Clinical Study Protocol

NCT03777917, redacted version v1.0, 15Mar2022

A Pilot Study to Assess the Effectiveness and Safety of Belotero Balance® Injection for Volume Augmentation of the Infraorbital Hollow

Study protocol number:	M930121001
Date of original clinical study protocol and all previous amendments:	08-NOV-2018 (Amendment no. 4.0, Version 5.0) 04-OCT-2018 (Amendment no. 3.0, Version 4.0) 05-DEC-2017 (Amendment no. 2.0, Version 3.0) 09-AUG-2017 (Amendment no. 1.0, Version 2.0) 13-MAR-2017 (original protocol, Version 1.0)
Development phase:	Device pre-market
Investigational product:	Belotero Balance®
Indication:	Correction of volume loss in the infraorbital hollow area
Sponsor:	Merz North America Inc. 6501 Six Forks Road Raleigh, NC 27615 Telephone: (919) 582-8000
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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]	12 NOV 2018	[redacted]
Merz Pharmaceuticals GmbH	Date (dd-MMM-yyyy)	Signature

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 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). Agree to provide written disclosure of any financial interest, in accordance with 21 CFR Part 54, and will 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-yyyy)***	***Signature***

PROTOCOL SYNOPSIS

Protocol Title	A pilot study to assess the effectiveness and safety of Belotero Balance® Injection for Volume Augmentation of the Infraorbital Hollow
Protocol Number	M930121001
Active Product	Belotero Balance®
Study Phase	Device pre-market
Indication	Correction of volume loss in the infraorbital hollow area
Number of Sites and Countries	The study will be conducted in the United States at approximately 3 sites.
Number of Study Subjects	Approximately 66 subjects will be enrolled and randomized, with approximately 44 subjects assigned to the treatment group and 22 subjects assigned to the untreated control group.
Objective	The pilot study aims to define safety, effectiveness, and patient-reported outcomes for Belotero Balance use in the infraorbital hollow (IOH) in order to utilize the results to inform the design of a future pivotal study.
Key Endpoints	Primary • Comparison of the responder rate between the treatment group and the untreated control group at Month 2, according to the Merz Infraorbital Hollow Assessment Scale (MIHAS) [redacted]. For subjects randomized to treatment, if no touch-up is performed, the primary effectiveness MIHAS assessment will occur at Month 2 post baseline injection. If a touch-up is performed, the primary effectiveness MIHAS assessment will be at 2-months post touch-up. For subjects randomized to the untreated control group, the primary effectiveness assessment will be at Month 2 from the baseline visit. Treatment response is defined as ≥ 1-point improvement on both IOHs compared to baseline. Secondary • Summary of the FACE-Q satisfaction with eyes scores for treated subjects at baseline and Month 2 post last injection (i.e., either baseline treatment or touch-up, if applicable) and for control subjects at baseline and Month 2. The subject's assessment is based on taking into consideration both eyes. • Descriptive summary of Global Aesthetic Improvement Scale (GAIS) scores for treated subjects at Month 2 post last injection (i.e., either baseline treatment or touch-up, if applicable), as completed by the treating investigator. This assessment is a measure of aesthetic improvement relative to the baseline pre-treatment condition, as assessed from photographs. • Descriptive summary of GAIS scores for treated subjects at Month 2 post last injection (i.e., either baseline treatment or touch-up, if applicable), as completed by the subject. This assessment is a measure of aesthetic improvement relative to the baseline pre-treatment condition, as assessed

	from photographs. • Summary of the responder rates in the treatment group and the control group at Month 2, according to the MIHAS, [redacted] using subject photographs. In addition to baseline photograph assessments, for subjects randomized to treatment, if no touch-up is performed, the photographs assessed will be those taken at 2-months post baseline injection. If a touch-up is performed, the photographs assessed will be those taken at 2-months post touch-up. For subjects randomized to the untreated control group, the photographs assessed will be taken at 2-months from the baseline visit. Treatment response is defined as ≥ 1-point improvement on both IOHs when comparing the change from baseline to Month 2. A subject will be considered a responder if a treatment response of at least a 1-point change on both IOHs is determined [redacted]. Safety • Evaluate the incidence and nature of device- and/or injection-related AEs and SAEs observed during the study. Additionally, the incidence, severity, and duration of pre-specified common treatment responses (CTRs) will be evaluated using subject diaries.
Study Design Overview	This is a prospective, [redacted] multi-center, randomized-controlled study in subjects with moderate to severe IOH deficit. Approximately 66 subjects will be enrolled from 3 sites in the United States. Subjects will be randomized to either a treatment group or an untreated control group using a 2:1 (treatment: control) allocation ratio. Approximately 70% of the total sample size will consist of subjects with a Fitzpatrick skin type of I, II, or III and approximately 30% of the subjects will be Fitzpatrick skin type IV, V, or VI. Subjects from the Fitzpatrick skin type IV, V, and VI group will be distributed as follows: ≥ 6 subjects will be enrolled in the IV Fitzpatrick skin type group and ≥ 12 subjects will be enrolled with Fitzpatrick Skin Types V and VI. Each clinical site will enroll a minimum of 6 subjects with Fitzpatrick skin types IV, V, VI. At least 5 males will be enrolled into the study. For subjects randomized to the treatment group, both right and left IOHs will receive treatment with Belotero Balance. To achieve symmetrical correction a touch-up injection will be given, with the subject's consent, in one or both IOHs if the treating investigator determines a treated subject has asymmetrical IOHs based on a visual assessment. For the primary effectiveness assessment, IOH deficit will be assessed according to the MIHAS [redacted]. The treated subjects will have a safety phone call 72 hours after baseline treatment and in-clinic safety visits at Week 2 and Months 2, 3, 6, 9, and 12 post baseline injection. Effectiveness assessments will be performed in clinic at baseline and Month 2 post baseline injection. Effectiveness assessments will consist of the [redacted] MIHAS assessment, treating investigator GAIS, the subject GAIS, and the FACE-Q instruments (a patient-reported assessment).

	All treated subjects will be assessed 1 month after baseline injection for asymmetry and safety. If a treated subject receives a touch-up injection for asymmetric correction the visits schedule will be re-calculated relative to the touch-up visit (i.e., 72 hour phone call, 2 weeks, 1, 2, 3, 6, 9 and 12 months). For these subjects effectiveness assessments will occur at baseline and 2 months after the touch-up injection. If subjects report a safety concern during the 72-hour phone call, an unscheduled visit will be scheduled to bring the subject into the clinic to address safety concerns. [redacted]
Key Inclusion Criteria/ Key Exclusion Criteria	To be eligible for the study, each subject must meet all of the following key inclusion criteria: [redacted] Has right and left IOH volume deficit with a rating of 2 or 3 (moderate or severe) on the [redacted] MIHAS. [redacted] Has the same MIHAS score on both IOHs (i.e., IOHs are symmetrical). [redacted] Is at least 22 years of age. [redacted] Patients meeting any of the following key exclusion criteria are not eligible to participate in the study: [redacted]

	■ Ever been treated with fat injections or permanent and/or semi-permanent dermal fillers in the midfacial region or plans to receive such treatments during participation in the study. ■ Received lower eyelid and/or malar region treatments with any absorbable or temporary fillers such as porcine-based collagen fillers, hyaluronic acid (HA) products, RADIESSE®, poly L-lactic acid (PLLA) or received mesotherapy treatment to the area within the past 24 months or plans to receive such treatments during participation in the study. [redacted]

Table of Contents

List of Abbreviations

Abbreviation/Term	Definition
ADE	Adverse device effects
AE	Adverse event
ATC	Anatomical Therapeutic Chemical classification system
BDDE	1,4-butanediol diglycidyl ether
CFR	Code of Federal Regulations
CI	Confidence interval
CRF	Case report form
CRO	Contract research organization
CSR	Clinical study report
CTR	Common treatment site response or common treatment response
eCRF	Electronic case report form
EDC	Electronic data capture
FACE-Q	Set of subject-reported questionnaire modules
FDA	Food and Drug Administration, US
G	Gauge
GAIS	Global Aesthetic Improvement Scale
GCP	Good clinical practice
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IFU	Instructions for use
IOH	Infraorbital hollow
[redacted]	
IRB	Institutional review board
ITT	Intent-to-treat
IUD	Intrauterine device
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MIHAS	Merz Infraorbital Hollow Assessment Scale
mL	Milliliter
mm	Millimeter
N	Number of non-missing observations
PI	Principal investigator
PLLA	Poly-L-lactic acid
PP	Per protocol population
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Statistical analysis plan
SP	Safety population

Abbreviation/Term	Definition
UADE	Unanticipated adverse device effects
US	United States
UV	Ultraviolet
[redacted]	

1 INTRODUCTION

1.1 Background and rationale

There is an increasing interest among patients to seek minimally invasive alternatives to aesthetic surgical procedures to improve the appearance of the face. As a result of the aging process, more specifically aging of the under-eye area, the development of a noticeable concave deformity occurs, resulting in a fatigued and noticeable aged appearance on the face. While many anatomical and physiological contributing factors must be considered for the cause of infraorbital hollowing, subjects with an inherent level of volume loss may benefit from filler augmentation. Treating the infraorbital hollow (IOH) may present challenges and only a few fillers are suitable for such a sensitive area.

