weeks. Subjects who do not receive a retreatment at Week 48 will also be followed until Week 60. Subjects randomized to the control group at baseline will remain untreated until completion of the primary endpoint assessment at Week 12. After all primary endpoint assessments have been completed, these control subjects will be treated with Radiesse (+) (i.e., delayed treatment) and will then be followed for 48 weeks post-treatment. Subjects [redacted] may have a touch-up injection in one or both jawline(s) for further correction at the discretion of the treating investigator and the subject. Control subjects will not be offered retreatment. [redacted]
Key Inclusion/ Exclusion Criteria	To be eligible for the study, each subject must meet all of the following main inclusion criteria: [redacted] Has right and left jawline ratings of 2 or 3 (moderate or severe) on the MJA [redacted] [redacted] Has the same MJAS rating on both jawlines (i.e., jawlines are symmetrical). [redacted] Is ≥ 22 and ≤ 65 years of age. [redacted] Subjects meeting any of the following main exclusion criteria are not eligible to participate in the study: [redacted]

	[redacted] - Ever been treated with fat injections or permanent fillers (e.g., silicone, polymethylmethacrylate (PMMA)) in the lower face and/or jawline area or plans to receive such treatments during participation in the study. - Been treated with semi-permanent dermal fillers (e.g., poly L-lactic acid) in the lower face and/or jawline area in the past 5 years or plans to receive such treatments during participation in the study. [redacted]

Table of Contents

List of Abbreviations

Abbreviation/Term	Definition
ADE	Adverse device effect
AE	Adverse event
ASADE	Anticipated serious adverse device effect
ASAPS	American Society for Aesthetic Plastic Surgery
BMI	Body mass index
CFR	Code of Federal Regulations
[redacted]	
eCRF	Electronic case report form
ET	Early termination
FDA	Food and Drug Administration, US
FIRS	Functional Impairment Rating Scale
GAIS	Global Aesthetic Improvement Scale
GCP	Good clinical practice
HA	Hyaluronic acid
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent ethics committee
[redacted]	
IRB	Institutional review board
ITT	Intent-to-treat
[redacted]	
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	
MJAS	Merz Jawline Assessment Scale
MNAR	Missing not at random
MVTF	Missing value treated as failure
OC	Observed cases
OR	Odds ratio
PI	Principal investigator
PLLA	Poly L-lactic acid
PMMA	Polymethylmethacrylate
PP	Per protocol population
PT	Preferred term
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System organ class

Abbreviation/Term	Definition
[redacted]	
Tx	Treatment
UADE	Unanticipated adverse device effects
UV	Ultraviolet
[redacted]	
Wk	Week

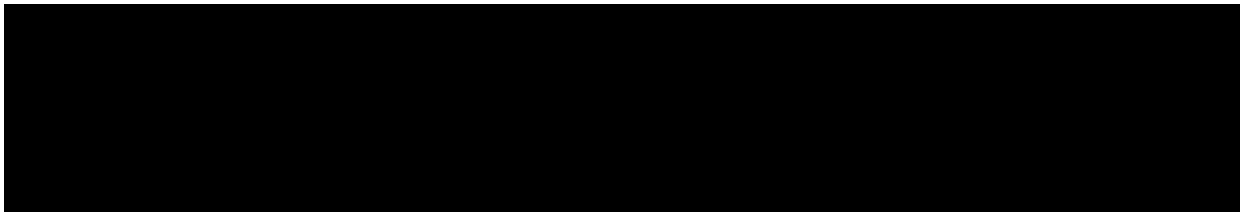
1 INTRODUCTION

1.1 Background and rationale

As part of the natural aging process, multiple factors lead to a decreased level of volume or noticeable contour of the jawline, including loss of bony structures, atrophy (volume loss) and descent of fat [1]. Volume loss in relation to the attachment points of the skin to the underlying superficial muscular aponeurotic system and/ or bone results in specific patterns of deflation, pseudoptosis, and shadowing – all of which characterize the aging face. As soft tissue fullness shifts from the upper face to the lower face, the aging face loses its youthful heart-shaped appearance and takes on a heavy, rectangular shape [2]. A surgical facelift is the standard treatment used to address these signs of aging and aid in redefining the jawline. However, it is, by definition, an invasive procedure and thus deemed less safe than other non-invasive alternatives, including radiofrequency/ ultrasonic skin tightening or the use of dermal fillers. As the demographics of aesthetic patients evolve, patients are seeking increasingly less invasive procedures with visible results and reduced downtime [3].

Dermal fillers have been identified as a treatment option to straighten and reestablish volume and contour of the jawline; fillers also provide an opportunity to enhance the size of the jaw by adding volume in the front at the chin and/or on the sides of the jaw. This enhancement can be achieved through filling volume and contour deficits, resulting in the enhancement of ptotic superficial compartments, repositioning of superficial fat, and/or tightening the skin around the jawline [3][4]. In order to reestablish or correct the mandibular angle and to achieve a satisfactory filling effect, a dermal filler with high elasticity and viscosity provides the best volumizing capacity [2].

Over a decade of clinical experience, multiple published reports have documented the use of dermal fillers, including Radiesse, to improve the jawline [4][5][6][7][8][9][10][11]. The available literature supports both the effectiveness and safety of Radiesse when used in the jawline, from the mentum through the mandibular angle. Multiple authors report favorable results at 6 and 12 months following placement of the product, noting both physician and patient satisfaction. A low number of procedure-related adverse events, such as pain, erythema, edema, and bruising, were reported – most of which were mild and resolved quickly without intervention. Overall, the safety profile of jawline treatment is favorable and comparable to other established treatment indications.



The published literature on the effectiveness and safety of Radiesse used in the jawline justifies the need for Merz North America, Inc. to conduct a large, robust randomized clinical trial among subjects who desire improvement of jawline volume and contour using Radiesse (+).

1.2 Potential benefits and risks

The potential benefit of Radiesse (+) when used in the jawline is to improve contour by adding volume to the jawline.

In a European observational study using calcium hydroxylapatite (CaHA) for the treatment of the jawline in a routine setting, the findings showed improvements in jawline contour compared with baseline, and these findings were statistically significant at each visit, with scores of 2.42 (moderate to severe sagging) at baseline, 1.02 (mild) at Day 30 ($p<0.0001$), 1.11 at Day 180 ($p<0.0001$), and 1.45 at Day 360 ($p<0.0015$). Overall, CaHA was found to be very effective for restoring jawline contour in clinical practice with high levels of physician and subject satisfaction [12].

The potential risks associated with the use of Radiesse (+) for deep (subdermal and/or supraperiosteal) injection into the jawline are similar to other lidocaine-containing, commercially available, cosmetic dermal fillers. No new risks have been identified for use of Radiesse (+) in the jawline, including product placement in deep (subdermal and/or supraperiosteal) injection planes.

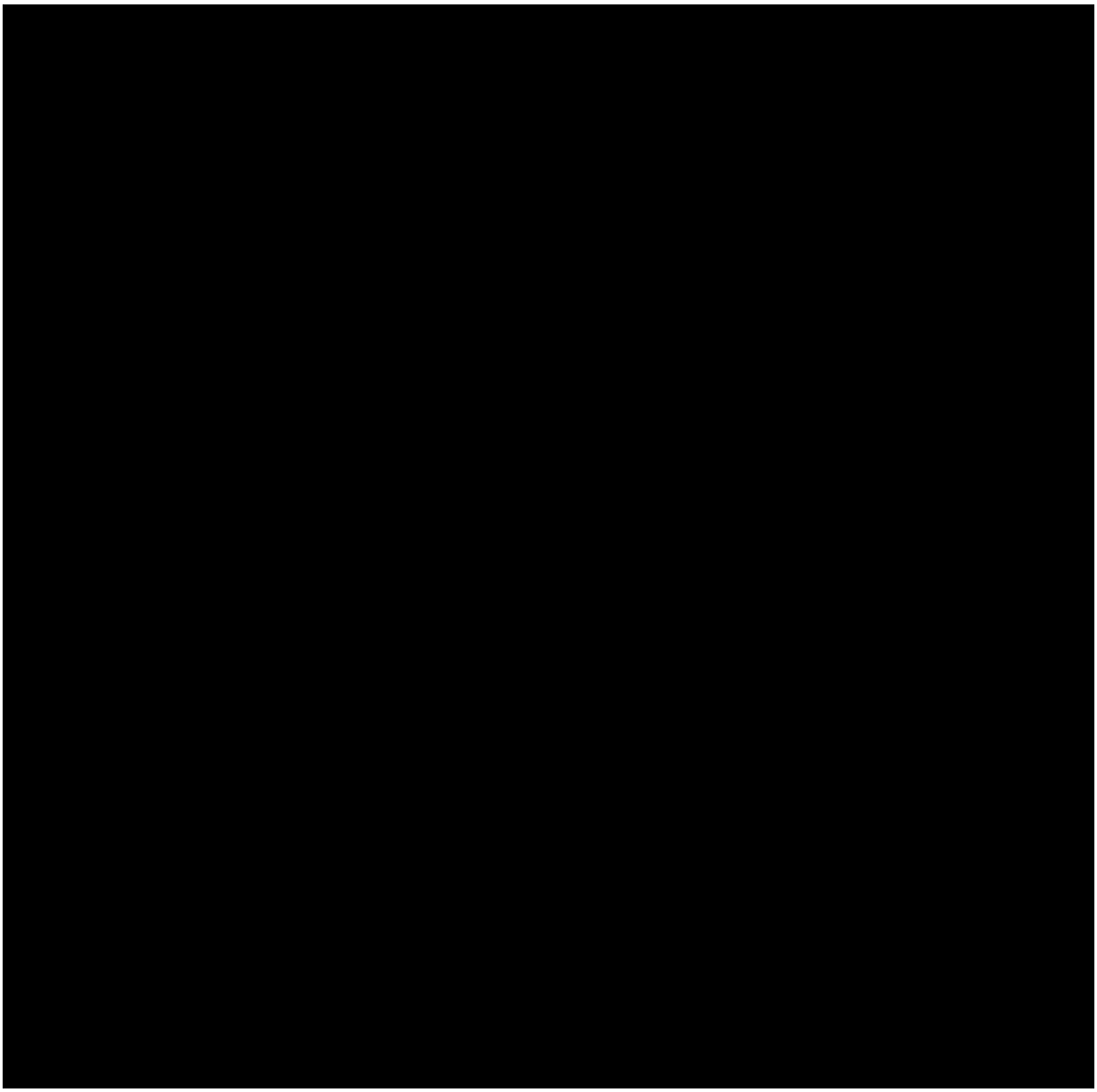
Potential treatment-site responses associated with Radiesse (+) consist mainly of ecchymosis, edema, erythema, pain, pruritus, discoloration, tenderness, mild infection, and the potential for nodule development. In previous studies, common injection-procedure reactions have generally resolved within seven days of treatment. Less common but possible side effects also include the following: migration, over-correction, reactivation of herpes, impact to jaw function, persistent swelling, persistent nodules, and/or serious infection.

An additional harm or risk, which is not an adverse event, includes disappointment due to lack of or reduced performance and/or undesirable aesthetic effect.

Rare but serious adverse events associated with the intravascular injection of soft-tissue fillers in the face have been reported and include: temporary or permanent vision impairment; blindness; cerebral ischemia or cerebral hemorrhage, leading to stroke; skin necrosis; abscesses; granulomas; and damage to the underlying facial structures. Unintentional implantation of Radiesse (+) into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction.

Lidocaine is commercially available and frequently used as a local and regional anesthetic agent. The potential benefit of lidocaine is the reduction of injection-related pain and discomfort. Potential side effects associated with lidocaine are a risk of participating in this study and include: lightheadedness; nervousness; apprehension; euphoria; confusion; dizziness; drowsiness; ringing noise in the ears; blurred or double vision; vomiting; sensations of heat, cold or numbness; twitching; tremors; convulsions; unconsciousness; respiratory depression and arrest; slow heartbeat; hypotension; and/or cardiovascular collapse, which may lead to cardiac arrest. However, these side effects are unlikely to occur at the low doses of lidocaine being used in this investigation. [redacted]

[redacted]



2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Effectiveness

The primary objective of the study is to demonstrate the effectiveness of Radiesse (+) following deep (subdermal and/or supraperiosteal) injection to improve the contour of jawline by adding volume to the jawline.

2.1.2 Safety

The safety objectives include the identification and description of adverse events (AEs) and serious adverse events (SAEs) during the course of the study. [redacted]

2.2 Endpoints

2.2.1 Primary endpoint

Comparison of the responder rate between the treatment group and the untreated control group at Week 12, according to the Merz Jawline Assessment Scale (MJAS) [redacted]. Treatment response is defined as ≥ 1-point improvement [redacted].