Patients seeking filler treatments, as well as physicians administering such treatments, need to be able to objectively analyze aesthetic outcomes post-treatment. The Merz Infraorbital Hollow Assessment Scale (MIHAS) was created to allow for a quantitative assessment of the infraorbital hollow area in clinical trials. [redacted]

Based on the findings from the aforementioned scale development activities, the MIHAS was determined to be fit-for-purpose to be used in the clinical setting to detect clinically meaningful changes to treatment (performed by oculoplastic surgeons) by improving the level of hollowing as a result of volume correction.

In this pilot study, the pre- and post-treatment MIHAS scores will be used to determine the effectiveness of Belotero Balance injection in the IOH region. Additionally, to further substantiate the MIHAS and demonstrate that the changes detected post-treatment on the MIHAS are clinically relevant from the perspective of aesthetically pleasing outcomes, other investigator and subject reported outcomes such as the Global Aesthetic Improvement Scale (GAIS) and FACE-Q assessments will be utilized to demonstrate treatment effectiveness. Additional details are provided in Section 2.1.

[redacted]

1.2 Potential benefits and risks

The potential benefit of Belotero Balance is the correction of volume loss in the infraorbital hollow area.

Adverse events have been identified during post-approval use of Belotero Balance; however, because the events are reported voluntarily, from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal connection to Belotero Balance. The following adverse events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to Belotero Balance: allergic reactions including Quincke's edema, anaphylaxis, rash, hives, necrosis, inflammation, granuloma, indurations, and/or nodules; hematoma; Tyndall effect; Cordon-like effect; bumps; pustule; scarring; swelling; erythema; pain; edema; bruising; lumps; discoloration; infection; migration/displacement; asymmetry; numbness; vascular occlusion; and/or visual disturbance.

Potential risks associated with the use of Belotero Balance are similar to those of other commercially available, deep soft-tissue fillers. Previously reported injection-site responses to Belotero Balance consisted mainly of short-term inflammatory symptoms including: swelling; induration; bruising; redness; erythema; pain; nodule formation; coloration or discoloration; pruritus; and rash. These observations started early after treatment and resolved in 7 days or less.

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; eyelid muscle degeneration and damage to the underlying facial structures. Implantation of Belotero Balance into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction.

An additional risk includes disappointment due to lack of or reduced performance and/or undesirable aesthetic effect.

The use of cannula may increase the duration of local site irritation or erythema by 1-2 days in comparison to the use of a needle.

Currently, there are no approved dermal fillers for volume correction around the eyes. Alternative options may include various surgical, non-invasive procedural and potentially topical therapy interventions or no treatment at all.

Additional information on product- and injection-related contraindications, warnings, and precautions can be found in the Instructions for Use (see Appendix 10.3).

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

The pilot study aims to define safety, effectiveness, and patient-reported outcomes for Belotero Balance use in the IOH in order to utilize the results to inform the design of a future pivotal study.

2.1.1 Effectiveness

The effectiveness and relevance of aesthetically pleasing outcomes following Belotero Balance injection will be established in the following manner:

- The primary endpoint (see Section 2.2.1) will establish effectiveness by using the MIHAS to demonstrate that clinically relevant changes of ≥ 1-point on both IOHs can be detected 2-months post-treatment.

- The secondary endpoints (See Section 2.2.2) including the validated FACE-Q satisfaction with eyes, the investigator GAIS, and the subject GAIS will be utilized to substantiate aesthetically pleasing outcomes. The GAIS assessments will be used in the treated subjects only. Improvements in the FACE-Q satisfaction with eyes scores from baseline to 2-months post-treatment will indicate that subjects are satisfied with treatment effects observed on their IOHs and such changes are considered to be clinically relevant from the subject's perspective. Responses for FACE-Q satisfaction with eye scores in the control group will be compared to that of the treatment group in order to show that changes in satisfaction post-treatment are clinically relevant to the subject.

  Additionally, the investigator and subject GAIS scores at Month 2 post last injection will be utilized to demonstrate the level of improvement, when compared to baseline photographs, resulting from treatment in the IOHs.

- The level of agreement in treated subjects between the MIHAS responders (≥ 1-point improvement on both IOHs), [redacted] and the level of improvement (score of ≥ 1) on the treating investigator- and subject-GAIS assessments will be obtained. Aesthetically pleasing outcomes that are clinically relevant will be established if the agreement between the MIHAS responders and the level of improvement on the investigator- and subject-GAIS scores, respectively, are met as per the pre-defined endpoints in Section 2.2.3.

[redacted]

In totality, the results from the MIHAS, as well as the supportive outcomes obtained from the treating investigator and subject perspectives regarding aesthetic improvements, will be used to establish that Belotero Balance injections in the IOH region are effective in producing clinically relevant and aesthetically pleasing outcomes.

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. In addition to standard safety assessments, eye assessments (including visual acuity, visual field, ocular motility, and undilated fundoscopic exam) will be evaluated. Common treatment responses (CTRs) will also be assessed.

2.2 Endpoints

2.2.1 Primary endpoint

The primary endpoint is a comparison of the responder rate between the treatment group and the untreated control group at Month 2, according to the MIHAS [redacted]. For subjects randomized to treatment, if no touch-up is performed, the primary effectiveness MIHAS assessment will occur at Month 2 post baseline injection. If a touch-up is performed, the primary effectiveness MIHAS assessment will be at 2-months post touch-up. For subjects randomized to the untreated control group, the primary effectiveness assessment will be at Month 2 from the baseline visit.

Treatment response is defined as ≥ 1-point improvement on both IOHs compared to baseline.

2.2.2 Secondary endpoints

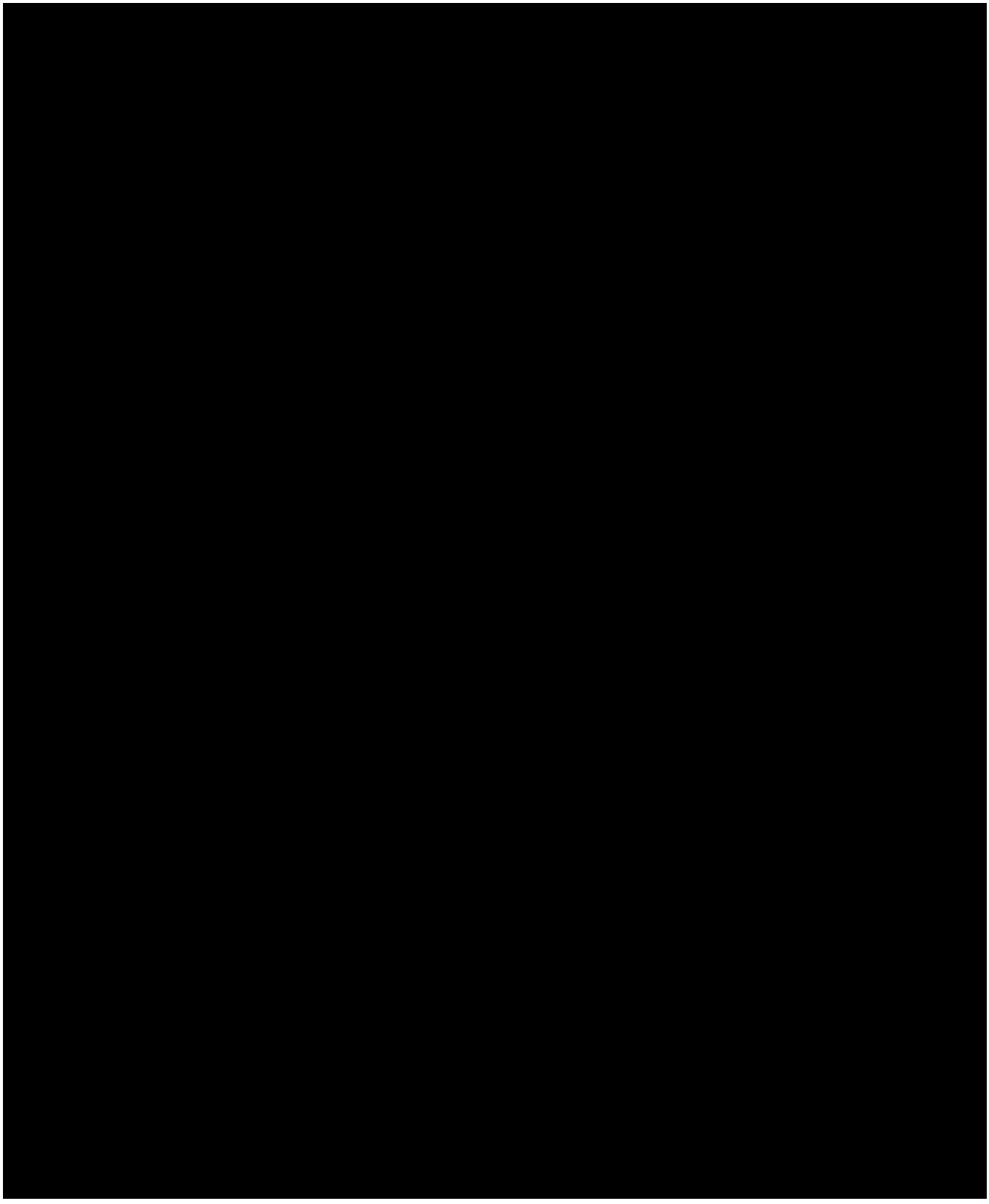
- Summary of the FACE-Q satisfaction with eyes scores for treated subjects at baseline and Month 2 post last injection (i.e., either baseline treatment or touch-up, if applicable) and for control subjects at baseline and Month 2. The subject's assessment is based on taking into consideration both eyes.

- Descriptive summary of GAIS scores for treated subjects at Month 2 post last injection (i.e., either baseline treatment or touch-up, if applicable), as completed by the treating investigator. This assessment is a measure of aesthetic improvement relative to the baseline pre-treatment condition, as assessed from photographs.

- Descriptive summary of GAIS scores for treated subjects at Month 2 post last injection (i.e., either baseline treatment or touch-up, if applicable), as completed by the subject. This assessment is a measure of aesthetic improvement relative to the baseline pre-treatment condition, as assessed from photographs.

- Summary of the responder rates in the treatment group and the control group at Month 2, according to the MIHAS, [redacted] using subject photographs. In addition to baseline photograph assessments, for subjects randomized to treatment, if no touch-up is performed, the photographs assessed will be those taken at 2-months post baseline injection. If a touch-up is performed, the photographs assessed will be those taken at 2-months post touch-up. For subjects randomized to the untreated control group, the photographs assessed will be taken at 2-months from the baseline visit.

  Treatment response is defined as ≥ 1-point improvement on both IOHs when comparing the change from baseline to Month 2. A subject will be considered a responder if a treatment response of at least 1-point change on both IOHs is determined [redacted].



[redacted]

2.2.4 Safety endpoints

- Incidence and nature of device- and/or injection-related AEs and SAEs observed during the study.
- Incidence, severity, and duration of pre-specified CTRs reported in subject diaries.

3 INVESTIGATIONAL PLAN

3.1 Overview of study design

This is a prospective, [redacted] multi-center, randomized-controlled study in subjects with moderate to severe IOH deficit. Approximately 66 subjects will be enrolled from 3 sites in the United States. Subjects will be randomized to either a treatment group or an untreated control group using a 2:1 (treatment: control) allocation ratio. Approximately 70% of the total sample size will consist of subjects with a Fitzpatrick skin type of I, II, or III and approximately 30% of the subjects will be Fitzpatrick skin type IV, V, or VI. Subjects from the Fitzpatrick skin type IV, V, and VI group will be distributed as follows: ≥ 6 subjects will be enrolled in the IV Fitzpatrick skin type group and ≥ 12 subjects will be enrolled with Fitzpatrick Skin Types V and VI Fitzpatrick skin type group. Each clinical site will enroll a minimum of 6 subjects with Fitzpatrick skin types IV, V, VI. At least 5 males will be enrolled into the study.

For subjects randomized to the treatment group, both right and left IOHs will receive treatment with Belotero Balance. To achieve symmetrical correction a touch-up injection will be given, with the subject's consent, in one or both IOHs if the treating investigator determines a treated subject has asymmetrical IOHs based on a visual assessment.

For the primary effectiveness assessment, IOH deficit will be assessed according to the MIHAS [redacted]

The treated subjects will have a safety phone call 72 hours after baseline treatment and in-clinic safety visits at Week 2 and Months 2, 3, 6, 9, and 12 post baseline injection. Effectiveness assessments will be performed in clinic at baseline and Month 2 post baseline injection. Effectiveness assessments will consist of the [redacted] MIHAS assessment, treating investigator GAIS, the subject GAIS, and the FACE-Q instruments (a patient-reported assessment).

All treated subjects will be assessed 1 month after baseline injection for asymmetry and safety. If a treated subject receives a touch-up injection for asymmetric correction the visits schedule will be re-calculated relative to the touch-up visit (i.e., 72 hour phone call, 2 weeks, Months 1, 2, 3, 6, 9 and 12). For these subjects effectiveness assessments will occur at baseline and 2 months after the touch-up injection.

If subjects report a safety concern during the 72-hour phone call, an unscheduled visit will be scheduled to bring the subject into the clinic to address safety concerns.

Control-group subjects will be evaluated at enrollment and Month 2 in the clinic. The only effectiveness assessment that will be performed in the control group is the [redacted]

[redacted]FACE-Q instruments. No investigator GAIS will be performed with control subjects, nor will these subjects self-report on the GAIS.

[redacted]

Section 5.1 and Appendices 10.1 (treated subjects) and Appendix 10.2 (control subjects) detail a full schedule of study events and a schedule of events for each visit.

3.2 Study assessments and definitions

3.2.1 Effectiveness assessments

3.2.1.1 Merz Infraorbital Hollow Assessment Scale (MIHAS)

The MIHAS was designed to assess the infraorbital hollow resulting from volume loss. Each grade of the MIHAS is distinct, where grade 0 is anchored to depict none to minimal signs of hollowing and grade 4 is anchored to depict extreme signs of hollowing (see Figure 1). For each of the five severity grades, three reference subjects are displayed. For each subject, a frontal view is presented to indicate specific characteristics of the IOH region. The left and right IOH of each subject is assessed independently with the MIHAS within this study. The MIHAS was developed to detect clinically relevant changes in the aforementioned pathology as a result of volume correction in the IOH area.

During the baseline and Month 2 visits, subjects in this study will be evaluated with the MIHAS [redacted].

[redacted]

The treating investigator will also attend an MIHAS-instructional session to ensure understanding of the subject-eligibility criteria of right and left IOH volume deficit with a rating of 2 or 3 (moderate or severe) at study entry.

[redacted]

Figure 1: Merz Infraorbital Hollow Assessment Scale (MIHAS)

3.2.1.2 Photographs

Subject photographs will serve as an accurate record of the subject's appearance and the subject's appearance after IOH injection and may reflect any relevant safety concerns. Standardized photographs will be taken for treated subjects at the baseline visit, Week 2 and Months 1, 2, 3, 6, 9, and 12 after the last injection (i.e., either baseline treatment or touch-up, if applicable). If subjects receive a touch-up 1-month after baseline injection, these subjects will also have standardized photographs taken 2-weeks and 1 month after the touch-up injection. Baseline photographs will be used for pre-treatment comparison/reference in the Month 2 post last injection (i.e., either baseline injection or touch-up, if applicable) GAIS assessments conducted by the treating investigator and the study subject (see Sections 3.2.1.3 to 3.2.1.4, respectively). Standardized photographs will be taken for control subjects at the baseline visit and Month 2. Every effort should be

made to have the same study personnel take photographs at every visit throughout the study. Photography procedures will be described in a separate user manual. The photographic lighting for this study will replicate that of the images used in the validated photo-numeric MIHAS; strobes will be set at fixed superior-oblique positions relative to the subject's face specifically located to illuminate the IOH target area for evaluation.

3.2.1.3 *Treating investigator Global Aesthetic Improvement Scale (GAIS)*

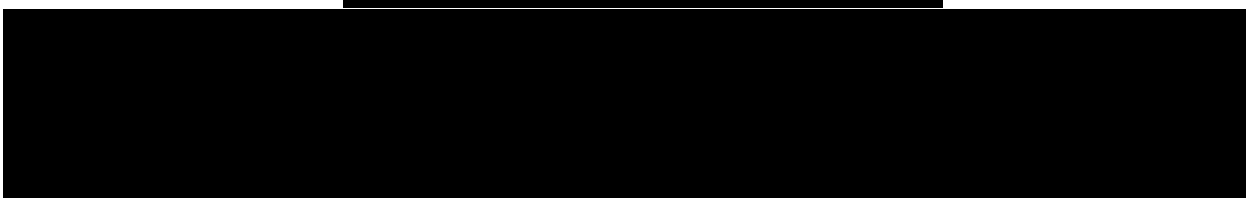
The treating investigator will use the GAIS to assess global aesthetic improvement among treated subjects using baseline, pre-treatment photos for comparison to Month 2 after the last injection (i.e., either baseline treatment or touch-up, if applicable) (see Table 1). The GAIS will not be completed for subjects randomized to the control group. The treating investigator must perform the GAIS rating based on the current cosmetic result for both IOHs based on photographic assessments. Investigators are to use photographs taken at baseline before injection to make a comparison to the cosmetic result at Month 2 after the last injection (i.e., either baseline treatment or touch-up, if applicable). The following 7-point scale will be used:

Table 1: Treating Investigator Global Aesthetic Improvement Scale (GAIS)

3.2.1.4 Subject Global Aesthetic Improvement Scale (GAIS)

Treated subjects will evaluate their overall facial aesthetic improvement on the subject GAIS using photographs from Month 2 after the last injection (i.e., either baseline treatment or touch-up, if applicable) and baseline pre-treatment photos for comparison (see Table 2). GAIS will not be completed for subjects randomized to the control group. The subject will be asked: "Considering both IOHs, what is your overall impression of change of your aesthetic result due to treatment, compared to the condition before the injection? Please tick the one option that best fits your overall impression of change." The following 7-point scale will be used:

Table 2: Subject Global Aesthetic Improvement Scale (GAIS)