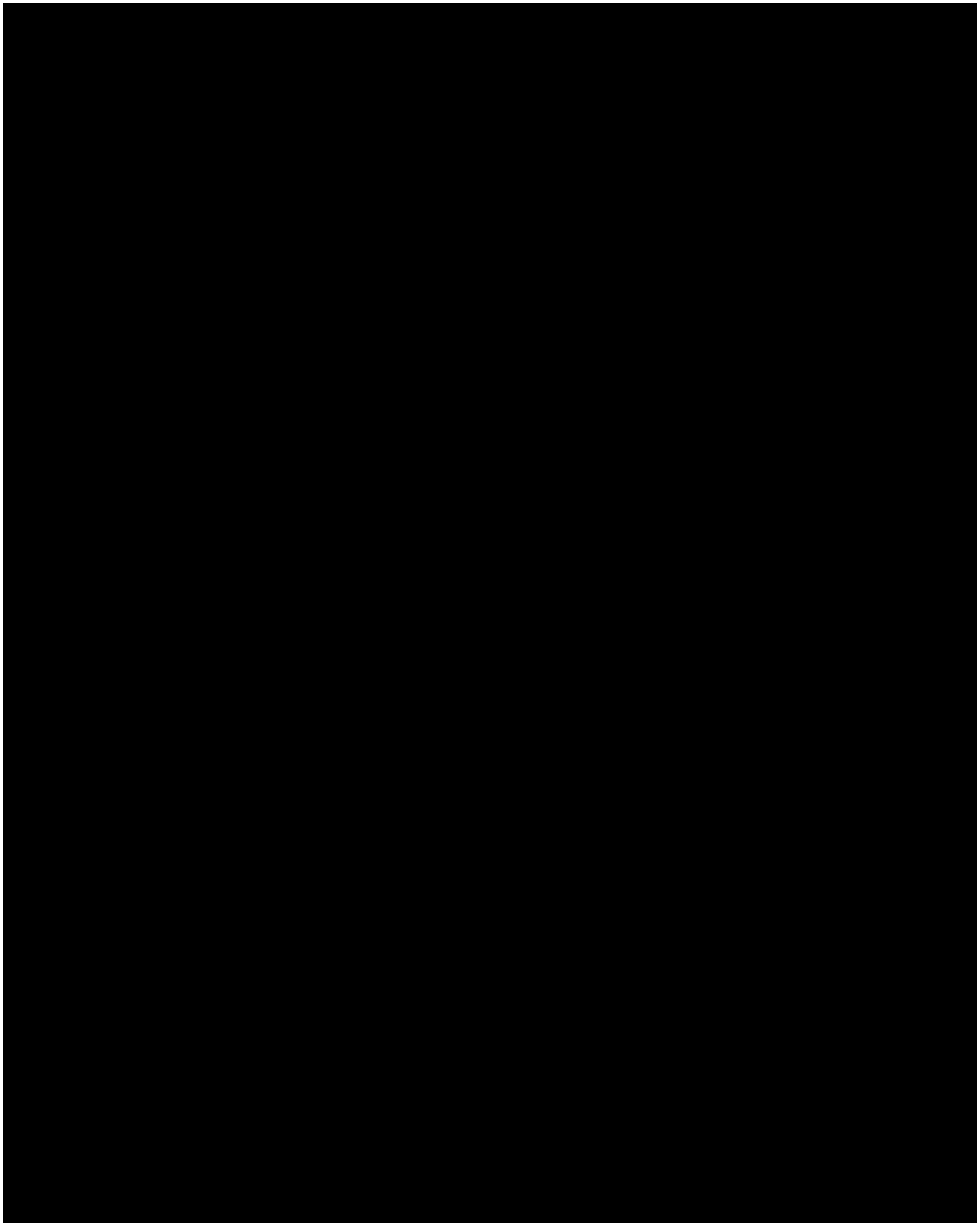
2.2.2 Secondary endpoints

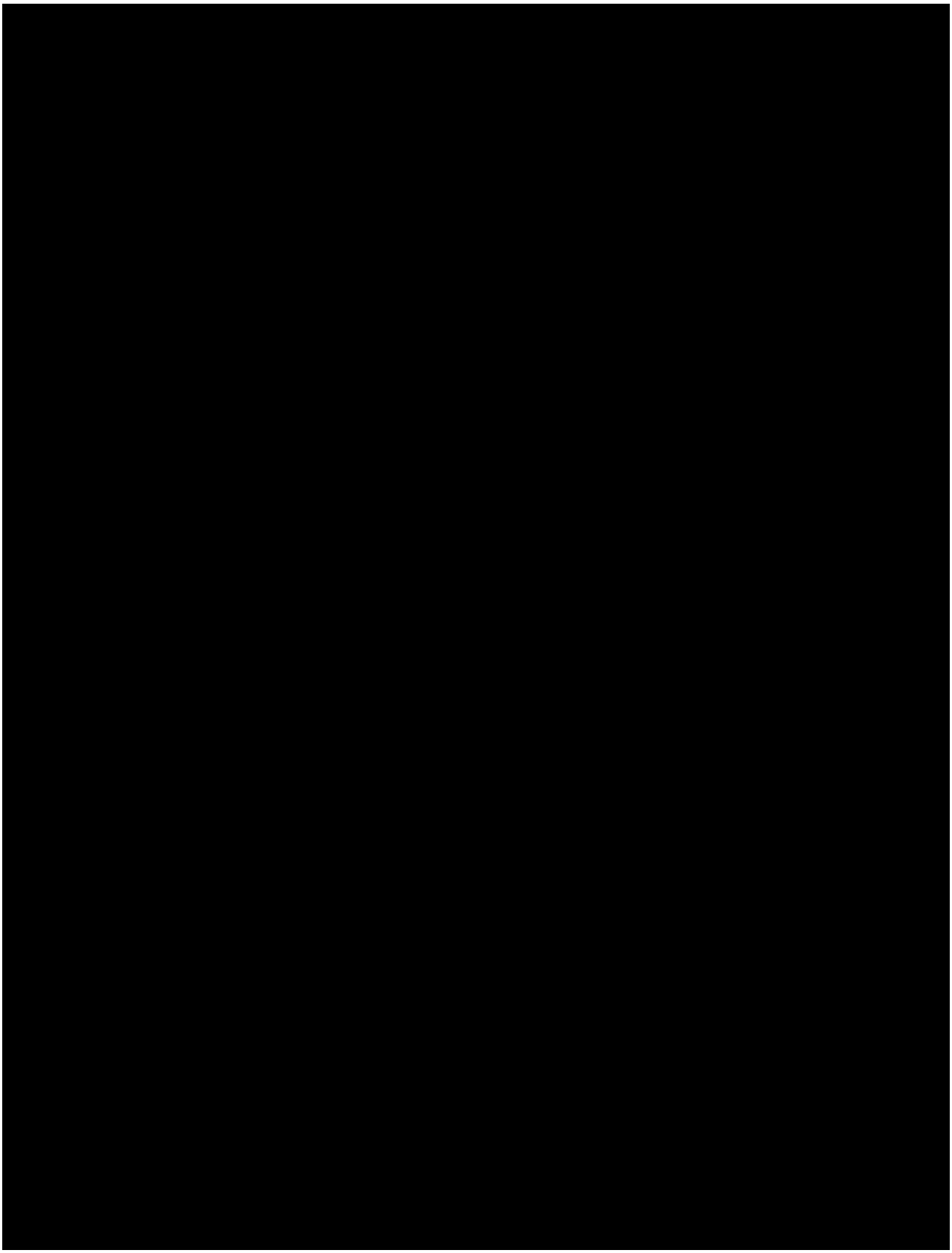
- [redacted] FACE-Q satisfaction of the lower face and jawline for treated subjects [redacted] as average percent change from baseline to Week 12. [redacted]
- [redacted] Global Aesthetic Improvement Scale (GAIS) scores for treated subjects at Week 12, as completed by the treating investigator [redacted]
- [redacted] GAIS scores for treated subjects at Week 12, as completed by the subject. [redacted]

[redacted] responder rates in the treatment group and the untreated control group at Week 12, according to the MJA [redacted] Treatment response is defined as ≥ 1-point improvement [redacted].

2.2.3 [redacted]

[redacted]





[redacted]

2.2.4 Safety endpoints

2.2.4.1 Primary safety endpoints

- Incidence and nature of device- and/or injection-related AEs and SAEs observed during the study.

[redacted]

2.2.4.2 [redacted]

[redacted]

3 INVESTIGATIONAL PLAN

3.1 Overview of study design

This is a 60-week, prospective, multicenter, randomized, controlled, [redacted] pivotal clinical study to investigate the effectiveness and safety of Radiesse (+) to improve the contour of jawline by adding volume to the jawline. Approximately 180 subjects with a grade of 2 or 3 on the MJAS will be enrolled into the study. [redacted] Subjects will be enrolled at up to 15 sites in the United States. [redacted]

At the baseline visit, enrolled subjects will be randomized (2:1 allocation ratio) to either treatment with Radiesse (+) or to untreated control. Those allocated to the control group at baseline will remain untreated until assessment of the primary effectiveness endpoint at Week 12; these subjects will then be eligible for delayed treatment with Radiesse (+) in the jawline at Week 12 and will be followed for 48 weeks post-treatment. [redacted] Subjects who did not achieve a ≥ 1-point improvement on the MJAS [redacted] will be required to have a touch-up injection [redacted]. [redacted]

Subjects [redacted] ay have a touch-up on one or both jawline(s) for further correction at the discretion of the treating investigator and the subject. The primary effectiveness endpoint will be assessed 12 weeks post-treatment. Subjects randomized to the treatment group at baseline will have the option for retreatment with Radiesse (+), upon agreement between the subject and the investigator, at Week 48 and will then be followed for an

additional 12 weeks, for a total study duration of 60 weeks. Subjects who do not receive a retreatment at Week 48 will also be followed until Week 60.

Subjects randomized to the control group at baseline will remain untreated until completion of the primary endpoint assessment at Week 12. After all primary endpoint assessments have been completed these control subjects will be treated with Radiesse (+) (i.e., delayed treatment) and will then be followed 48 weeks post-treatment. Subjects who did not achieve a ≥ 1-point improvement on the MJAS [redacted] will be required to have a touch-up injection [redacted]

Subjects who achieve a ≥ 1-point improvement on the MJAS [redacted] ay have a touch-up [redacted] at the discretion of the treating investigator and the subject. Control subjects will not be offered retreatment.

[redacted]

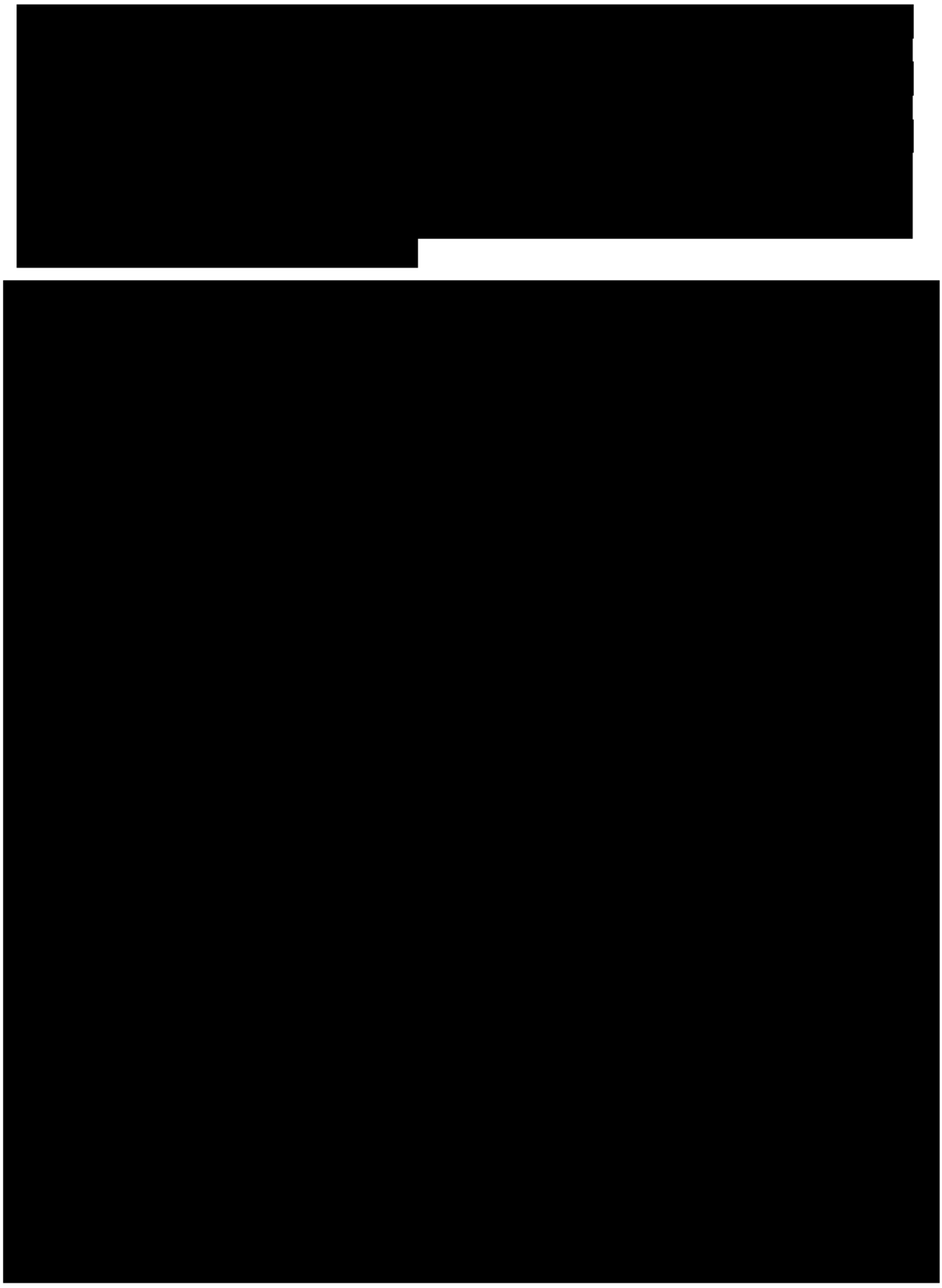
[redacted]

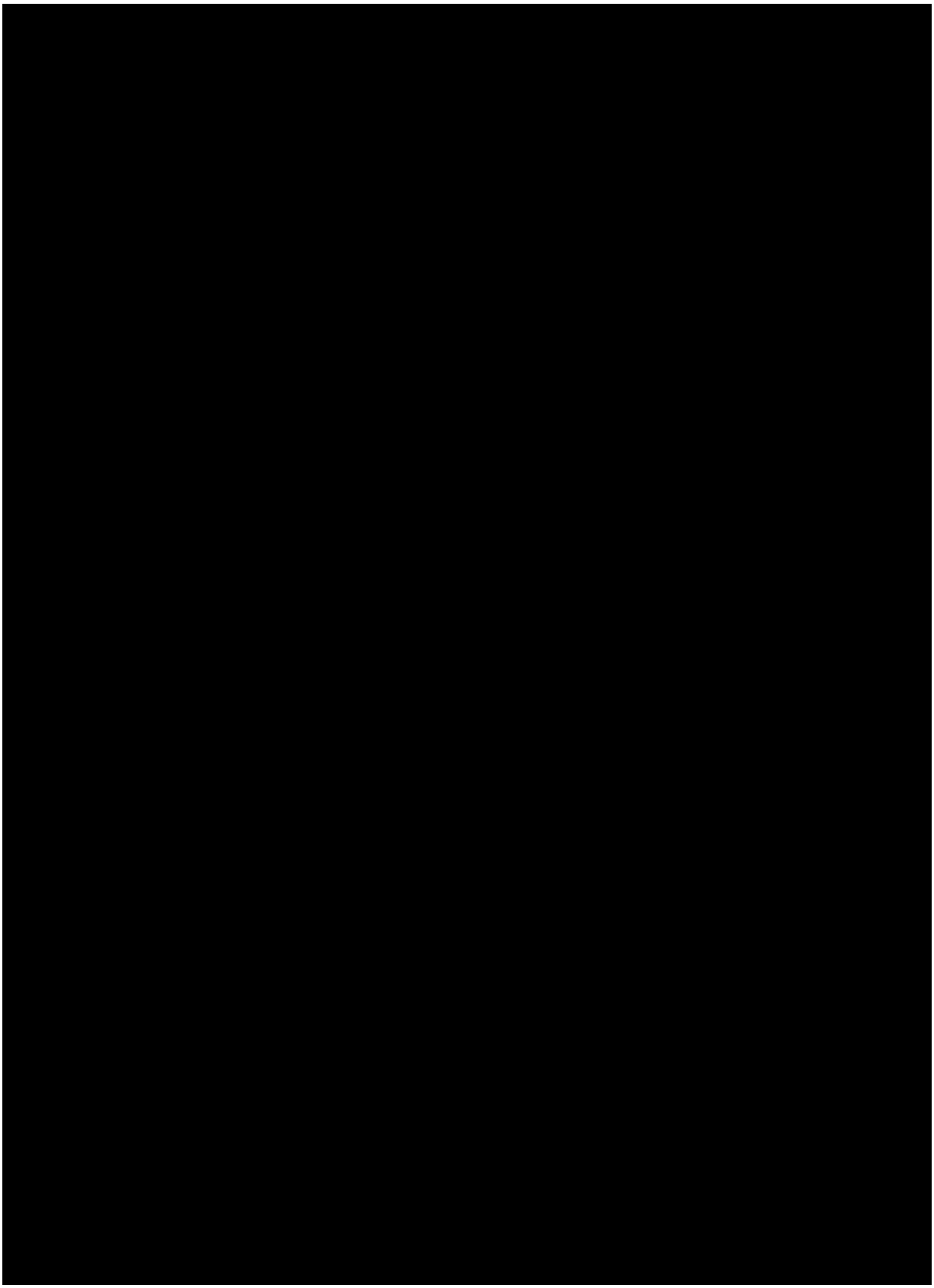
3.2 Study assessments and definitions

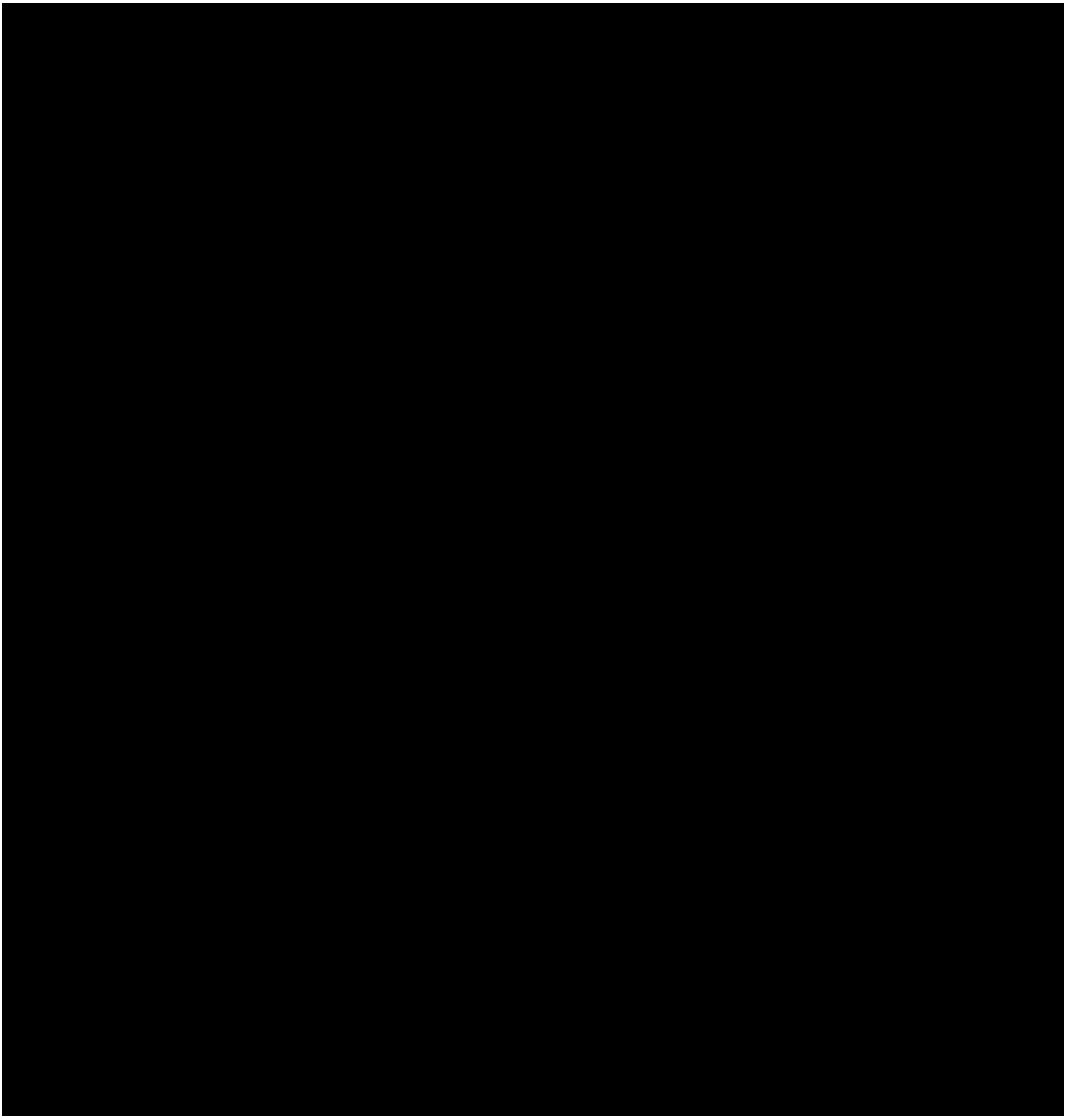
3.2.1 Effectiveness assessments

3.2.1.1 Merz Jawline Assessment Scale (MJAS)

As individuals age, the loss of volume and the descent of the jowl and facial soft tissue creates a defined, contour irregularity with formation of a post-jowl and possibly a pre-jowl defect. The MJAS [redacted] was developed to grade the loss of volume and disruption of contour in the jawline region. The 5-point MJAS illustrates the progression of severity [redacted]







3.2.1.3 Treating Investigator Global Aesthetic Improvement Scale (GAIS)

The treating investigator will use the GAIS to assess global aesthetic improvement among treated subjects .