3.2.1.5 *FACE-Q instruments* [redacted]

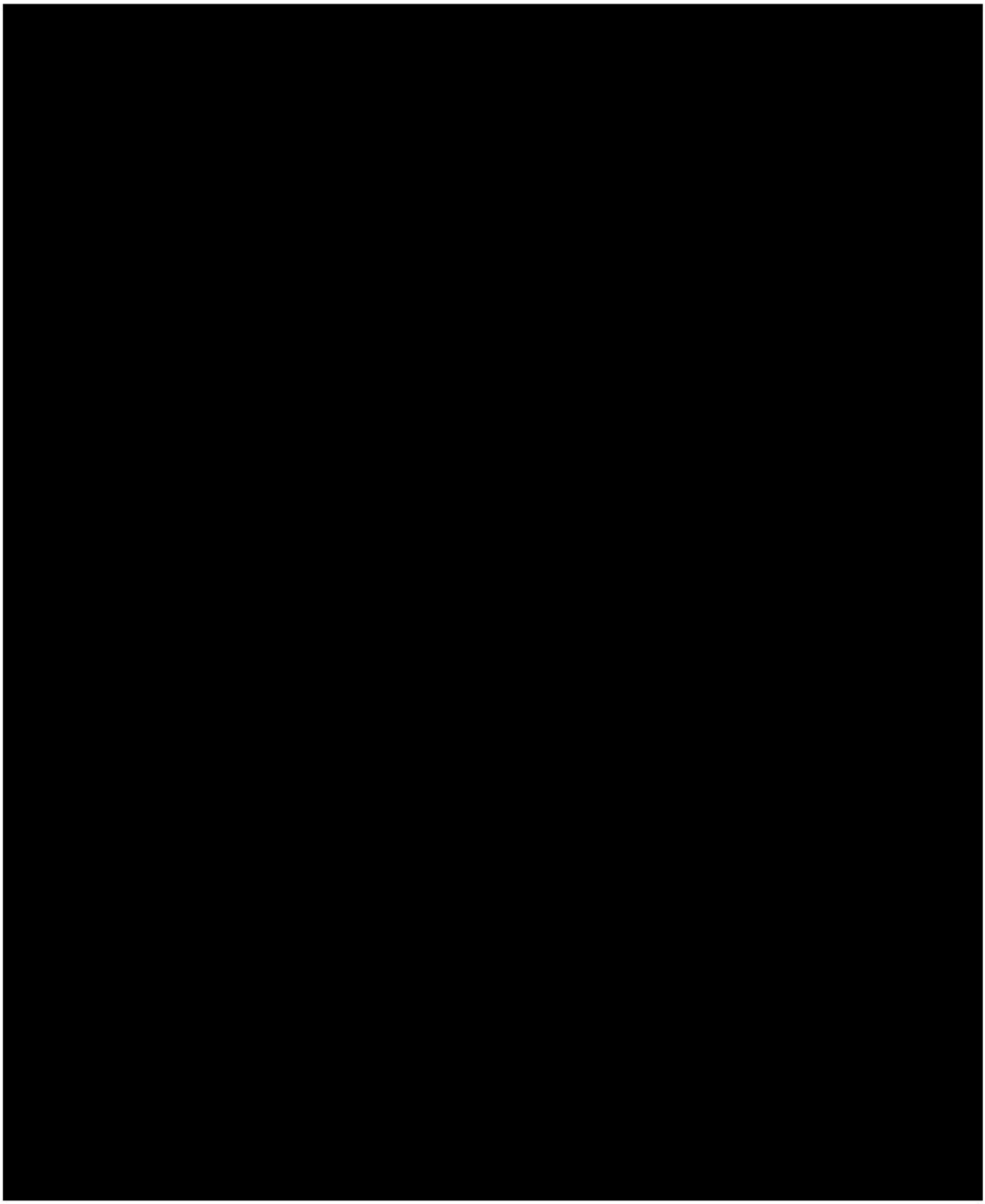
Treated and control subjects will evaluate the treatment outcome using FACE-Q instruments (see Appendix 10.4). [redacted]

[redacted] FACE-Q satisfaction with eyes

[redacted]

Table 3: FACE-Q satisfaction with eyes

[redacted]



3.2.2 Safety assessments

3.2.2.1 Adverse events and common treatment responses

All AEs reported by study subjects, investigators, or other study staff after the time of informed consent through end of study will be recorded. Events will be recorded regardless of causality. Note: End of study will be 13-months from baseline treatment for subjects who receive a touch-up, 12-months from baseline treatment for subjects who do not receive a touch-up, and Month 2 for control subjects.

A subject diary will be dispensed on the day of treatment to collect CTR information as well as specific safety concerns. The diary will be collected daily for 4-weeks post-treatment. Another 4-week diary will be distributed and completed following touch-up treatment at Month 1, if applicable.

Subjects will be asked to record daily on the diary any pre-defined CTRs and other safety events that may occur. The treating investigator will review and determine if any entries should be captured as AEs. Subjects assigned to the control group will not be provided or asked to complete the diary.

After the baseline treatment, treated subjects will receive a 72-hour post-treatment phone call and return to the clinic for a 2-weeks post-injection visit. During these safety checks, the subject diary will be reviewed for potential AEs. Subjects will continue their diary for 1-month after baseline treatment. If a subject receives an optional touch-up 1-month after baseline treatment, the subject will receive a 72-hour post touch-up phone call and return to the clinical 2-weeks post touch-up. Touch-up diaries will be reviewed for potential AEs and subjects will continue to complete the diary for 1-month after the touch-up injection.

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

3.2.2.2 Visual safety assessments

Although the incidence of SAEs associated with retinal artery occlusion is very low, treated subjects will undergo visual examinations to potentially identify several associated ophthalmic signs and/or symptoms that may represent ophthalmic artery occlusion.

All injecting physicians will be oculoplastic surgeons. In addition to plastic surgery expertise, these physicians have all completed ophthalmology training and have the knowledge and skill set specifically suited to injecting and treating issues in this anatomic area.

For subjects assigned to the treatment group, prior to injection, each subject will undergo a series of bilateral, visual safety assessments. These assessments will also be completed post injection at Week 2 and Months 1, 2, 3, 6, 9, and 12 after the last injection (i.e., either baseline treatment or touch-up, if applicable). If subjects received a touch-up 1-month after the baseline injection, a visual assessment will be performed immediately post touch-up. Visual assessments will include a visual acuity test (using a Snellen chart), a visual field test and an ocular motility exam. The investigator will also perform an undilated fundoscopic exam with an ophthalmoscope.

For subjects assigned to the control group visual safety assessments will be performed at baseline and Month 2.

3.2.2.2.1 Visual acuity

Visual acuity will be determined using the Snellen chart. Each site is equipped with a Snellen chart. The lane and distance from the chart will be confirmed by the monitor.

The site will follow standard directions for using the Snellen chart in determining visual acuity. The subject will be asked to cover one eye (if the subject wears glasses/contacts for distance vision they will be asked to keep them on/in). The examiner will point to each line as the subject reads the letters out loud. The smallest line where the subject identified the majority of letters correctly (i.e., if he/she could read 5 out of 8 letters on line 8, the visual acuity would be 20/20.) Visual acuity is expressed as a fraction. The top number refers to the distance the subject stands from the chart while the bottom number indicates the distance at which a person with normal eyesight could read the same line. The visual acuity per eye will be recorded in the electronic case report form (eCRF).

3.2.2.2.2 Visual field test

The Visual field test will measure how sensitive the vision is in different parts of the visual axis. To measure the visual field, the examiner will use the standard finger test according to the American Academy Ophthalmology.

3.2.2.2.3 Ocular motility exam

The examiner should determine if the subject's motility is intact in each direction of gaze. The subject should be instructed to voice if they have any double vision in any of these fields of gaze.

3.2.2.2.4 Undilated central retinal fundoscopic exam using an ophthalmoscope

In this procedure, the oculoplastic surgeon will perform a focused exam of the central retina and blood vessels to evaluate for any evidence of vascular occlusion.

After the injection of the first IOH (either baseline treatment or touch-up, if applicable), subjects will be asked to wait 30 minutes and then repeat the visual safety assessments for the already treated side. The subsequent side will then be injected once these assessments are completed on the first side and the investigator confirms that it is safe to proceed with treatment on the second IOH. The subject will then receive the Belotero Balance to treat the second IOH, wait 30 minutes, and then repeat the visual safety assessments for that side. When the subject returns for the 2-week safety follow-up visit and any subsequent visits, these visual assessments will be repeated and compared to baseline for any changes that could indicate a safety signal or concern.

NOTE: If only injecting one side for touch-up, only the side being injected will need the visual safety assessments 30-minutes post-treatment.

A local retinal specialist will be identified in advance to address any visual changes and potential retinal artery occlusion (i.e., investigator-determined, clinically significant changes in vision, such as blindness, blurriness, double vision, pain in or around the eye [other than typical injection-induced pain], blind spots, or restriction of eye motility).

3.2.2.2.5 Directions for intravascular injection or embolic event

In the event of intravascular injection or embolic event, the treating physician will provide prompt medical attention and follow the proper protocol for handling these symptoms. If in progress, best practices should be used to stop the injection. The treating physician should consider the following: an immediate referral to the retinal specialist, injection of hyaluronidase in the anatomic area of treatment and/or retrobulbar, and consideration of active reduction of intraocular pressure. The investigator should treat in accordance with the American Society for Dermatologic Surgery guidelines. The subject will be closely monitored by the treating investigator, and if applicable, a retinal specialist.

3.2.3 Definitions

3.2.3.1 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.

3.2.3.2 Subject completion

Subjects are considered to have completed the study if they are randomized, received treatment (for treatment group), and completed all visits defined in the Schedule of Events (see Section 5.1 and Appendices 10.1 and 10.2). Control group subjects are considered to have completed the study after all Month 2 assessments have been completed.

3.2.3.3 End of study and Total Study Duration

Subjects will be screened and enrolled/randomized at the first study visit. For subjects randomized to the treatment group, treatment will occur at this baseline visit. The time from the baseline visit to the end of study is 13 months for subjects who receive a touch-up, 12 months for treated subjects, and 2 months for control subjects.

The primary effectiveness endpoint is at Month 2 after the last injection (i.e., either baseline treatment or touch-up, if applicable); however, treated subjects will continue to be followed-up for safety after the effectiveness endpoint via clinical visits at Months 3, 6, 9, and 12 after the last injection received (i.e., either baseline treatment or touch-up, if applicable). Additional details regarding the timing of database lock and statistical analyses are provided in Section 8.5.

4 STUDY POPULATION AND RESTRICTIONS

4.1 Number of subjects and sites

Approximately 66 subjects will be enrolled and randomized, targeting approximately 44 subjects in the treatment group and 22 subjects in the control group. Subjects will be enrolled from up to 3 sites in the United States. Approximately 70% of the total sample size will consist of subjects with a Fitzpatrick skin type of I, II, or III and approximately 30% of the subjects will be Fitzpatrick skin type IV, V, or VI. Subjects from the Fitzpatrick skin type IV, V, and VI group will be distributed as follows: ≥ 6 subjects will be enrolled in the IV Fitzpatrick skin type group and ≥ 12 subjects will be enrolled with Fitzpatrick Skin Types V and VI Fitzpatrick skin type group. Each clinical site will enroll a minimum of 6 subjects with Fitzpatrick skin types IV, V, VI. At least 5 males will be enrolled into the study. Additional information regarding subject enrollment is provided within the sample size justification in Section 8.1.

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 IOH volume deficit with a rating of 2 or 3 (moderate or severe) on the [redacted] MIHAS.
- Has the same MIHAS score on both IOHs (i.e., IOHs are symmetrical).
- [redacted]
- Is at least 22 years of age.
- [redacted]

4.3 Exclusion criteria

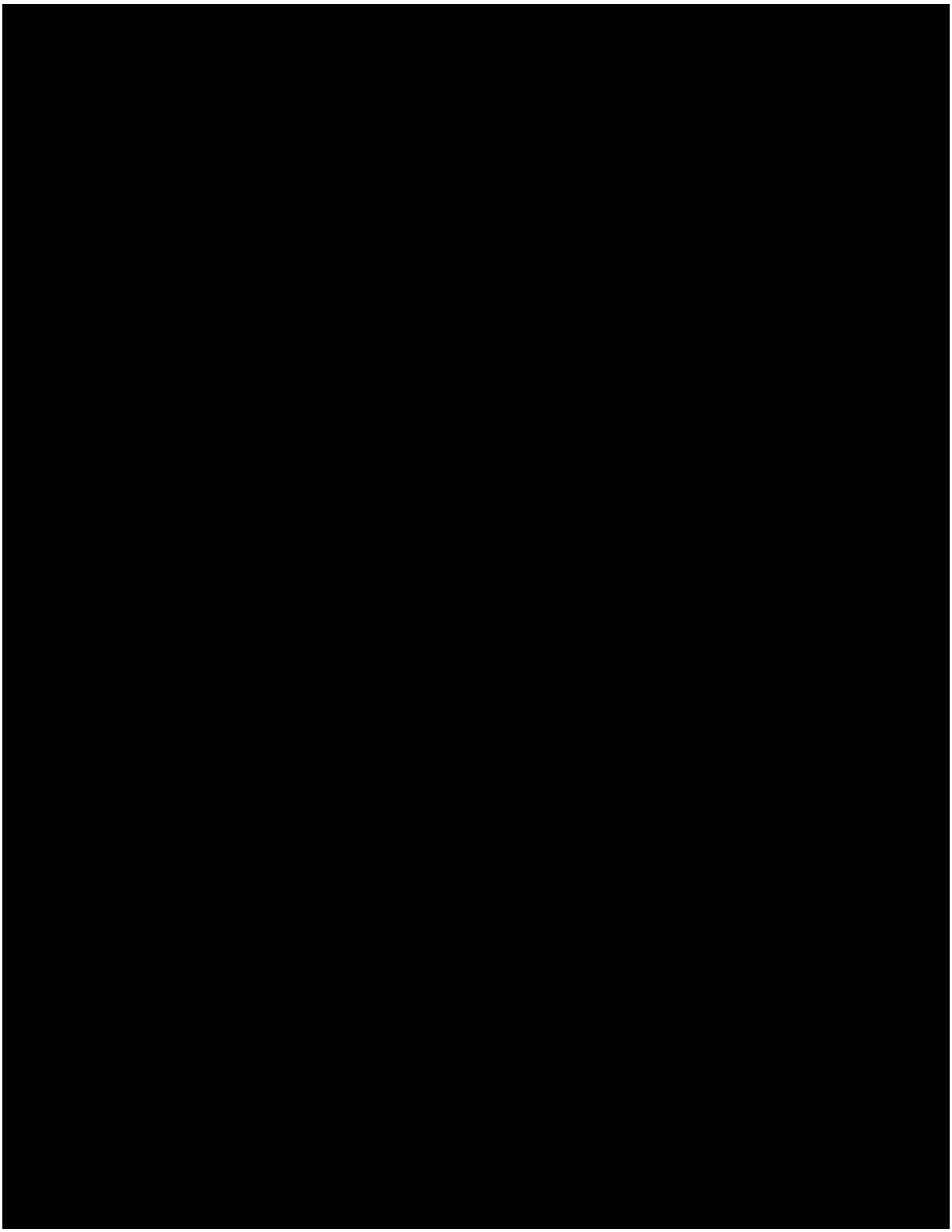
Subjects meeting any of the following criteria are not eligible to participate in the study:

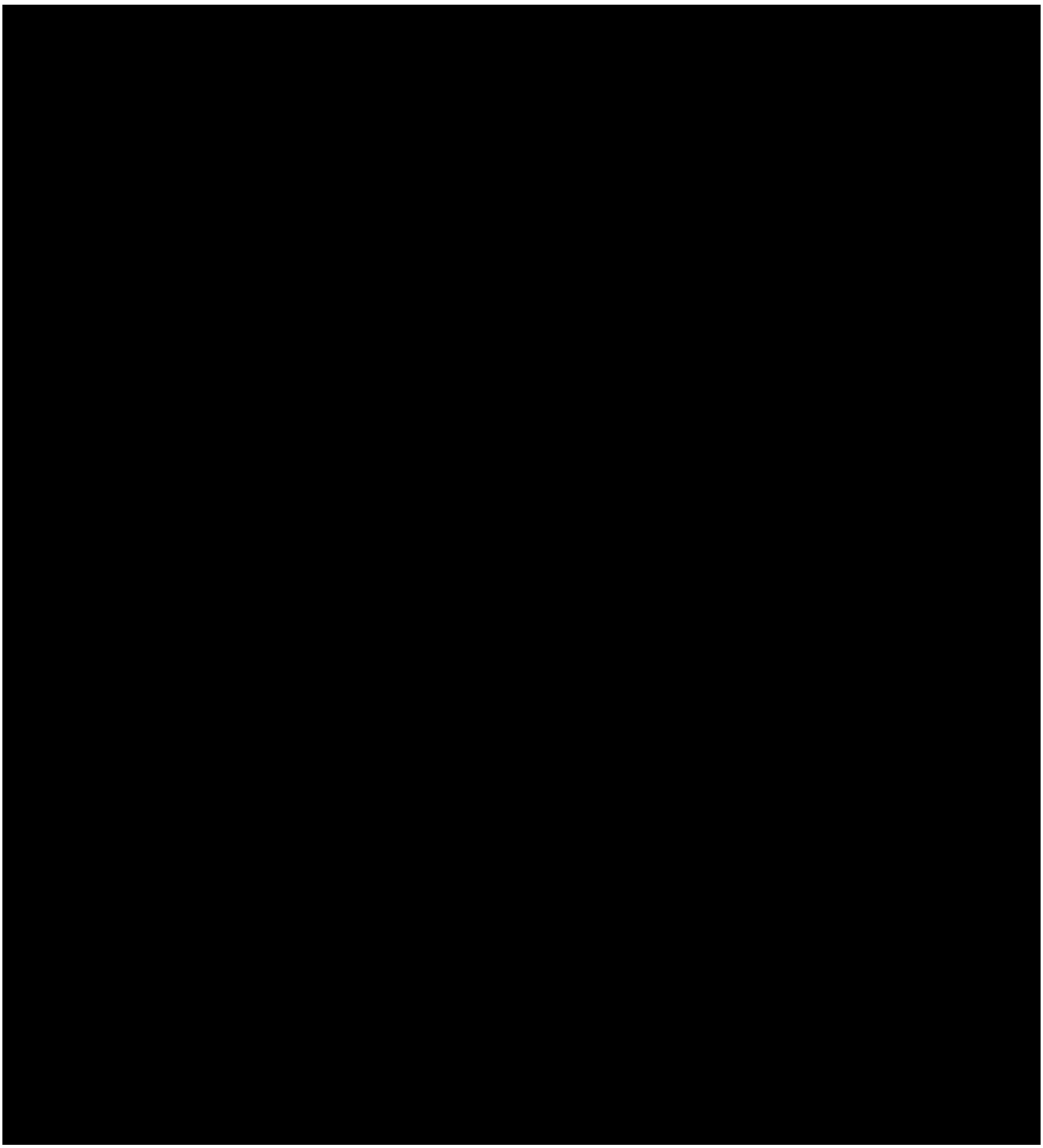
[redacted]

- Ever been treated with fat injections or permanent and/or semi-permanent dermal fillers in the midfacial region or plans to receive such treatments during participation in the study.