Refer to the study endpoints (see Section 2.2) and visit schedules (see Sections 5.1.1 and 5.1.2) for additional information regarding the GAIS assessments and the associated reference time points.

3.2.1.4 Subject Global Aesthetic Improvement Scale (GAIS)

Treated subjects will evaluate their overall aesthetic improvement on the subject GAIS

[redacted]

3.2.1.5 FACE-Q Instruments [redacted]

Treated subjects will evaluate the treatment outcome using [redacted] FACE-Q instruments. [redacted] With respect to the jawline treatment within this

study, [redacted] FACE-Q assessments will be completed by all subjects at baseline and at multiple study visits [redacted]

[redacted]

[redacted]

3.2.2 [redacted]

[redacted]

3.2.3 Safety assessments

3.2.3.1 72-hour follow-up phone call

Subjects in the treatment group will receive a follow-up phone call 72 hours (± 1 day) after the initial treatment at baseline and after the Week 48 retreatment, if applicable. Subjects in the control/delayed-treatment group will receive a follow-up phone call 72 hours (± 1 day) after the initial treatment at Week 12.

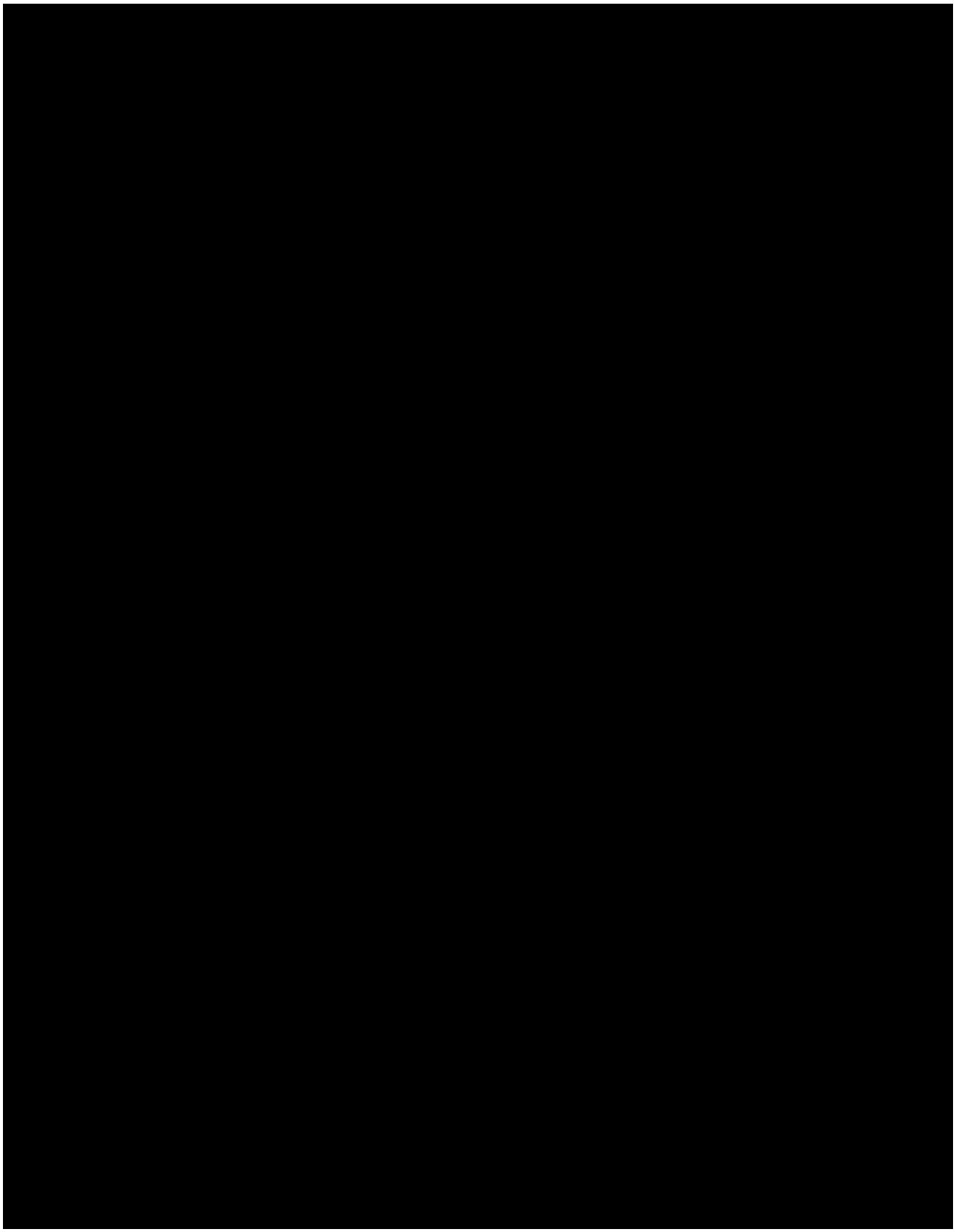
During this phone call, study personnel will discuss and record any changes in concomitant medications/procedures and confirm that the subject remains compliant with any applicable study restrictions. [redacted] f there are any safety concerns that would necessitate an unscheduled visit to the site, this visit should be scheduled during the phone call.

The subjects should also be asked if they are experiencing any new or unusual symptoms related to a potential vascular occlusion (e.g., signs of a stroke, changes in vision, tissue necrosis) as noted in the Study Information Guide for Subjects. If the subjects report any signs or symptoms of a stroke, they must call 911 immediately. If the subjects report any changes in vision associated with vascular occlusion, they must contact the site identified Ophthalmologist prior to contacting the site investigator. If any other symptoms related to a potential vascular occlusion are reported by the subjects, they should be assessed, and referred for immediate medical treatment as deemed necessary per best medical practices. If any change to vision is reported during the 72-hour follow-up phone call, the subject may be asked to come in immediately for an examination or referred immediately to an ophthalmologist for further evaluation.

3.2.3.2 Adverse events [redacted]

All AEs observed by study subjects, investigators, or other study staff from the time of informed consent through the last study follow-up visit will be recorded. Events will be recorded regardless of causality.

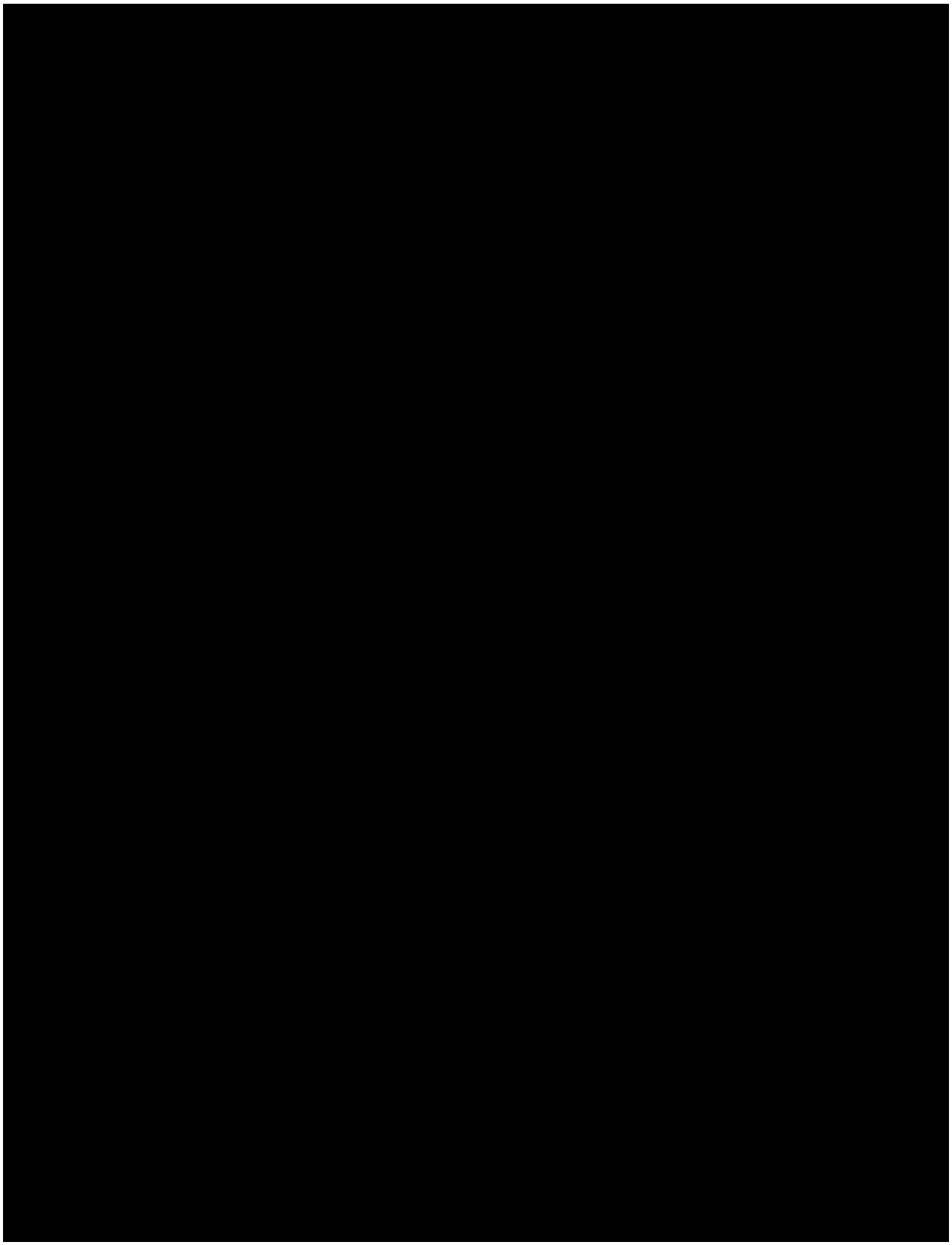
[redacted]

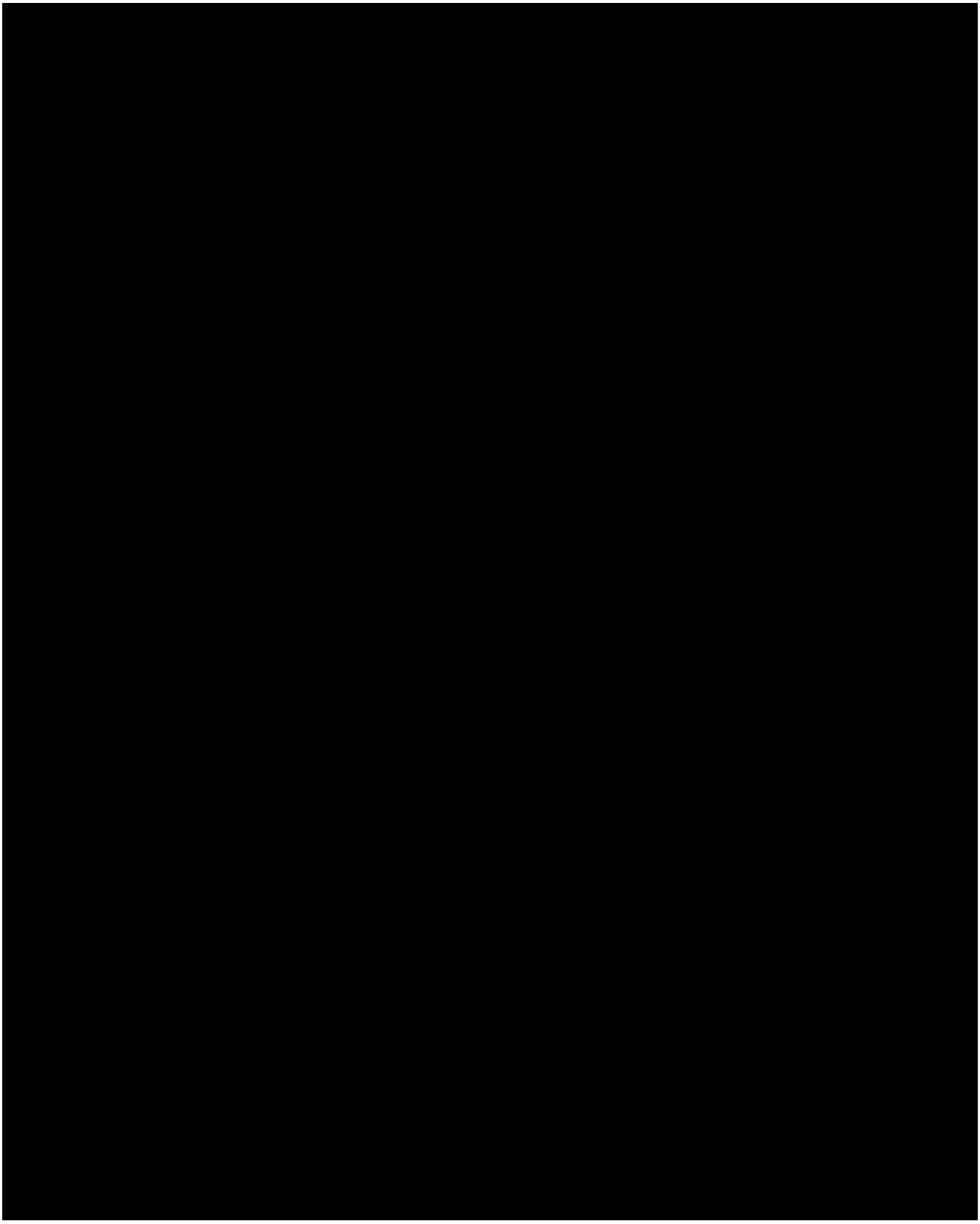


Subjects must be informed that, at any time over the study interval, if they experience any signs or symptoms of a stroke, they must call 911 immediately. If they experience any changes in vision associated with vascular occlusion, they must contact the site identified Ophthalmologist prior to contacting the site investigator. If any other new or unusual symptoms related to a potential vascular occlusion (e.g., tissue necrosis), they must seek immediate medical attention and notify the study doctor immediately. The study doctor must refer the subject to a specialist if additional medical attention is deemed necessary. A list of symptoms related to potential vascular occlusion will be provided to all subjects in a separate Study Safety Information Guide and in the Informed Consent Form (ICF) for the subject's reference.

If any change to vision is reported over the study interval (e.g., during a telephone follow-up, scheduled or unscheduled visit), the subject may be asked to come in immediately for an examination or referred immediately to an ophthalmologist for further evaluation.

Additional information on safety assessments and procedures is discussed in Section 7.





3.2.4 Definitions

3.2.4.1 Subject enrollment and randomization

Subjects are considered to be enrolled after they sign informed consent, meet all eligibility criteria, and are randomized in the electronic randomization system.

Screen failures are defined in Section 4.5.

3.2.4.2 Subject completion

Subjects are considered to have completed the study if they are randomized and completed all visits defined in the Schedule of Events (see Section 5.1 and Appendices 11.1 and 11.2).

3.2.4.3 End of study

The end of the study is defined as when the last subject completes the last visit and the database is locked.

3.2.5 Duration of study

Subjects are screened and enrolled at the baseline visit. For subjects randomized to the treatment group, treatment will occur at the baseline visit. For subjects randomized to the control/delayed-treatment group, treatment will occur at Week 12. The time from the baseline visit to the end of study is 60 weeks (± 10 days) for all subjects.

4 STUDY POPULATION AND RESTRICTIONS

4.1 Number of subjects and sites

Approximately 180 subjects will be enrolled, with approximately 120 subjects in the treatment group and 60 subjects in the control/delayed-treatment group. Subjects will be enrolled from up to 15 sites in the United States. [redacted]

4.2 Inclusion criteria

In order to be eligible for study participation, each subject must meet all of the following criteria:

- Has right and left jawline ratings of 2 or 3 (moderate or severe) on the [redacted]
- Has the same MJAS rating on both jawlines (i.e., jawlines are symmetrical).

[redacted]

- Is ≥ 22 and ≤ 65 years of age.