- Received lower eyelid and/or malar region treatments with any absorbable or temporary fillers such as porcine-based collagen fillers, hyaluronic acid (HA) products, RADIESSE®, poly L-lactic acid (PLLA) or received mesotherapy treatment to the area within the past 24 months or plans to receive such treatments during participation in the study.

[redacted]

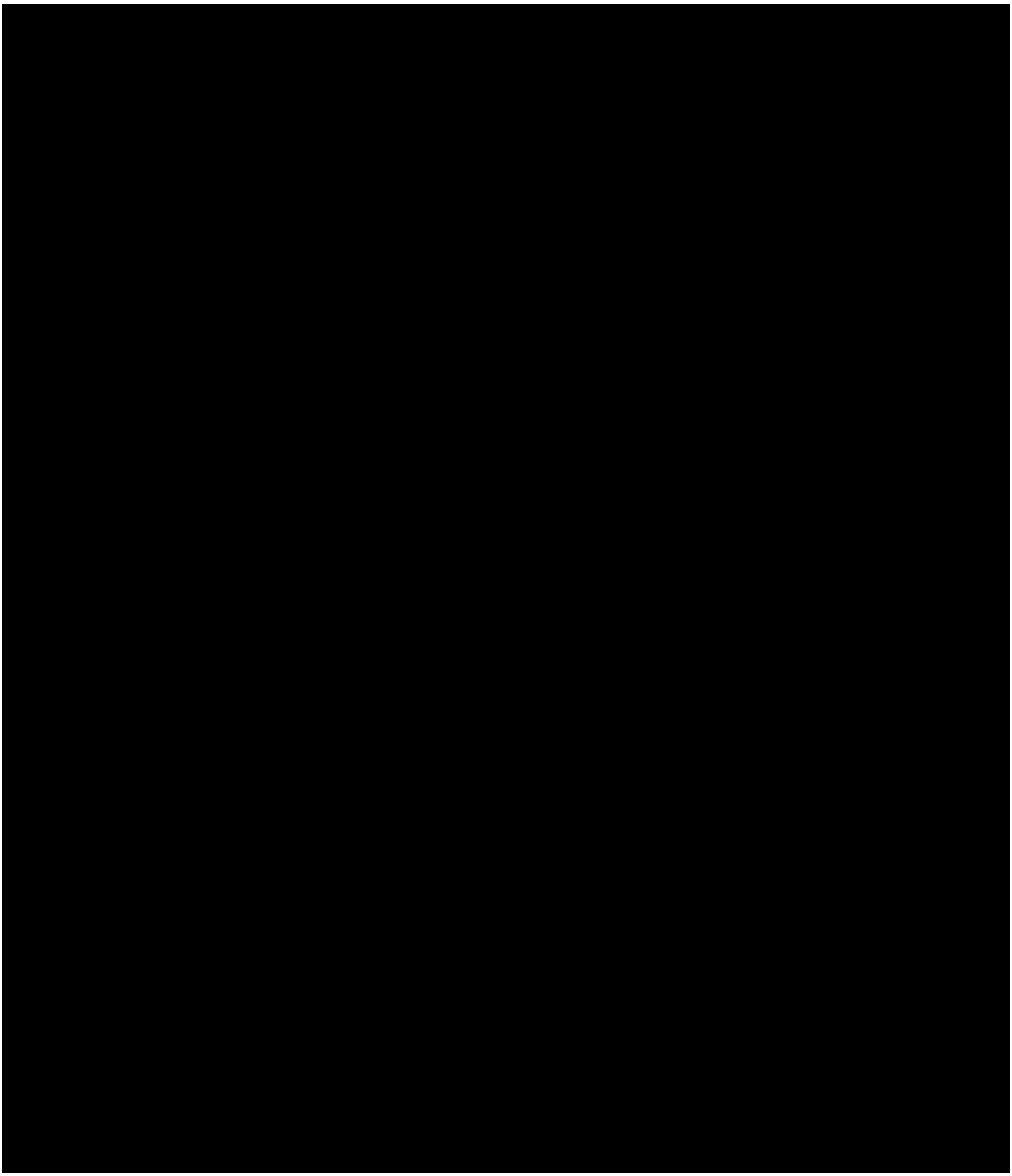




4.4 Subject restrictions during the study

By providing informed consent, subjects commit to refrain from receiving any of the following therapies, procedures, and/or exposures during the study interval (through 13

months for subjects who receive a touch-up, 12 months for treated subjects, or 2 months for control subjects):



[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 (EDC) system for screen failures, such as date of informed consent, demographics, reason for screen failure.

Individuals who do not initially meet the criteria for participation in this study (screen failure) may be rescreened one time. A subject is eligible for rescreening only if the reason for failure is due to inclusion/exclusion criteria other than his/her MIHAS rating (i.e., baseline MIHAS rating of 0, 1, or 4 or asymmetrical MIHAS scores). Subjects who are screen failures due to MIHAS ratings are not eligible for rescreening.

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 case report form (CRF).

5 STUDY PROCEDURES

5.1 Schedule of events by visit

The Schedule of Events is presented in Appendices 10.1 (treated subjects) and 10.2 (control subjects).

Day 0 (-28 Day) – Baseline Treatment (BT) / No Treatment (Control) includes Screening, Enrollment, and Baseline Assessments

The following procedures will be performed at this visit in the following order:

- 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.
- Assign subject identification.
- Collect demographic information.
- Collect height and weight. Height will be collected at the baseline visit only.
- Record medical history.
  - Record ocular history.
- Review and record concomitant medications/therapies.
- Perform urine pregnancy test (if female of childbearing potential). Negative test required prior to randomization.
- Confirm subject meets all eligibility criteria.
  - Treating physician confirms that the subject meets all eligibility criteria prior to randomization.
- Take standardized baseline IOH photographs.
- [redacted] perform the MIHAS assessment.

[redacted]

- Visual safety assessments on both eyes.
  - Visual acuity test (using a Snellen chart);

- Visual field test;
- Ocular motility exam; and
- Fundoscopic (opthalmoscopic) view of the eye (not dilated).

- Administer FACE-Q assessments to subject.
  - Satisfaction with eyes

[redacted]

- Randomize subject.

NOTE: Subjects randomized to the control group (no treatment) have completed this visit and will be scheduled for the Month 2 visit.

- Injection (for subjects randomized to the treatment group):
  - Administer treatment injection **to first IOH.**

[redacted]

  - Wait 30 minutes.
  - Perform visual safety assessments on first eye (where IOH area was treated).
  - Administer treatment injection to second IOH if treating investigator agrees that it is safe to proceed with injecting the second IOH.
  - Wait 30 minutes.
  - Perform visual safety assessments on other eye (where second IOH area was treated).
- Dispense subject diary and discuss completion instructions.
- Review and record AEs.
- Schedule 72-hour follow-up phone call and Week 2 visit.

Follow-up Phone call (72-hours ±1 day post treatment)

NOTE: This phone call is only for subjects assigned to the treatment group.

- Review and record changes in concomitant medications/therapies. Confirm subject remains compliant with any applicable study restrictions (see Section 4.4).
- Review and record AEs. Site staff will review subject diary responses to identify any safety concerns.

- If subject reports a safety concern, the subjects will be scheduled for an unscheduled visit, referred to a specialist, or be provided means of emergency medical care as determined by the investigator.
- Remind subject to continue the diary.
- Schedule and/or confirm Week 2 visit.

Week 2: Day 14 (+3 days)

NOTE: This visit is only for subjects assigned to the treatment group.

- Review and record changes in concomitant medications/therapies. Confirm subject remains compliant with any applicable study restrictions.
- Review subject diary for potential AEs. Remind subject to continue to record in the diary until Month 1 visit.
- Review and record AEs.
- Take standardized IOH photographs.
- Visual Safety Assessments on both eyes.
  - Visual acuity test (using a Snellen chart);
  - Visual field test;
  - Ocular motility exam; and
  - Fundoscopic (opthalmoscopic) view of the eye (not dilated).
- Schedule and/or confirm Month 1 visit.

Month 1: Day 28 (+3 days) Safety and assessment for Touch-up (TU)

NOTE: This visit is only for treated subjects

- Review and record changes in concomitant medications/therapies. Confirm subject remains compliant with any applicable study restrictions.
- Take standardized IOH photographs.
- Review and collect subject diary. The investigator will review the diary and determine if any diary entries should be recorded as AEs on the AE eCRF.
- Visual Safety Assessments on both eyes.
  - Visual acuity test (using a Snellen chart);
  - Visual field test;

- Ocular motility exam; and
- Fundoscopic (opthalmoscopic) view of the eye (not dilated).

- Review and record AEs.
- Schedule and/or confirm Month 2 visit.
- Asymmetry assessment based on a visual assessment completed by the treating investigator.

NOTE: Subjects who don't receive a touch up to address asymmetry based on the treating investigator's assessment have completed this visit and will be scheduled for the Month 2 visit.

Month 1: Touch-up (TU)

If the treating investigator determines a touch-up is needed to address asymmetry the following procedures will be done:

- Perform urine pregnancy test (if female of childbearing potential and for treated subjects only). Negative test required prior to touch-up injection.
- Injection (only if treating investigator notes asymmetry):
  - Administer touch-up injection **to first IOH.**

  - Wait 30 minutes.
  - Perform visual safety assessments on first eye (where IOH area was treated).
  - Administer treatment injection to second IOH if treating investigator agrees that it is safe to proceed with injecting the second IOH.
  - Wait 30 minutes.
  - Perform visual safety assessments on other eye (where second IOH area was treated).

NOTE: If only injecting one side, only the side being injected will need the visual safety assessment 30 minutes post treatment.

- Dispense subject diary and discuss completion instructions.

- Review and record AEs.
- Schedule 72-hour follow-up phone call and Week 2 visit.

NOTE: For subjects receiving a touch-up refer to the Follow-up 72 hour Phone Call, Week 2 and Month 1 (safety) assessments as described above. Then subject will continue with Month 2 assessments.

Month 2: Day 56 (+3 days) **ALL SUBJECTS**

Visit to occur 2 months after last injection (either baseline treatment or touch-up, if applicable) or 2 month after baseline visit for control subjects.

- Review and record changes in concomitant medications/therapies. Confirm subject remains compliant with any applicable study restrictions.
- Perform urine pregnancy test (if female of childbearing potential and for treated subjects only).
- Take standardized IOH photographs.
- Collect weight.
- Review and collect subject diary (touch-up subjects only). The investigator will review the diary and determine if any entries should also be recorded as AEs on the AE eCRF.
- Visual Safety Assessments on both eyes.
  - Visual acuity test (using a Snellen chart);
  - Visual field test;
  - Ocular motility exam; and
  - Fundoscopic (opthalmoscopic) view of the eye (not dilated).
- [redacted] perform MIHAS assessment.

[redacted]

- Have the treating investigator complete the investigator GAIS (treated subjects only).

NOTE: Standardized photographs, previously taken during the baseline visit, will be available for the treating investigator to reference when completing the Month 2 GAIS assessment.

- Have subjects complete the subject GAIS (treated subjects only).

NOTE: Standardized photographs, previously taken during the baseline visit, will be available for the subject to reference when completing his/her Month 2 GAIS assessment.

- Administer FACE-Q assessments to subject.
  - Satisfaction with eyes

[redacted]

- Review and record AEs.
- Schedule and/or confirm Month 3 visit (treated and touch-up subjects only).

Note: This is the last visit for subjects assigned to the control group.

Month 3 (Day 84), 6 (Day 168), 9 (Day 252), and 12 (Day 336) (± 7 days)

- Review and record changes in concomitant medications/therapies. Confirm subject remains compliant with any applicable study restrictions.
- Take standardized IOH photographs.
- Visual Safety Assessments on both eyes.
  - Visual acuity test (using a Snellen chart);
  - Visual field test;
  - Ocular motility exam; and
  - Fundoscopic (opthalmoscopic) view of the eye (not dilated).
- Review and record AEs.
- Schedule and/or confirm the next visit. Study participation ends after Month 12 visit.

5.1.1 Scheduled visits

All scheduled visits and applicable study assessments must occur as noted in Sections 5.1 and the Schedule of Events (Appendices 10.1 (treated subjects) and 10.2 (control subjects)).

5.1.2 Unscheduled visits

To ensure subject safety during the study, any subject who requires additional follow-up during the study for any reasons (that does not fall on a scheduled study visit) should

have that visit recorded as an unscheduled visit and all applicable CRFs for that unscheduled visit completed. Treated subjects will be followed at 72 hours via a safety follow up phone call. These phone calls may result in an unscheduled visit if any safety concerns are identified. Treated subjects will be completing a diary for 28 days post baseline injection and for 28 days post touch-up injection, which may alert site staff to schedule an unscheduled visit if any safety concerns are identified.

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 will 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 assessments specified in the Schedule of Events (Appendices 10.1 (treated subjects) and 10.2 (control subjects).

5.2.2 Premature suspension or termination of study

Should the investigator, the sponsor, the 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 treatment related vascular embolic event leading to skin necrosis, vision loss, or stroke, the study will be suspended and a root-cause investigation will be conducted to determine the cause of the embolic event and whether the outcome was anticipated or unanticipated. If the latter situation is observed, the study will be immediately suspended and no subjects will be enrolled or treated until the event can be properly characterized and an appropriate treatment strategy to avoid this unanticipated event can be devised.

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, lost to follow-up (e.g., moving away from study site; unresponsive to attempts to contact the subject), any AE or adverse device effect (ADE).

If a subject withdraws consent to continue in the study, the investigator should make every attempt to complete the final study visit. If a non-serious AE is unresolved at the time of the subject's final study 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 serious adverse events (SAEs)/unanticipated adverse drug effects (UADEs) 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 treatment 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

Belotero Balance is a sterile, bioresorbable, non-pyrogenic, viscoelastic, clear, colorless, homogeneous gel device. Belotero Balance is a bacterially fermented, injectable, hyaluronic-acid-based dermal filler. After extraction and purification, hyaluronic acid manufactured from streptococcal cultures is cross-linked with a binding agent 1,4-butanediol diglycidyl ether (BDDE) in two consecutively executed reactions and reconstituted in a physiologic buffer at pH 7 and concentration of 22.5 mg/mL.

6.2 Usage

Belotero Balance should be used in the IOH treatment region according to the information and injection instructions presented in Section 6.3.3. Additional information on product usage is provided in Appendix 10.3.

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. Study treatment (injection) will be administered only to eligible subjects by a qualified oculoplastic surgeon. Subjects will not be dispensed any investigational material. Any noncompliant subject or site may be discontinued from the study (Section 5.2).

6.3.1 Planned treatment procedure and administration

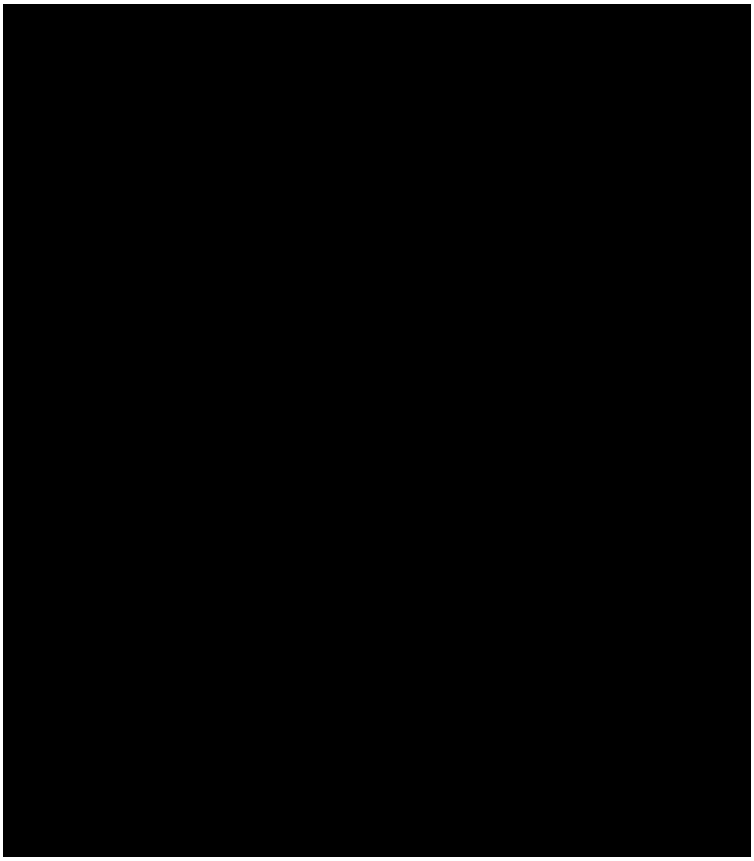
Approximately 44 subjects will be randomized to receive treatment and 22 subjects will serve as the controls. Subjects will be randomized using a 2:1 allocation ratio for treatment to control.

For subjects randomized to the treatment group, both right and left IOHs will receive treatment with Belotero Balance per the administration instructions specified below.