[redacted]

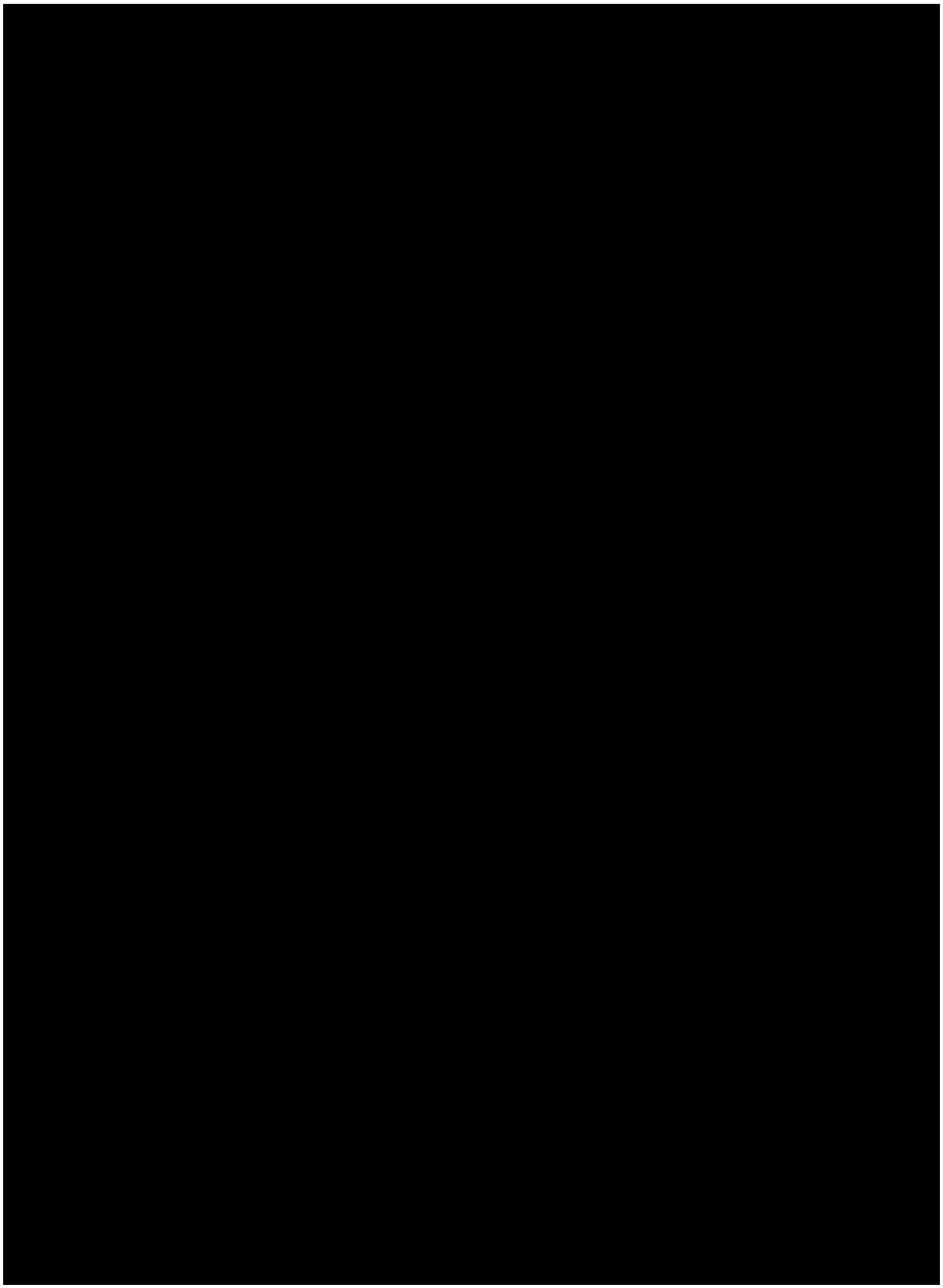
4.3 Exclusion criteria

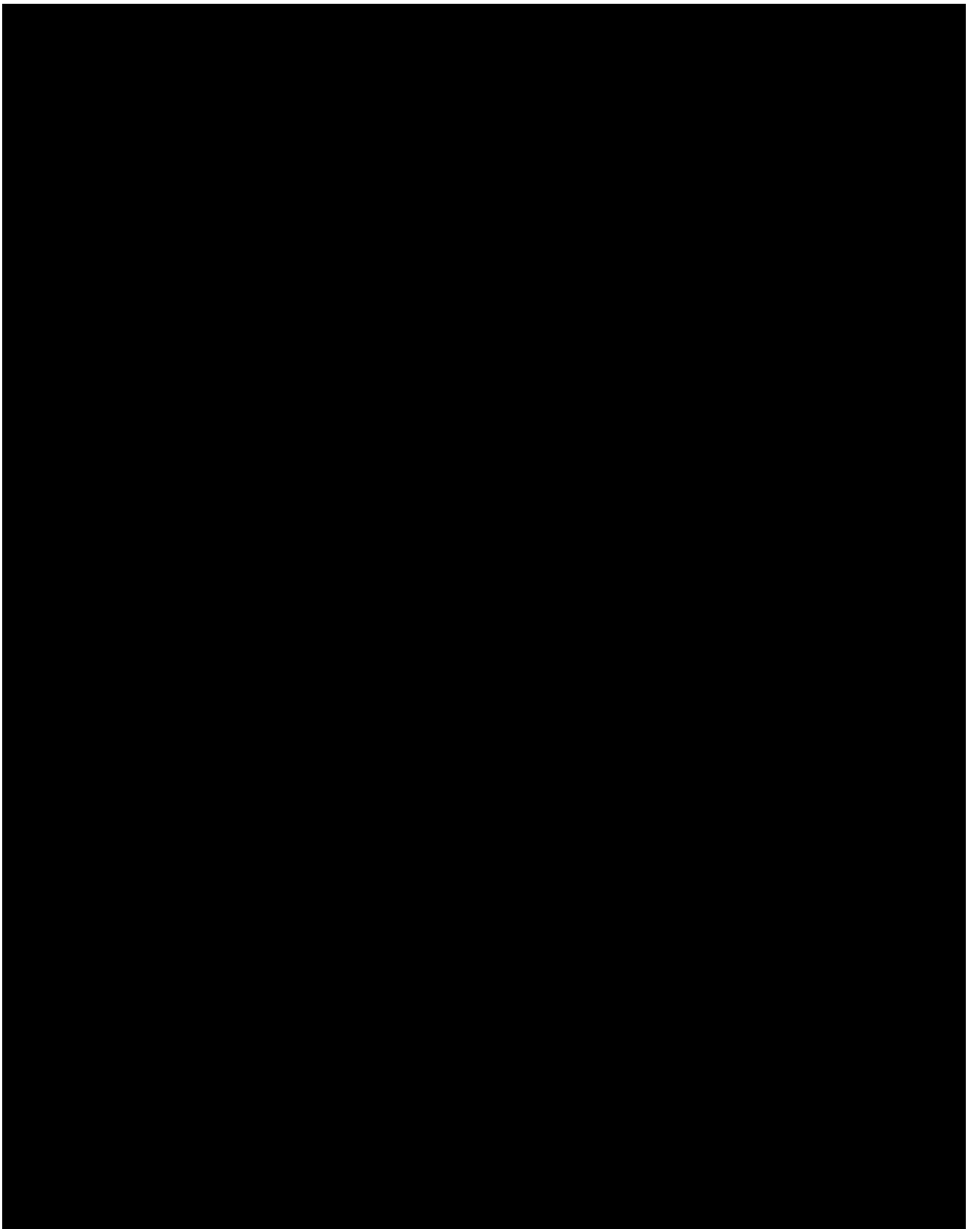
Subjects meeting any of the following criteria are not eligible to participate in the study:

[redacted]

- Ever been treated with fat injections or permanent fillers (e.g., silicone, poly-methylmethacrylate (PMMA)) in the lower face and/or jawline area or plans to receive such treatments during participation in the study.
- Been treated with semi-permanent dermal fillers (e.g., poly L-lactic acid (PLLA)) in the lower face and/or jawline area in the past 5 years or plans to receive such treatments during participation in the study.

[redacted]





[redacted]

4.5 Screen failures

Subjects who sign informed consent but who do not meet eligibility criteria or who withdraw consent prior to being randomized in the electronic randomization system will be defined as screen failures. The investigator will maintain all source documentation for all subjects who are considered screen failures. Minimal information will be collected in the electronic data capture system for screen failures, such as date of informed consent, demographics, and reason for screen failure.

Individuals who do not meet the eligibility criteria for participation in this study (screen failure) may not be rescreened.

4.6 Subject withdrawal criteria

A subject may withdraw from the study at any time at his/her own request without prejudice to future medical care. Subjects may also be withdrawn at any time at the discretion of the investigator for safety, compliance, or administrative reasons.

If a subject does not attend a required study visit, the following actions will be taken:

- The site will attempt to contact the subject at least twice and reschedule the missed visit as soon as possible. Every effort to regain contact with the subject will be made (e.g., telephone contact on different dates/times, registered mail). All contact attempts will be documented.
- If attempts to contact the subject are not successful, then the subject will be considered lost to follow-up and withdrawn from the study. The reason for early withdrawal will be documented in the eCRFs.

5 STUDY PROCEDURES

5.1 Schedule of events by visit

The Schedule of Events, for both treatment and control/delayed-treatment groups, are presented in Appendices 11.1 and 11.2, respectively.

5.1.1 Schedule of events by visit for subjects randomized to the treatment group only

Visit 1 – Day 1/Baseline (Screening/Enrollment/Treatment)

The following procedures will be performed at baseline for subjects randomized to the **treatment group**:

Pre-Treatment Assessments:

- Obtain written informed consent. A subject must be informed of the study requirements, including the risks and benefits of participation. An IEC/IRB-approved informed consent must be signed and dated by the subject prior to any study-related activities or procedures being performed, including discontinuation of any prohibited medications.
- Record demographics/medical history [redacted].
- Record height and weight for BMI.
- Review and record concomitant medications/procedures.
- Perform urine pregnancy test (if female of childbearing potential). Negative test required prior to randomization.
- [redacted] JAS assessments [redacted]
- Administer FACE-Q assessments to subject.

[redacted]

- Treating physician confirms that the subject meets all eligibility criteria prior to randomization.

Randomization:

- Randomize subject to either the treatment group or control/delayed-treatment group [redacted].

[redacted]

Injection (initial treatment):

- Administer treatment injections (see Section 6.3.1 for injection instructions).
- Review and record any AEs (since the time of signing the Informed Consent Form (ICF).

[redacted]

- Schedule 72-hour follow-up phone call.

Follow-up phone call (72-hours post-treatment): Day 4 (± 1 day)

- Discuss and record any changes in concomitant medications/procedures. Confirm subject remains compliant with any applicable study restrictions.
- Discuss and record any AEs.
- If subject reports a safety concern, arrange an unscheduled visit.

[redacted]

- Ask whether the subject is experiencing any new or unusual symptoms related to a vascular occlusion (e.g., signs of a stroke, changes in vision, tissue necrosis) as noted in the Study Safety Information Guide for Subjects.
- If the subject reports any such symptoms, they should be assessed and referred for immediate medical treatment as deemed necessary per best medical practices. If any change to vision is reported, the subject may be asked to come in immediately for an examination or referred immediately to an ophthalmologist for further evaluation.

Visit 2 (Week 2 post-treatment): Day 14 (± 3 days)

- Review and record changes in any concomitant medications/procedures. Confirm subject remains compliant with any applicable study restrictions.
- Review and record any AEs.

[redacted]

[redacted]

Visit 3 (Week 4 post-treatment): Day 29 (+ 3 days)

[redacted]

- Review and record changes in any concomitant medications/procedures. Confirm subject remains compliant with any applicable study restrictions.
- Review and record any AEs.

[redacted]

- [redacted] MJAS assessment.

[redacted]

- Have subject complete the Subject GAIS.

[redacted]

- Administer FACE-Q assessments to subject.

[redacted]

- Administer Treating Investigator GAIS.

[redacted]

Injection (only for subjects who receive a touch-up treatment):

- Perform urine pregnancy test (if female of childbearing potential).
- Administer touch-up injection as follows:
  - If a subject does not achieve a ≥ 1-point improvement [redacted]

[redacted], a touch-up will be required to achieve optimal correction.

- If a subject achieves a ≥ 1-point improvement on the MJAS [redacted] a touch-up may be don [redacted]

[redacted]

Visit 4 (Week 6 post-treatment): Day 42 (± 3 days)

***Note*: This visit is only for subjects who received a touch-up at Week 4.**

- Review and record changes in any concomitant medications/procedures. Confirm subject remains compliant with any applicable study restrictions.
- Review and record any AEs.

[redacted]

Visit 5 (Week 12 post-treatment): Day 84 (± 3 days)

- Review and record changes in concomitant medications/procedures. Confirm subject remains compliant with any applicable study restrictions.
- Review and record any AEs.

[redacted]

- Record height and weight for BMI.
- [redacted] MJAS assessment.

[redacted]

- Have subject complete the Subject GAIS.

[redacted]

- Administer FACE-Q assessments to subject.

[redacted]

- Administer Treating Investigator GAIS.

[redacted]

Visit 6 (Week 24 post-treatment): Day 168 (± 10 days)

- Review and record changes in concomitant medications/procedures. Confirm subject remains compliant with any applicable study restrictions.
- Review and record any AEs.
- [redacted] MJAS assessment.

[redacted]

- Administer FACE-Q assessments to subject.

[redacted]

- Administer Treating Investigator GAIS.

[redacted]

Visit 7 (Week 36 post-treatment): Day 252 (± 10 days)

- Review and record changes in concomitant medications/procedures. Confirm subject remains compliant with any applicable study restrictions.
- Review and record any AEs.
- [redacted] MJAS assessment.

[redacted]

- Have subject complete the Subject GAIS.

[redacted]

- Administer FACE-Q assessments to subject.

[redacted]

- Administer Treating Investigator GAIS.

[redacted]

Visit 8 (Week 48 post-treatment): Day 336 (± 10 days)

[redacted]

- Review and record changes in concomitant medications/procedures. Confirm subject remains compliant with any applicable study restrictions.
- Review and record any AEs.
- [redacted] MJAS assessment.

[redacted]

- Have subject complete the Subject GAIS.

[redacted]

- Administer FACE-Q assessments to subject.

[redacted]

- Administer Treating Investigator GAIS.

[redacted]

Injection (only for subjects who receive retreatment):

- Perform urine pregnancy test (if female of childbearing potential).
- Retreatment injections may be administered [redacted] at the discretion of the treating investigator [redacted].

[redacted]

- Schedule 72-hour follow-up phone call.

Follow-up phone call (72-hours post retreatment): Day 339 (± 1 day)

Note: This phone call is only for subjects who received a retreatment at Week 48.

- Discuss and record any changes in concomitant medications/procedures. Confirm subject remains compliant with any applicable study restrictions.
- Discuss and record any AEs.
- If subject reports a safety concern, arrange an unscheduled visit.

[redacted]

- Ask whether the subject is experiencing any new or unusual symptoms related to a vascular occlusion (e.g., signs of a stroke, changes in vision, tissue necrosis) as noted in the Study Information Guide for Subjects.
- If the subject reports any such symptoms, they should be assessed and referred for immediate medical treatment as deemed necessary per best medical practices. If any change to vision is reported, the subject may be asked to come in immediately for an examination or referred immediately to an ophthalmologist for further evaluation.

Visit 9 (Week 50 post-treatment): Day 350 (± 3 days)

Note: This visit is only for subjects who received a retreatment at Week 48.

- Review and record changes in any concomitant medications/procedures. Confirm subject remains compliant with any applicable study restrictions.
- Review and record any AEs.

[redacted]

[redacted]

Visit 10 (Week 60 post-treatment)/ End of Study/Early Termination: Day 420 (± 10 days)

- Review and record changes in concomitant medications/procedures. Confirm subject remains compliant with any applicable study restrictions.
- Review and record any AEs.
- Record height and weight for BMI.
- Perform urine pregnancy test (if female of childbearing potential).
- [redacted] MJAS assessment.

[redacted]

- Have subject complete the Subject GAIS.

[redacted]

- Administer FACE-Q assessments to subject.

[redacted]

- Administer Treating Investigator GAIS.

[redacted]

5.1.2 Schedule of events by visit for the control/delayed-treatment group

Visit 1 – Pre-Treatment Baseline (Screening/Enrollment)

The following procedures will be performed at baseline for subjects randomized to the **control/delayed-treatment group**:

- Obtain written informed consent. A subject must be informed of the study requirements, including the risks and benefits of participation. An IEC/IRB-

approved informed consent must be signed and dated by the subject prior to any study-related activities or procedures being performed, including discontinuation of any prohibited medications.

- Record demographics/medical history [redacted].
- Record height and weight for BMI.
- Review and record concomitant medications/procedures.
- Review and record any AEs (since the time of signing the ICF).
- Perform urine pregnancy test (if female of childbearing potential). Negative test required prior to randomization.
- [redacted] MJAS assessments. [redacted]
- Administer FACE-Q assessments to subject.
- [redacted]
- Treating physician confirms that the subject meets all eligibility criteria prior to randomization.

Randomization:

- Randomize subject to either the treatment group or control/delayed-treatment group [redacted].

[redacted]

Visit 2 (Follow-up; 4 weeks post enrollment) (± 3 days)

- Review and record changes in any concomitant medications/procedures. Confirm subject remains compliant with any applicable study restrictions.
- Review and record any AEs (since the time of signing the ICF).

[redacted]

Visit 3 – Week 12 (Treatment): Day 1/Baseline (+3 days)

[redacted]

- Review and record changes in concomitant medications/procedures. Confirm subject remains compliant with any applicable study restrictions.
- Perform urine pregnancy test (if female of childbearing potential). Negative test required prior to treatment.
- Record height and weight for BMI.
- [redacted] MJAS assessment [redacted]

[redacted]

- Administer FACE-Q assessments to subject.

[redacted]

Injection (delayed treatment):

- Administer treatment injections [redacted]
- Review and record any AEs.

[redacted]

- Schedule 72-hour follow-up phone call.

Follow-up phone call (72 hours post-treatment): Day 4 (± 1 day)

- Discuss and record changes in concomitant medications/procedures. Confirm subject remains compliant with any applicable study restrictions.
- Discuss and record any AEs.
- If subject reports a safety concern, arrange an unscheduled visit.

[redacted]

- Ask whether the subject is experiencing any new or unusual symptoms related to a vascular occlusion (e.g., signs of a stroke, changes in vision, tissue necrosis) as noted in the Study Information Guide for Subjects.

- If the subject reports any such symptoms, they should be assessed and referred for immediate medical treatment as deemed necessary per best medical practices. If any change to vision is reported, the subject may be asked to come in immediately for an examination or referred immediately to an ophthalmologist for further evaluation.

Visit 4 - Week 14 (2 weeks post-treatment): Day 14 (± 3 days)

- Review and record changes in any concomitant medications/procedures. Confirm subject remains compliant with any applicable study restrictions.
- Review and record any AEs.

[redacted]

Visit 5 – Week 16 (4 weeks post-treatment): Day 29 (+ 3 days)

[redacted]

- Review and record changes in any concomitant medications/procedures. Confirm subject remains compliant with any applicable study restrictions.
- Review and record any AEs.

[redacted]

- [redacted] MJAS assessment.

[redacted]

- Have subject complete the Subject GAIS.

[redacted]

- Administer FACE-Q assessments to subject.

[redacted]

[redacted]

- Administer Treating Investigator GAIS.

[redacted]

Injection (only for subjects who receive a touch-up treatment):

- Perform urine pregnancy test (if female of childbearing potential).
- Administer touch-up injection as follows:
  - If a subject does not achieve a ≥ 1-point improvement [redacted], a touch-up will be required [redacted].
  - If a subject achieves a ≥ 1-point improvement on the MJA [redacted] a touch-up may be don [redacted]

[redacted]

Visit 6- Week 18 (6 weeks post-treatment): Day 42 (± 3 days)

***Note*: This visit is only for subjects who received a touch-up at Visit 5.**

- Review and record changes in any concomitant medications/procedures. Confirm subject remains compliant with any applicable study restrictions.
- Review and record any AEs.

[redacted]

Visit 7- Week 24 (12 weeks post-treatment): Day 84 (± 3 days)

- Review and record changes in concomitant medications/procedures. Confirm subject remains compliant with any applicable study restrictions.

- Review and record any AEs.
- Record height and weight for BMI.
- MJAS assessment.
- Have subject complete the Subject GAIS.
- Administer FACE-Q assessments to subject.
- Administer Treating Investigator GAIS.

Visit 8- Week 36 (24 weeks post-treatment): Day 168 (± 10 days)

- Review and record changes in concomitant medications/procedures. Confirm subject remains compliant with any applicable study restrictions.
- Review and record any AEs.
- MJAS assessment.
- Have subject complete the Subject GAIS.

- Administer FACE-Q assessments to subject.

[redacted]

- Administer Treating Investigator GAIS.

[redacted]

Visit 9- Week 48 (36 weeks post-treatment): Day 252 (± 10 days)

- Review and record changes in concomitant medications/procedures. Confirm subject remains compliant with any applicable study restrictions.
- Review and record any AEs.
- [redacted] MJAS assessment.

[redacted]

- Have subject complete the Subject GAIS.

[redacted]

- Administer FACE-Q assessments to subject.

[redacted]

- Administer Treating Investigator GAIS.

[redacted]

Visit 10- Week 60 (48 weeks post-treatment)/End of Study/Early Termination: Day 336 (± 10 days)

- Review and record changes in concomitant medications/procedures. Confirm subject remains compliant with any applicable study restrictions.
- Review and record any AEs.
- Record height and weight for BMI.
- Perform urine pregnancy test (if female of childbearing potential).
- [redacted] MJAS assessment.

[redacted]

- Have subject complete the Subject GAIS.

[redacted]

- Administer FACE-Q assessments to subject.

[redacted]

- Administer Treating Investigator GAIS.

[redacted]

5.1.3 Scheduled visits

All scheduled visits and applicable study assessments must occur as noted in Section 5.1 and the Schedule of Events table (Appendices 11.1 and 11.2).

5.1.4 Unscheduled visits

To ensure subject safety, any subject who requires additional follow-up during the study for safety (that does not fall on a scheduled study visit) should be seen for an unscheduled visit and the following safety assessments completed: review of adverse events/ concomitant medications/procedures, [redacted] if applicable. An unscheduled for a reason other than safety, will be done at the discretion of the investigator and documented appropriately.

5.2 Stopping rules

5.2.1 Criteria for treatment discontinuation

If study treatment is discontinued at any time during the treatment administration, the investigator will record the reason for treatment discontinuation in the study records. The

investigator may request that a subject discontinuing treatment continue to participate in the study and complete all remaining visits and assessments. If a subject declines to continue study participation, the investigator will make every effort to perform the appropriate end of study assessments specified in the Schedule of Events (Section 5.1 and Appendices 11.1 and 11.2).

5.2.2 Premature suspension or termination of study

Should the investigator, the sponsor, the Food and Drug Administration (FDA), or local regulatory authorities become aware of conditions arising during the conduct of this study that may warrant the cessation of the study, such action may be taken. Prior to such action, consultation between the sponsor, the investigator, and, as appropriate, the FDA and/or local regulatory authorities will occur.

In the case of a reported vascular embolic event leading to skin necrosis, vision loss, or stroke, a root-cause investigation will be conducted to determine the cause, the outcome of the event and status of subject. The investigator and Merz will conduct a thorough evaluation of the event. Merz will then immediately make a determination if the study should be suspended.

Reasons for the premature suspension or termination of the study include, but are not limited to, the following:

- Determination of a potential safety risk to subjects;
- Inadequate subject enrollment;
- Decision by the IEC/IRB to suspend or terminate approval/favorable opinion for the study;
- Sponsor decision; and/or
- Other.

In the event of premature study suspension or termination for safety reasons, the sponsor will inform all investigators and relevant regulatory authorities promptly of the study suspension/termination and reason for the action. The investigator will conduct site closure activities in accordance with all applicable sponsor and local/international guidelines and regulations.

5.2.3 Study site discontinuation

Study participation by individual sites may be discontinued by the sponsor for any of the reasons listed in Section 5.2.2. Additional reasons for the premature discontinuation of study sites include, but are not limited to, the following:

- Investigator request;
- Serious or persistent noncompliance with the protocol, local regulations and/or GCP;
- Failure to accrue subjects at an acceptable rate;
- Ethical issues; and/or
- Other.

In the event of study site discontinuation, the sponsor will provide to the study site written notification documenting the reason for discontinuation. The investigator will conduct site closure activities in accordance with all applicable sponsor and local/international guidelines and regulations.

5.2.4 Discontinuation criteria for a subject

Each subject will be followed to the end of the study, or/if when the sponsor decides to terminate the study, whichever comes first. The only reasons a subject will not be followed for all scheduled visits are withdrawal of consent or loss to follow-up (e.g., moving away from study site; unresponsive to attempts to contact the subject).

If a subject withdraws consent to continue in the study, the investigator should make every attempt to complete the End of study/early termination visit. If a non-serious AE is unresolved at the time of the subject's early termination visit, an effort will be made to follow-up until the AE is resolved or stabilized, the subject is lost to follow-up, or there is some other resolution of this event. The investigator should make every attempt to follow all SAEs/SADEs to resolution. Information on pregnancy and the outcome for any woman who becomes pregnant during the study will be collected. Additional information on subject withdrawal criteria is provided in Section 4.6.

5.2.5 Provision of care for subjects after study discontinuation

The investigator is responsible for ensuring the adequate and safe medical care of subjects during the study. After completion of the study, the sponsor will follow all applicable local or international regulations and guidelines with regard to follow-up care for subjects. The investigator will ensure that appropriate consideration is given to a subject's post-study care.

6 STUDY DEVICE AND TREATMENT OF SUBJECTS

6.1 Description of the study device

Radiesse (+) injectable implant is a sterile, non-pyrogenic, semi-solid whose principle component is synthetic calcium hydroxylapatite suspended in a gel carrier of glycerin, sodium carboxymethylcellulose, 0.3% lidocaine hydrochloride, sodium phosphate, and sterile water for injection. The gel is dissipated *in vivo* and replaced with soft tissue growth, while the calcium hydroxylapatite remains at the site of injection. The result is long-term, yet non-permanent, restoration and augmentation. The Radiesse (+) Premarket Approval (PMA) supplement submission (P050052/S052) was approved in January 30, 2015 by the FDA and by Health Canada (License 95140) on May 15, 2015.

[redacted]

6.2 Usage

Radiesse (+) should be used in the jawline treatment region according to the information and injection instructions presented in Section 6.3.

[redacted]

6.3 Study treatment

All protocol-specific criteria for the administration of study treatment must be met and documented prior to administration of any study treatment. All device administration (injection) will be performed on site by the treating investigator. Subjects will not be dispensed any investigational material. Any noncompliant subject or site may be discontinued from the study (see Section 5.2).

6.3.1 Planned treatment procedure and administration

Approximately 120 subjects will be randomized to receive Radiesse (+) and 60 subjects will serve as the controls/delayed treatment. Subjects will be randomized using a 2:1 allocation ratio for treatment to control. [redacted]

[redacted]

Subjects randomized to treatment at baseline will receive an initial Radiesse (+) injection in both jawlines.

Subjects who do not achieve a ≥ 1-point improvement on the MJAS [redacted] will be required to have a touch-up injection [redacted] the treating investigator will be responsible for establishing whether the ≥ 1-point MJAS improvement threshold is me [redacted]

In addition, subjects who achieve a ≥ 1-point improvement on the MJAS [redacted] may have a touch-up [redacted] at the discretion of the treating investigator and the subject. These subjects are also eligible for retreatment at Week 48 if the subject and investigator are in agreement that retreatment is needed. [redacted]

After completion of all study assessments associated with the primary endpoint at Week 12, subjects randomized to the control group will be treated with Radiesse (+) (i.e., delayed treatment).

Subjects who did not achieve a ≥ 1-point improvement on the MJAS [redacted] will be required to have a touch-up injection [redacted] the treating investigator will be responsible for establishing whether the ≥ 1-point MJAS improvement threshold is met [redacted].

In addition, subjects who achieve a ≥ 1-point improvement on the MJAS [redacted] may have a touch-up [redacted] at the discretion of the treating investigator and the subject. [redacted]

[redacted]

6.3.1.1 *Jawline region and treatment area*

All study injections will be performed by the site's principal investigator (PI). The PI is also described as the treating investigator in this document.

[redacted]
Observed adverse events will also be recorded.

[redacted]

The jaw region is defined as follows:

- Anterior to posterior boundaries: from the anterior aspect of the pre-jowl sulcus to just anterior to the earlobe.
- Superior to inferior boundaries: upper palpable bony boundary to the lower palpable bony boundary of the mandible.

[redacted] he treatment area does not include lips, oral commissures, or the mental area.

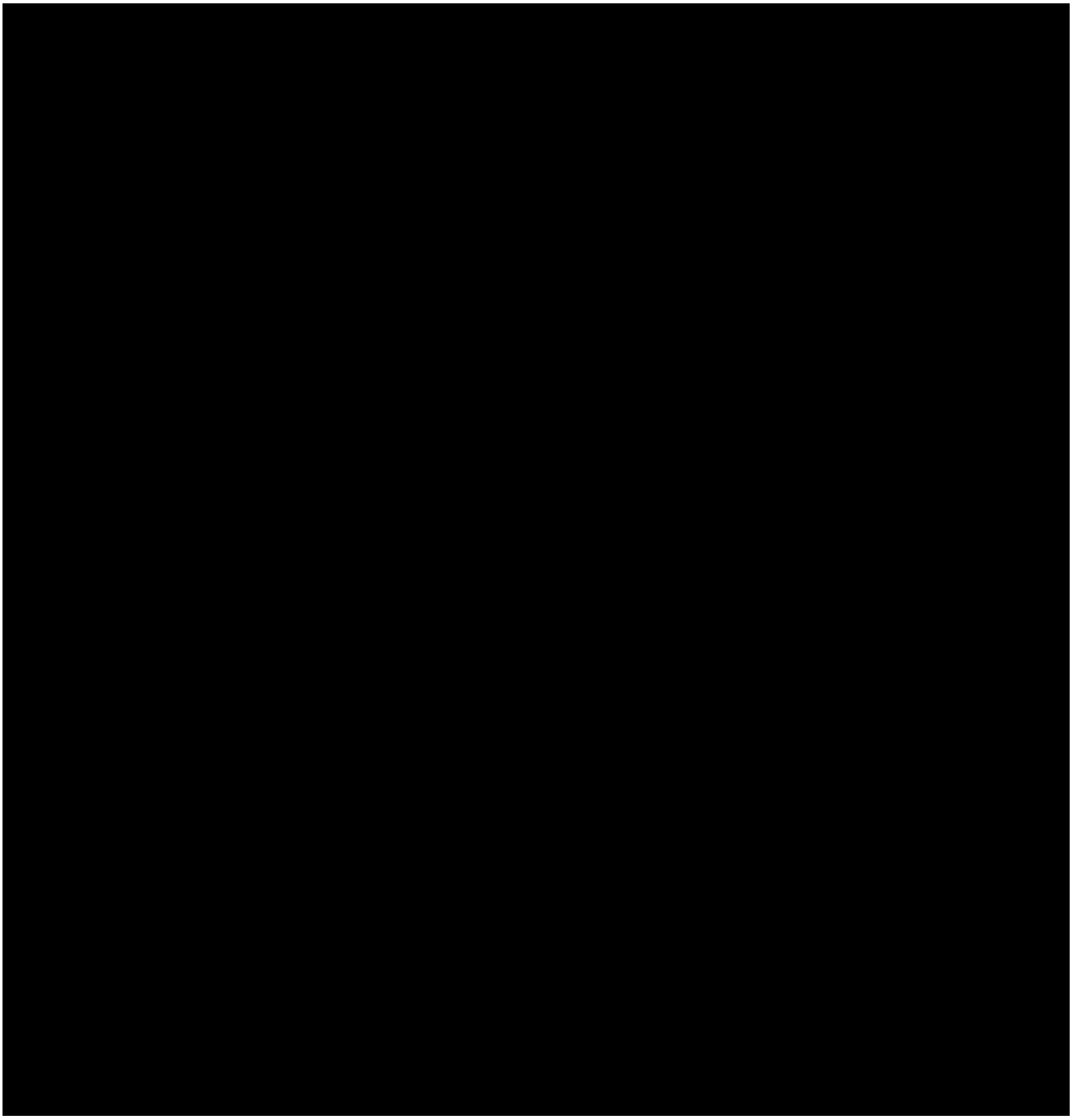
[redacted]

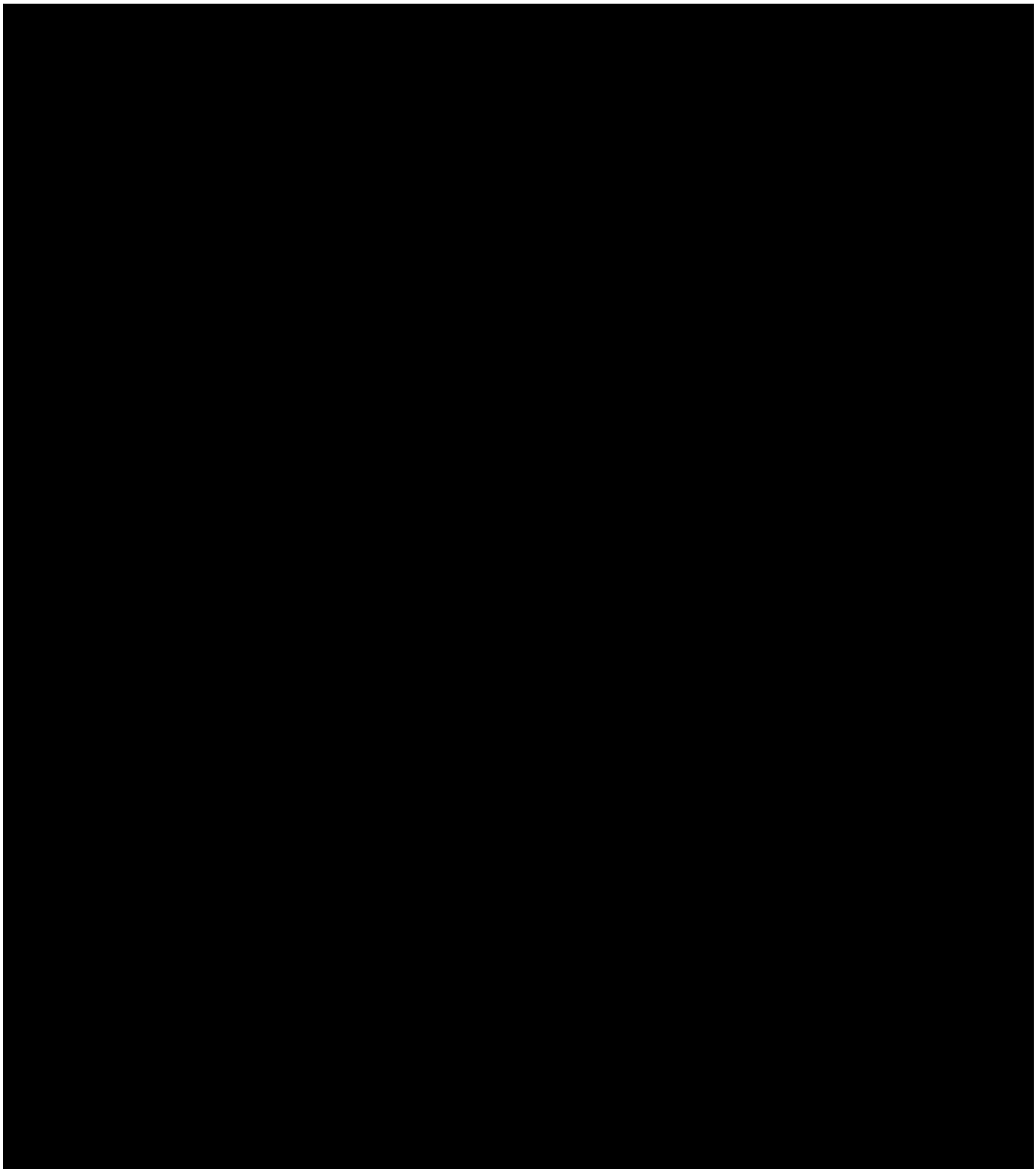
6.3.1.2 *Injection procedure*

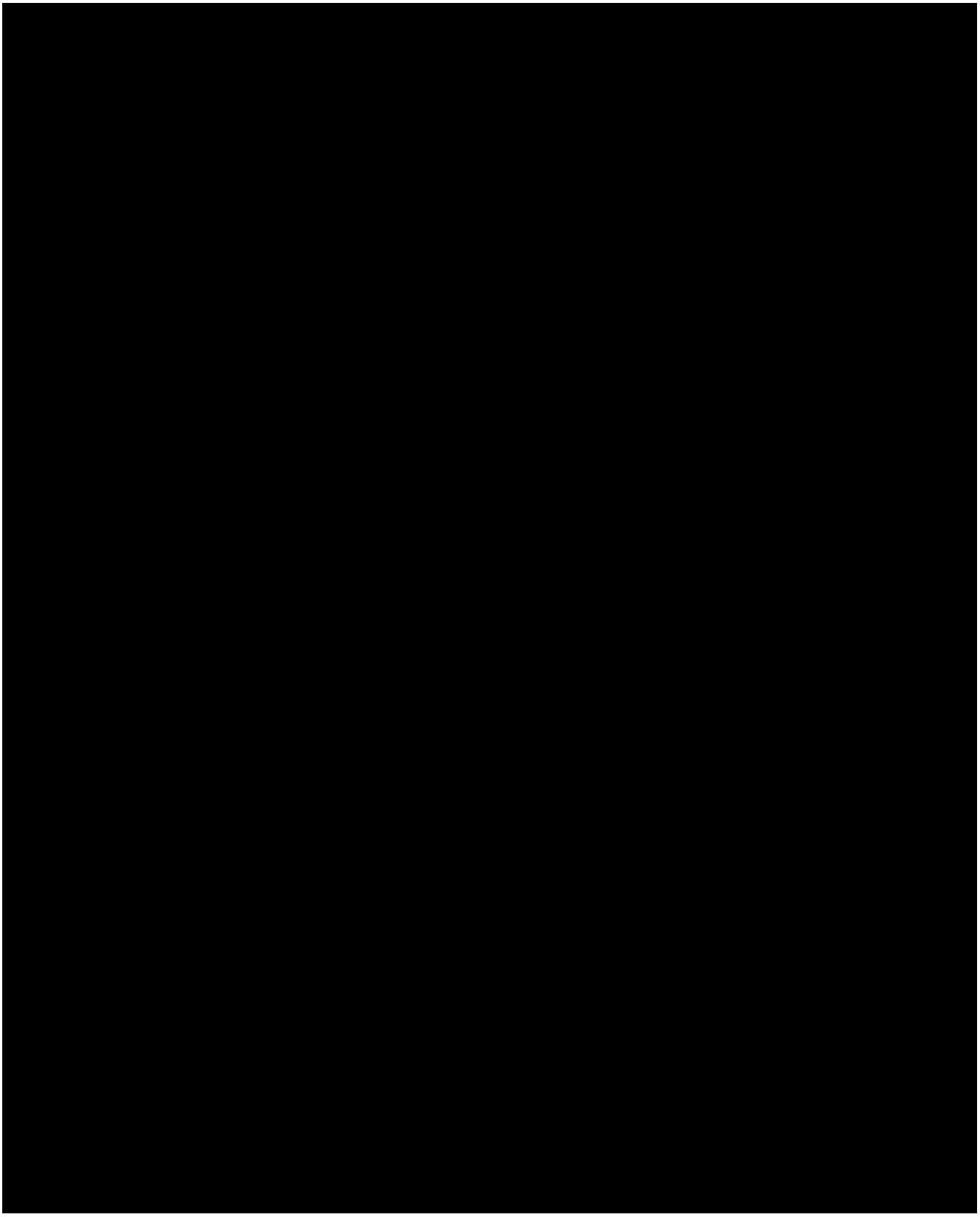
Injection occurs for the treatment-group subjects at baseline, at Week 4 (for touch-up, if necessary), at Week 48 if a retreatment is agreed upon between the treating investigator and subject. Control-group subjects will be treated at Week 12 (delayed treatment) and at Week 16 (for touch-up, if necessary).

Note: Subjects will be randomized to treatment or control during the baseline visit. [redacted]

[redacted]







[redacted]

6.4 [redacted]

[redacted]

6.5 Packaging of treatment supplies

Radiesse (+) kits will be provided by the study sponsor. The sponsor will package study materials according to applicable regulatory requirements. The sponsor will provide all pertinent labeling information as well as a description of the specific device-packaging conditions.

[redacted]

6.6 Receipt, storage, dispensing, and return/disposal

Upon receipt, the site personnel will verify the contents of all study supplies received and promptly notify the appropriate contacts of any discrepancies or damages. The investigator is responsible for ensuring that an accurate record of inventory is maintained. The investigator will keep a current record of the study product delivery to the study site, inventory, and dispensing, and this record will be made available to the sponsor upon request. Study sites will be queried about any discrepancies.

All study devices must be stored in a secure, environmentally controlled, monitored area in accordance with the labelled storage conditions.

Only authorized study personnel may supply, dispense, and/or administer study treatment, and only subjects enrolled in the study may receive study treatment. The investigator is responsible for maintaining a current, accurate record of all study treatment dispensation.

Any used syringes of Radiesse (+) [redacted] should be discarded per the appropriate handling and disposal procedures at the site. Any unused/unopened product, [redacted] and/or outer packaging [redacted] should be retained so the monitor can perform device-accountability procedures.

At the end of the study and after verification of study device accountability, it is the investigator's responsibility to return or destroy all unused study supplies, as directed by the sponsor. Appropriate records of return or disposal must be maintained for accountability purposes. For the return of supplies, the following address shall be used:

To: Merz North America, Inc.
Attn: Receiving
1340 Grandview Parkway, Suite 2
Sturtevant, WI 53177-1261

[redacted]

All study-accountability procedures must be completed before the study is considered complete.

6.7 Accountability procedures

The sponsor will provide the investigator with all necessary study supplies. Accountability for study supplies at the study site is the responsibility of the investigator.

Access to investigational medical devices will be controlled, and the investigational medical devices will be used only in the clinical investigation and according to the clinical study protocol. The sponsor will keep records to document the physical location of all investigational medical devices from shipment to the investigation sites until return or disposal. The PI or an authorized designee will keep records documenting the receipt, use, return, and disposal of the investigational medical devices, which will include the following:

1. The date of receipt.
2. Identification of each investigational medical device (batch number/serial number or unique code).
3. The expiry date (if applicable).
4. The date of use.
5. Subject identification number.
6. Date on which the investigational medical device was returned.
7. The date of return of unused, expired, or malfunctioning investigational medical devices (if applicable).

6.8 [redacted]

[redacted]

7 SAFETY AND ADVERSE EVENTS

7.1 Definitions

7.1.1 Investigational medical device

An investigational medical device is defined as a medical device being assessed for safety or effectiveness in a clinical investigation. This definition includes medical devices already on the market that are being evaluated for new intended uses, new populations, new materials, and/or design changes. In this protocol, the terms "investigational medical device" and "investigational device" are used interchangeably.

7.1.2 Adverse event (AE)

An AE is defined as an untoward medical occurrence, which does not necessarily have a causal relationship to the investigational medical device. An AE can therefore be any unfavorable, unintended, or untoward clinical sign (including an abnormal laboratory finding), unintended disease or injury, and/or a symptom or disease temporally associated with the use of the investigational medical device, whether or not considered related to that investigational medical device.

- Definition includes events related to the investigational medical device.
- Definition includes events related to the procedures involved.
- AEs may include, but are not limited to, subjective or objective symptoms spontaneously offered by the subject, uncovered by review of concomitant medications or therapies, and/or observed by the investigation-site staff. The investigator will determine the description (sign, symptom, or diagnosis), onset, outcome, seriousness, severity, cause, and action taken for any event.

In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE, rather than the procedure itself.

Pre-existing conditions that do not worsen during the course of the clinical investigation are not reportable as AEs. Recurring symptoms associated with pre-existing conditions are not considered AEs unless they have a clinically significant increase in severity and/or frequency. To determine whether a condition has worsened, it is compared to the condition of the subject at screening.

Elective treatments planned before screening, which are documented in the subject's source data, are not typically regarded as AEs. The subject's course must be monitored

until the event has subsided, or in a case of permanent impairment, until the event stabilizes and the overall clinical outcome has been ascertained.

7.1.3 Adverse device effect (ADE)

An ADE is defined as an adverse event related to the use of an investigational medical device.

- Definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.
- Definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

7.1.4 Serious adverse events (SAE)

A SAE is any adverse event that results in:

- Death
- Life-threatening illness or injury (or places the subject at immediate risk of death from this event as it occurred) or
- Hospitalization or prolonged hospitalization, or
- Disability/incapacity or permanent impairment of a body structure or a body function, or
- An important medical event for which medical or surgical intervention is required to prevent life-threatening illness or injury, or permanent impairment of a body structure or body function, or
- Fetal distress, fetal death, or a congenital abnormality/birth defect.

  Note: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. Pre-planned admissions must be recorded in the subject's source documentation.

If a subject experiences an additional AE that prolongs a pre-planned hospitalization, this event is considered to be an SAE and should be reported as an SAE.

In the case of a fatality, the primary cause of death (the event leading to death) is considered the SAE, and death is considered the outcome. "Fatal" will be recorded as the outcome. Death may be reported as an SAE only when no cause of death can be determined (e.g., sudden death, unexplained death).

7.1.5 Serious ADE (SADE)

A SADE is defined as a serious adverse event related to the use of an investigational medical device.

- Definition includes SAEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation or any malfunction of the investigational medical device.
- Definition includes any SAE resulting from use error or from intentional misuse of the investigational medical device.

7.1.6 Unanticipated adverse device effect (UADE)

A UADE is defined as:

- Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), risk analysis report, or product labeling, or
- Any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

7.1.7 Anticipated serious adverse device effect (ASADE)

An ASADE is defined as:

Any serious adverse effect which by its nature, severity, or degree of incidence or outcome has been identified in the risk analysis report or product labeling.

7.1.8 [redacted]

[redacted]

7.1.9 Device deficiency

A device deficiency is defined as any inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling.

Device deficiencies include events that did not lead to an adverse event, but could have led to a medical occurrence if either suitable action had not been taken, if intervention had not been made, or if circumstances had been less fortunate.

All device deficiencies shall be documented on a Device Technical Complaint Form and reported by the PI throughout the clinical investigation and appropriately managed by Merz North America, Inc. in accordance with Sections 7.2.4.3 and 7.3.

7.1.10 Malfunction

Malfunction is defined as failure of an investigational medical device to perform in accordance with its intended purpose, when used in accordance with the instructions for use or the protocol.

All malfunctions shall be documented on a Device Technical Complaint Form and reported by the PI throughout the clinical investigation and appropriately managed by Merz North America, Inc. in accordance with Sections 7.2.4.3 and 7.3.

7.2 Reporting requirements

7.2.1 Determining severity/intensity

The investigator is required to grade the severity/intensity of each AE. The clinical severity/intensity of an AE will be classified as follows:

- ***Mild:*** Signs and symptoms that can be easily tolerated. Symptoms can be ignored and disappear when the subject is distracted.
- ***Moderate:*** Signs and symptoms that cause discomfort and interfere with normal functioning, but are tolerable. They cannot be ignored and do not disappear when the subject is distracted.
- ***Severe:*** Signs and symptoms that affect usual daily activity and incapacitate the subject, thereby interrupting his/her daily activities.

The definitions above are difficult to apply for some data (e.g., clinically relevant laboratory values that are documented and evaluated on the AE eCRF). In such situations, the investigator should exercise medical and scientific judgment.

7.2.2 Determining causal relationship

An AE is considered to be "related" to the investigational medical device if a causal relationship between the investigational medical device and the AE is at least a reasonable possibility (i.e., the relationship cannot be ruled out).

Note: The expression "reasonable causal relationship" is intended to convey that there are facts (evidence) or arguments to suggest a causal relationship. Otherwise, the relationship should be considered as "not related".

7.2.3 Determining outcome

The reportable outcomes and/or sequelae of an AE may include the following:

- Recovered/resolved
- Recovering/resolving
- Not recovered/not resolved
- Recovered/resolved with sequelae
- Fatal
- Unknown

Note: If a subject experiences more than one AE, only the AE leading to death will be attributed with a "fatal" outcome.

7.2.4 Procedures for reporting specific events

7.2.4.1 Adverse event (AE) and adverse device effect (ADE)

Subjects will be carefully monitored during the clinical investigation for possible AEs and ADEs.

For all randomized subjects, the period of observation for AEs and ADEs extends from signing of the ICF until the subject's last visit. Any medical occurrence between the time the ICF is signed and the first treatment with the investigational medical device is classified as an AE or ADE and must be documented in the subject's file and in the eCRF. New AEs or ADEs reported to the investigator during the observational period (i.e., after the start of treatment with the investigational medical device) must also be documented, treated, and followed.

Any AE, ADE, malfunction and/or device deficiency observed during study conduct will be fully investigated, documented, and followed until the event is either resolved, until

the condition stabilizes, until the event is otherwise explained, or the subject is lost to follow-up.

The investigator will assess and record any AE or ADE in detail in the subject's file (medical record) and in the AE eCRF. At a minimum the following information will be recorded:

- AE diagnosis or main symptom
- Location of AE: systemic or restricted to injection area. In case of local reaction, the corresponding area should be reported.
- Start and stop dates
- Severity/intensity
- Causal relationship
- Seriousness (yes or no)
- Outcome
- Action taken with investigational medical device
- AE resulting in subject discontinuation

7.2.4.2 Serious adverse event (SAE) and serious adverse device effect (SADE)

The investigator must report all SAEs and SADEs that occur during the observational period on the SAE form, within 24 hours, whether considered related or not related to the investigational device.

The investigator must report SAEs and SADEs to Merz and designee, via the designated safety email address or other means of contact, as defined in Section 7.3 and the site's IEC/IRB per their reporting guidelines.

Although all information required for completing an SAE report form may not be available within the specified time period, an initial report should be submitted and the following minimal information should be provided:

- An identifiable subject number;
- Adverse event;
- Investigational device name;
- Causality or relationship of investigational device; and/or
- Investigator/investigational site name.

Within 10 working days after Merz first receives notice of the SAE/SADE, Merz Product Safety will conduct an evaluation of the SAE/SADE and report the results of such evaluation to regulatory agencies, IECs/IRBs, and investigators, as applicable.

Follow-up SAE/SADE reports should be sent without delay to the sponsor or designee as an SAE form (marked as a "follow-up" report). The SAE/SADE has to be followed until the SAE/SADE is resolved/recovered or a plausible explanation is available.

In the case of a reportable death, the investigator shall make every effort to obtain a copy of the autopsy report and/or death certificate. The investigator will be required to review any post-mortem findings, including histopathology, and provide a synopsis of all pertinent findings by updating the SAE form.

SAEs/SADEs occurring after Week 60 would need to be reported to Merz Product Safety if the investigator considers the event to be related to the investigational medical device. Following the database lock for the study, all ongoing SAEs/SADEs will be followed until resolution or stabilization under the responsibility of the investigator per his/her standard of care.

7.2.4.3 Technical device complaints

For device deficiencies or device malfunctions, the investigator will attempt to evaluate if the deficiency or malfunction might have led to an AE if suitable action had not been taken, intervention had not been made, or circumstances had been less fortunate.

Complaints are defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, or performance of a medical device.

- A Device Technical Complaint form must be completed and submitted by the investigative site, irrespective of the seriousness of the case and/or whether the complaint led to an AE. All AEs that occur as a result of a technical complaint must be reported in the AE eCRF.
- If a technical complaint is associated with an SAE, the investigative site must also complete and submit an SAE form (see Section 7.2.4.2) in addition to the Device Technical Complaint form. SAE forms for device clinical trials should be sent to Merz Product Safety for processing (as defined in Section 7.3).

Any technical complaints should be reported to the sponsor. The investigator will complete the Device Technical Complaint form and send **within 24 hours** to the Merz Technical Complaint Department for processing using the following email address: [redacted]

7.2.4.4 Pregnancy

Any female subject who experiences pregnancy during the study must be reported by the investigator to Merz Product Safety or designee upon learning of the pregnancy. Pregnancies and pregnancy follow-up should be reported on a Pregnancy Report Form. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous discontinuation; details of the birth; the presence or absence of any congenital abnormalities, birth defects, maternal or newborn complications, and their relation, if any, to the investigational medical device. Pregnancy will be reported in the eCRF. Subjects who become pregnant during the course of the study should not be retreated (i.e. touch-up, optional retreatment), but will remain in the study.

7.3 Submission procedure

The investigator should complete and send any SAE forms or the pregnancy forms (including any follow-up forms) to Merz North America Product Safety via the fax number and/or email provided below:

Merz North America, Inc. Product Safety
6501 Six Forks Road
Raleigh, NC 27615
USA

[redacted]

7.4 [redacted]

[redacted]

8 STATISTICAL METHODS

This section describes the statistical analyses foreseen at the time of study planning. Further details on the statistical and analytical aspects will be presented in the statistical analysis plan (SAP) that will be prepared and completed prior to database lock.

Any deviations from planned analyses, the reasons for such deviation, and all alternative or additional statistical analyses that may be performed before database close will be described in amendments to the clinical study protocol and/or the SAP. All deviations and/or alterations will also be summarized in the clinical study report.

8.1 Estimation of sample size

[redacted]

The statistical power calculation software, nQuery Advisor Version 7.0, was used for sample size calculations.

8.2 Randomization

The randomization procedure that will be implemented for this study will be a block-stratified technique [redacted]. The randomization will be computer generated by a statistician independent of the study team. Block stratification will ensure there is an adequate statistical power for demonstrating the effectiveness [redacted]. Accordingly, approximately 120 subjects will be randomized to treatment and 60 subjects to control. [redacted] All subjects in the control/delayed-treatment group (60 subjects) will receive treatment at their Week 12 [redacted]

8.3 Populations for analysis

The following analysis sets will be defined for the statistical analysis of this study:

- The Intent-to-Treat (ITT) population will consist of all randomized subjects. This will be the primary population used for the effectiveness analyses and all safety analyses. All effectiveness endpoints will be analyzed as randomized; all safety endpoints will be analyzed as per actual treatment received.
- The Per Protocol (PP) population is a subset of subjects in the ITT population without major protocol deviations. Final determination of what constitutes major or minor protocol deviations will be made prior to database lock.

The primary and secondary effectiveness endpoints will be summarized using the ITT population, and additionally, for sensitivity purposes, on the PP population. [redacted] All safety

endpoints will be summarized using the ITT population. Additional information related to the usage of the analysis populations as it relates to the statistical analyses of study results will be described in the SAP.

8.4 Statistical analyses

Effectiveness and safety endpoints are provided in Sections 2.2.1 to 2.2.4.

The sponsor will finalize the SAP prior to database lock. Deviations from the analyses outlined in this protocol will be documented in the SAP within a section discussing changes to the planned analyses.

8.4.1 Effectiveness analyses

8.4.1.1 Primary effectiveness endpoint

The primary effectiveness endpoint is the proportion of responders with ≥ 1-grade improvement of both jawlines on the MJAS from baseline to Week 12.

Two hypothesis tests will be performed for the primary endpoint, in a sequential order. The first hypothesis is to demonstrate at least 50% of treated subjects are responders and the second hypothesis is to compare the treatment group with the control group. Each hypothesis test is a one-sided test at a significance level of 0.025.

Hypothesis test 1:

$$H_{01}: P_{treatment} \leq 50\%$$

$$H_{11}: P_{treatment} > 50\%$$

Hypothesis test 2:

$$H_{02}: P_{treatment} \leq P_{control} \quad H_{12}: P_{treatment} > P_{control}$$

For hypothesis testing of at least 50% of treated subjects are responders (H_{01} versus H_{11}), the binomial test will be utilized and for testing the statistical superiority of treatment over control (H_{02} versus H_{12}), the Fisher's exact test will be used.

[redacted]

[redacted]

8.4.1.2 *Secondary effectiveness endpoints*

- For the FACE-Q satisfaction with the lower face and jawline assessment, among treated subjects, sum scores and the equivalent Rasch-transformed scores will be summarized using descriptive statistics [redacted]
- The investigator GAIS for treated subjects will be descriptively summarized at Week 12 using counts (n) and percentages (%) for each GAIS category [redacted] The investigator GAIS will be evaluated relative to baseline.
- The subject-rated GAIS for treated subjects will be summarized at Week 12 using counts (n) and percentages (%) for each GAIS category [redacted]

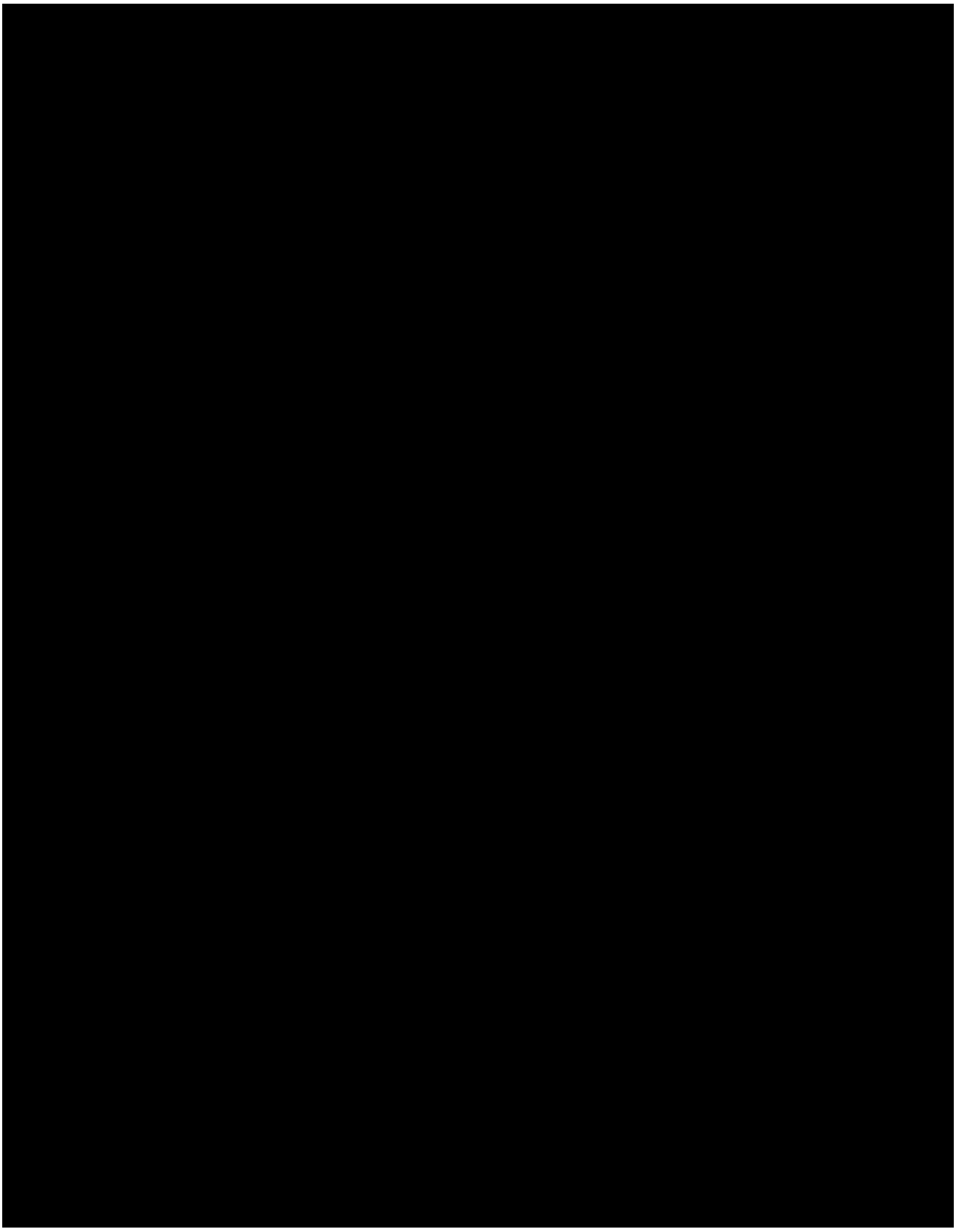
[redacted] The subject-rated GAIS will be evaluated relative to baseline.

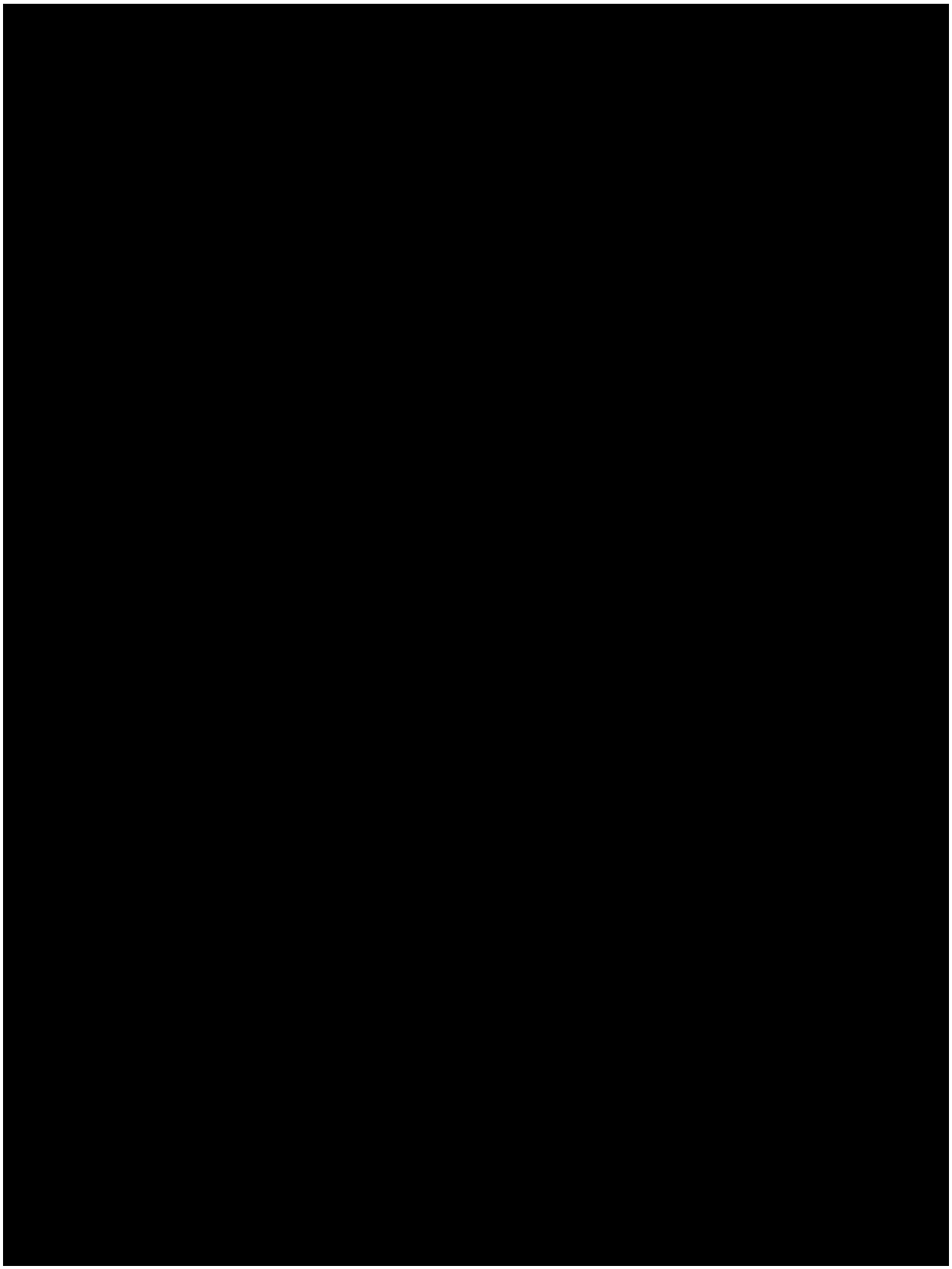
[redacted]

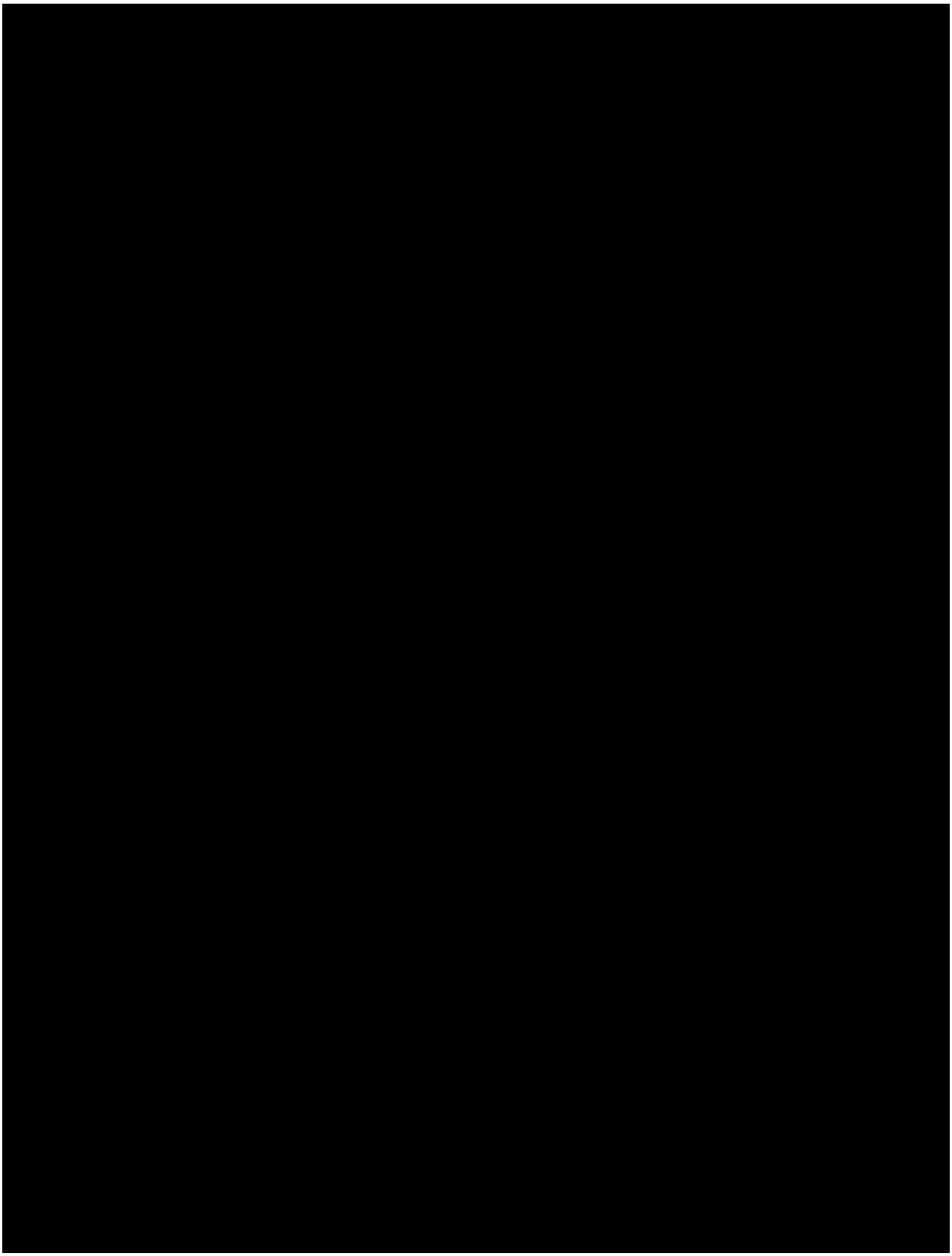
- The proportion of responders in the treatment group and the untreated control group at Week 12, according to the MJAS[redacted] will be summarized using counts and percentages. Treatment response is defined as ≥ 1-point improvemen[redacted]

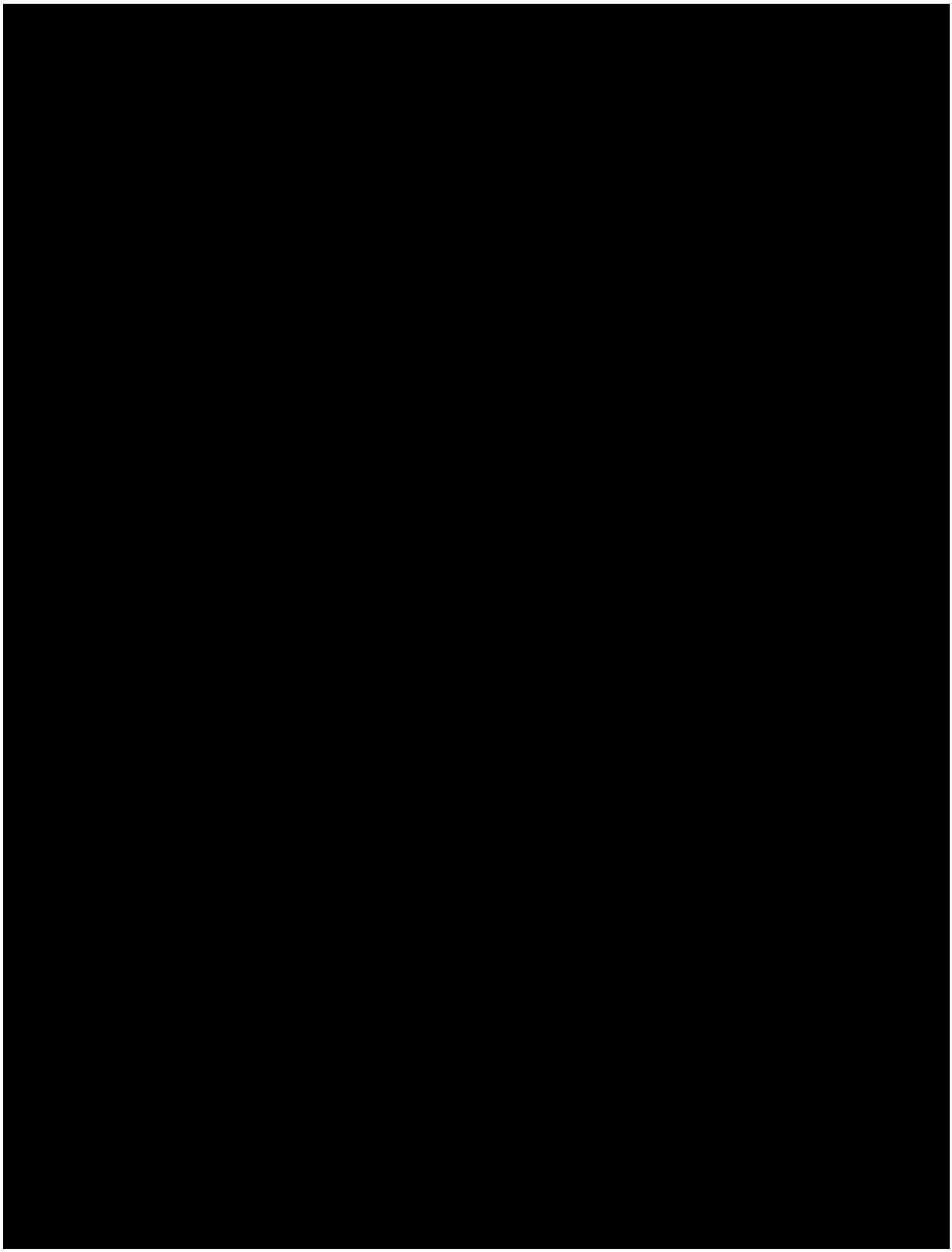
8.4.1.3 [redacted]

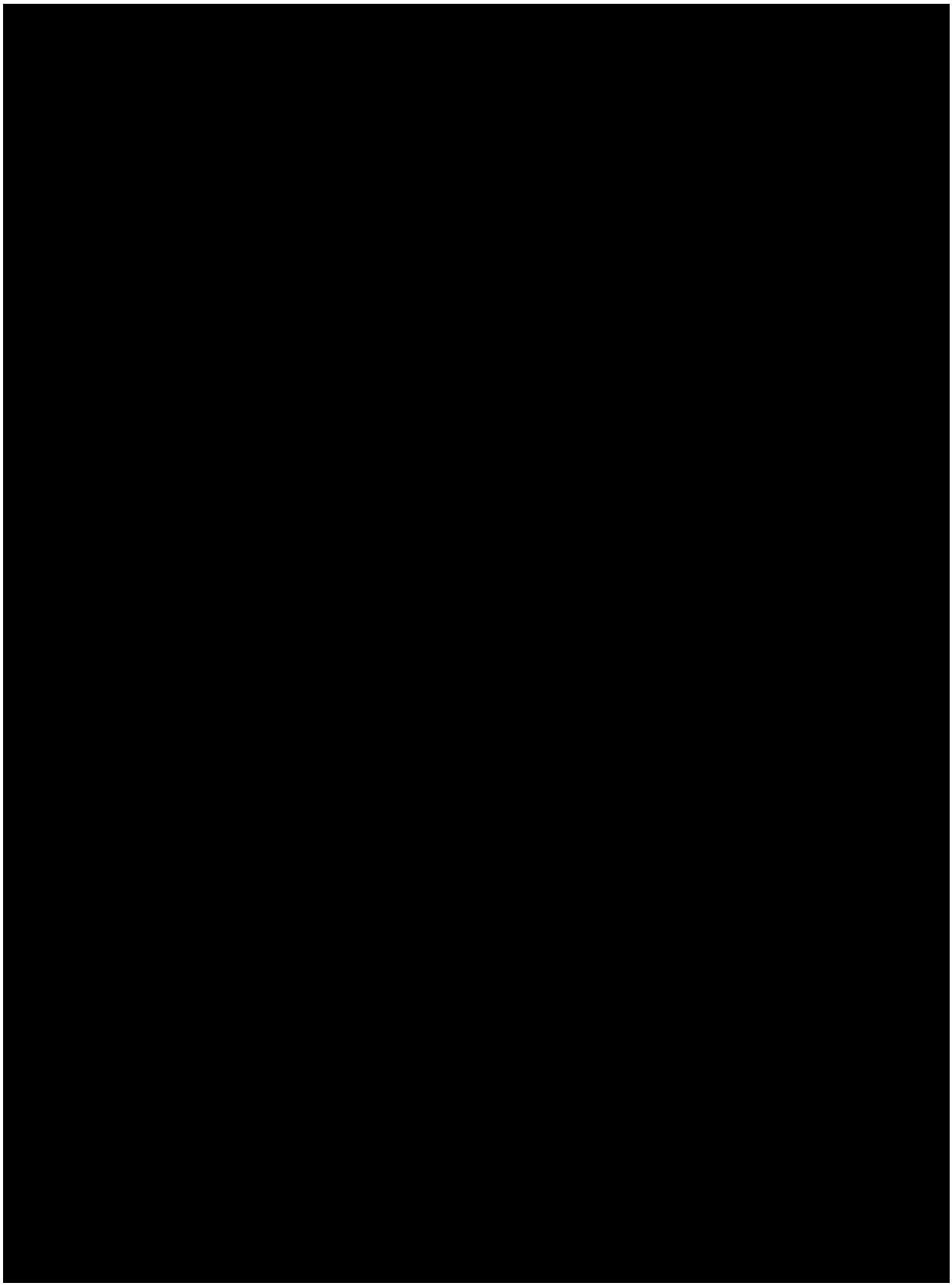
[redacted]











[redacted]

8.4.2 Safety analyses and endpoints

Nature, frequency, and severity of AEs and SAEs will be recorded. All AEs and SAEs will be descriptively summarized by treatment and control/delayed-treatment groups according to type, duration, severity, relationship to study device, and the need for touch-up (for those in the treatment and control/delayed-treatment groups), and/or retreatment (for those randomized to the treatment group).

The assessment of safety will be based mainly on the frequency of AEs and SAEs. Only treatment-emergent AEs (TEAEs) will be summarized for each treatment group (as applicable) by the incidence of at least one event, the number of events, and the incidence using Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) within the system organ classes (SOCs). AEs will be coded according to MedDRA.

[redacted]

8.5 Special statistical / analytical issues

[redacted]

8.5.2 Interim data reporting

Data listings pertaining to annual reporting updates to the FDA will be produced as necessary. The annual reports will contain enrollment updates (i.e., number of subjects recruited at each site, number screened and enrolled, number randomized, etc.), subject disposition, and safety listings.

9 ETHICS AND ADMINISTRATIVE PROCEDURES

9.1 Ethical considerations

This study will be performed in accordance with the principles outlined in the Declaration of Helsinki and in compliance with the standards for Good Clinical Practice described in ISO 14155, the Code of Federal Regulations, and any applicable regional or national laws and regulations. The study will adhere to all applicable subject privacy requirements.

All required approvals, favorable opinions, or additional requirements of the appropriate IEC, IRB or other regulatory authority will be obtained prior to initiation of the trial.

The investigator and all study personnel will conduct the study in compliance with this protocol. The investigator will ensure that all personnel involved in the conduct of this study are qualified to perform the assigned study responsibilities. Investigators will adhere to all applicable study reporting requirements.

9.2 Informed consent

Written informed consent must be obtained from every subject or his/her legal representative prior to the initiation of any screening or study procedures. The investigator will follow a standard process for obtaining consent that complies with all applicable regulatory requirements. If applicable, a certified translation of the informed consent form into the relevant local language will be provided. The original and any amended signed and dated ICF must be retained at the study site; and a copy must be given to the subject or subject's legally authorized representative(s).

It is not anticipated that members of a vulnerable population will participate in this study.

If the ICF is amended during the study, the investigator must follow all applicable regulatory requirements pertaining to approval of the amended ICF by the IEC/IRB and use of the amended form (including for ongoing subjects).

During the course of the study, the subject will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study. In case of AEs, the subject should inform the investigator, who then will make a judgment whether continuing in the study serves the subject's best interests. The subject, however, is free to withdraw consent at any time and for any reason, whether expressed or not.

Each ICF will include contact information (with a phone number) the subject should use to communicate any medical concerns 24 hours a day. Each ICF will also include the contact information for an ophthalmologist and an oral surgeon, who are identified by the Investigator, for instances in which a subject requires evaluation by an ophthalmologist (e.g., subjects experiences sudden visual changes following treatment injections) and/or referral to an oral surgeon.

9.3 Confidentiality of subject information

Subject anonymity is to be maintained during the study. Subjects will be identified by an assigned number on all study documentation. Documents that identify the subject must be maintained in strict confidence by the investigator to the extent permitted by applicable laws and regulations, unless their disclosure is necessary to allow auditing by regulatory authorities, the sponsor, or the sponsor's designee.

Subject medical information obtained during the study is confidential. At a subject's request, the subject's medical information may be provided to the subject's personal physician or other appropriate medical personnel. Disclosure of subject medical information to third parties other than those noted above is not permitted.

9.4 Study monitoring

Study monitoring will conform to all applicable regulatory standards and guidelines. The sponsor or designee will monitor the study through periodic site visits to verify the following:

- Data authenticity, accuracy, and completeness.
- Protection of subject rights and safety.
- Conduct of the study is in accordance with the currently approved protocol and all applicatory regulatory requirements and guidelines.

Investigators agree to grant access to all relevant documents and provide support at all times for study monitoring activities. Study monitoring activities will be performed in a manner that ensures maintenance of subject confidentiality (Section 9.3).

9.5 Data quality assurance

9.5.1 Standardization procedures

Standardization procedures will be implemented to ensure accurate, consistent, complete, and reliable data, including methods to ensure standardization among sites (e.g., training,

newsletters, investigator meetings, monitoring, centralized evaluations, and validation methods).

This study will be monitored regularly by a qualified monitor from the sponsor or its designee according to GCP guidelines and the respective SOPs (see Section 9.4).

9.5.2 Data management

The investigator will prepare and maintain complete and accurate eCRFs recording all observations and data pertinent to the study for each subject. Data reported on eCRFs should be derived from source documents and must be consistent with the sources from which they derive. Investigators will sign and date the eCRFs as appropriate to verify the accuracy of the reported data. It is the responsibility of the Investigator to ensure that all data are submitted to the sponsor in a timely manner.

9.5.3 Data review and clarification procedures

All data required by this clinical study protocol are to be entered into a validated database. Individual subject data is to be recorded in eCRFs within 5 days of each study visit.

By signing and dating the eCRFs, the investigator is confirming that all investigations have been completed and conducted in compliance with the clinical study protocol, and that reliable and complete data have been entered into the eCRFs.

If corrections in the questionnaires are necessary, the subject should be instructed to make a correction by drawing only a single line through the error, leaving the incorrect entry legible. The subject should date and initial the correction. The investigator should not make any changes to these documents.

Essential documents should be retained per applicable regulations and as instructed by the study sponsor. Essential documents at the investigational site include but are not limited to:

- Subject files
- Subject identification code list
- A copy of the study protocol and any amendments
- Investigator’s copies of the eCRFs and any associated subject-related source data
- Signed ICFs
- Copies of all direct correspondence with the IEC/IRB and with the regulatory authority(ies), and with the sponsor

[redacted]

- Copies of investigational device disposition records

Study documents may not be destroyed by study site personnel prior to the end of the required retention period as specified by local regulations. The PI or the institution must inform the sponsor in due time if the PI leaves the institution during the retention period. This rule also applies when the institution closes within the retention period.

9.5.4 Study auditing

To ensure compliance with applicable standards and regulations, the sponsor, IEC/IRB, or regulatory authorities may conduct a quality assurance assessment or audit of site records at any time during or after completion of the study. In the event of an audit, investigators must grant access to all relevant documents (including source documents, electronic records, and other applicable study documentation) and provide support at all times for auditing activities.

9.6 Record retention

Upon closure of the study, the investigator must maintain all study site records in a safe and secure location. The investigator is responsible for the integrity, retention, and security of all study-related records. The investigator must ensure that any reproductions of the original records are legible and provide a true and accurate copy of the original. Accurate, complete, and current records must be stored in such a way as to permit easy and timely retrieval for the sponsor or any applicable regulatory authorities.

The sponsor will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements, with the minimum retention time being the longest of those times dictated by institutional requirements, local laws or regulations, or the sponsor's standard procedures. The investigator must notify the sponsor in the event of any changes to archival arrangements due to withdrawal of the investigator's responsibility for keeping study records to ensure that suitable arrangements for the retention of study records are made.

9.7 Publication policy

The study protocol, study data, and information related the study or the sponsor's products or research programs are to be kept confidential and may not be disclosed without the consent of the sponsor. The investigators have the responsibility to provide complete study data, records, and reports for inspection by the appropriate regulatory authorities, the sponsor, or the IEC/IRB, as appropriate.

The investigator agrees that the results of this study may be used for submission to national or international registration and supervising authorities. The sponsor may disclose the information obtained during the study to regulatory authorities or other personnel as required. If necessary, the sponsor may disclose the names, contact information, and qualifications of all investigators as well as their roles in the study. Upon completion of the study, publication or disclosure of the study results is to follow the terms contained in the sponsor's publication policy.

9.8 Financial disclosure

The US FDA Financial Disclosure by Clinical Investigators (21 CFR 54) regulations require sponsors to obtain certain financial information from investigators participating in covered clinical studies. By participating in the study, the investigator agrees to provide the required financial information and to promptly update the sponsor with any relevant changes to this financial information throughout the course of the study and for up to one (1) year after its completion if necessary.

9.9 Investigator compliance

The investigator will conduct the study in compliance with the protocol provided by the sponsor and in accordance with all relevant regulatory guidelines and requirements.

Modifications to the protocol should not be made without the agreement of the investigator and sponsor. The sponsor will submit all protocol modifications to the appropriate regulatory authority in accordance with applicable regulations. All protocol modifications require written IEC/IRB approval/favorable opinion, except in the case of an immediate hazard to subjects.

If an immediate deviation from the protocol is required to eliminate an immediate hazard to subjects, the investigator must contact the sponsor, if possible, to discuss the planned course of action. The investigator must thoroughly document any departure from the protocol and submit appropriate documentation to the sponsor without delay.

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11 APPENDICES