6.3.2 Infraorbital hollow treatment region

Belotero Balance is to be deposited in the supraperiosteal plane. Injection volume will be recorded. Figure 3 illustrates the region of the IOH that may be treated. The infraorbital treatment area is at the junction of the lower eyelid and mid-face where a volume deficit has formed. The area is bordered by the nasal sidewall medially, the temporal region of the bony orbit laterally, the bulk of the lower eyelid superiorly, and the superior aspect of the mid-face inferiorly.

Figure 3: Treatment region



6.3.3 Injection procedure

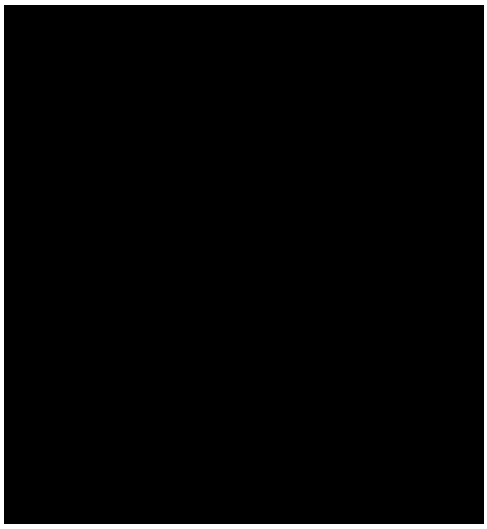
6.3.3.1 Preparation of the injection region

- Any makeup in the IOH area should be removed.
- As with all transcutaneous procedures, Belotero Balance injection carries a risk of infection and should be conducted with aseptic technique.
- Only topical anesthetic, at the preference of the treating physician, or ice may be applied. Any medication or therapy must be recorded in the CRF.

6.3.3.2 Directions for use of cannula

1. To attach the cannula to the syringe, open the cannula packaging to expose the hub. Use only the cannula provided with the clinical trial supply.
2. Remove the Luer lock syringe cap from the distal end of the syringe prior to attaching the cannula (see Figure 4).

Figure 4: Removing the Luer lock syringe cap from the syringe



3. Holding the Luer lock fitting of the syringe, twist the cannula onto the syringe. The cannula must be tightened securely to the syringe. Do not over-tighten as this may break the cannula and/or dislodge the syringe (see Figure 5).

Figure 5: Placing the needle or cannula onto the syringe

4. Pull off the cannula guard to expose cannula (see Figure 6).

Figure 6: Removing the cannula guard

5. Prime the cannula with Belotero Balance.

6. If excess implant is on the surface of the Luer lock fitting, it will need to be wiped clean with sterile gauze. Slowly push the syringe plunger until the implant material exudes from the end of the cannula. If leakage is noted at the Luer lock fitting, it may be necessary to remove the cannula, clean the surfaces of the Luer lock fitting, and reattach the cannula. In extreme cases, replace both the syringe and the cannula.

6.3.3.3 Depth of injection and injection technique

Standard precautions associated with injectable materials should be followed.

- The cannula injection technique of Belotero Balance with regard to the angle and orientation of the bevel, the depth of injection, and the quantity administered may vary. Fewer injection points are usually used when a cannula is utilized instead of a needle. Insertion sites will typically be at the malar and zygomatic regions. For insertion of the cannula, first a skin puncture should be made at the desired insertion point using the provided needle. The needle will be of slightly larger gauge then the cannula. After the needle is withdrawn the cannula will be inserted through the established skin puncture. Subsequently, a tunneling, fanning, or combination injection technique will be used to achieve optimal results. Care must be used to avoid intravascular injection regardless of technique used.

- In general, when the needle and then cannula are inserted, it will be at an approximate angle of 30° or less parallel to the skin. Belotero Balance will be placed at the junction of the lower eyelid and midface along the inferior orbital rim in the supraperiosteal plane. The injection should be performed with a constant low-to-moderate pressure on the plunger, while slowly and gradually withdrawing the cannula. Slight elevation of the skin should be observed without significant blanching of the skin. To avoid visible lumps and/or discoloration,

avoid injection of Belotero Balance superficially when removing the cannula. When the injection is complete, the site may be gently massaged, if necessary.

6.3.3.4 Additional injection information

- If blanching occurs, the injection should be stopped and the area massaged until it returns to a normal color. Blanching may be a sign of a vascular occlusion. If normal skin coloring does not return, do not continue with the injection. Treat in accordance with the American Society for Dermatologic Surgery guidelines, which include possible hyaluronidase injection.
- Correct to the desired volume effect. Do not overcorrect. The degree and duration of the correction depend on the character of the defect treated, the tissue stress at the implant site, the depth of the implant in the tissue, and the injection technique. Markedly indurated defects may be difficult to correct.
- Follow national, local, or institutional guidelines for use and disposal of medical sharp devices. To help avoid needle or cannula breakage, do not attempt to straighten a bent needle or cannula Discard it and complete the procedure with a replacement needle from the clinical supply. Do not reshield used needles and cannulas. Recapping by hand is a hazardous practice and should be avoided. Discard unshielded needles and cannulas in approved sharps containers. For additional product handling information, see Section 6.2.

6.3.3.5 Post-treatment care/pain management

- To manage pain, once the injection is complete ice may be applied as needed.
- Acetaminophen may be taken if instructed by the physician. Any medication or therapy used by the subject must be recorded in the CRF.
- The following information should be shared with subjects:
  - Within the first 24 hours, subjects should avoid lower eyelid makeup, strenuous exercise, extensive sun, or heat exposure, aspirin or non-steroidal anti-inflammatory drugs and alcoholic beverages. Exposure to any of the above may cause temporary redness, swelling and/or itching at the injection site.
  - Any and all medications used throughout study participation should be reported by the subject to site personnel for recording in the CRF.

6.3.4 [redacted]

[redacted]

6.3.5 Packaging of treatment supplies

The following components are supplied for the injection procedure:

- Belotero Balance box containing one sterile 1-mL prefilled glass syringe of Belotero Balance with two 27G ½" or 30G ½" needles. [redacted]
  More than one Belotero Balance box may be used depending on injection volume.
- A peel-off patient label, indicating product, to be placed in the source documents.
- A separate bulk supply of 27G 40 millimeter (mm) blunt-tipped cannula with a 25G pre-hole needle will be sent for the injection procedure.

6.3.6 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, and monitored area in accordance with the labeled storage conditions.

Only authorized study personnel may supply, dispense, 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 Belotero Balance, pre-hole needles, and cannulas should be discarded per the appropriate handling and disposal procedures at the site. Any unused/unopened product, needles/cannulas and outer packaging (of used kits) should be retained for the monitor to perform device accountability procedures.

At the end of the study and after verification of study device kit 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 samples, 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.

6.3.7 Accountability procedures

The sponsor will provide the investigator with 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 Principal Investigator or an authorized designee will keep records documenting the receipt, use, return, and disposal of the investigational medical devices, which will include:

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 or dates of use.
5. Subject identification number.
6. Date on which the investigational medical device was returned/explanted from subject, if applicable.
7. The date of return of unused, expired, or malfunctioning investigational medical devices (if applicable).

[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 or the comparator.
- 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 adverse events 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 AE 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 a serious adverse event. 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 as 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 adverse device effect (SADE)

A SADE is defined as an SAE related to the use of an investigation 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, Investigator Brochure (IB), or Instructions for Use (IFU), 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, IB, or product labeling.

7.1.8 Common treatment responses (CTRs)

CTRs are common clinical presentations and/or side effects that a study subject may experience following treatment. Subjects will self-report CTRs, as defined *a priori* in the protocol, on a diary provided to them. The treating investigator will review the diary and determine if any diary entries should be captured as AEs. A CTR that is more severe than what is generally expected and/or is not resolving should also be evaluated by the investigator as a possible AE or SAE. CTRs include the following: swelling; visible lumps; bumps you can feel; bruising or discoloration; redness; rash; pain/discomfort (including burning/stinging); itching; blistering/peeling skin; and/or scabby/crusty skin.

Treated subjects will be instructed (within the diary) to seek immediate medical attention if any of the following symptoms are observed: changes in vision; fever; dizziness;

confusion; weakness in arms/legs; changes in alertness/consciousness; difficulty speaking; face droop; change in skin color comparing one side to the other; a blue or white spot of skin; and/or a headache that is more intense or longer than you usually experience. They will also have the opportunity to self-report any unforeseen/ unanticipated events on the diary.

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 AE, but could have led to a medical occurrence if 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 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 product labeling or the protocol.

All device malfunctions shall be documented 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 intensity of an AE will be classified as:

- ***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 eCRF AE report form). 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
- Recovered/resolved with sequelae
- Not recovered/not resolved
- Fatal
- Unknown

NOTE: If there is 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.

The period of observation for AEs and ADEs extends from signing of the informed consent form (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 eCRFs. 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, and/or device deficiency observed will be fully investigated, documented, and followed until the event is either resolved or adequately explained at the End of Study visit.

The investigator will assess and record any AE or ADE in detail in the subject's file (medical record) and in the eCRF AE report form. 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
- Serious (yes or no)
- Outcome
- Action taken with investigational medical device

In this study, any adverse event of visual disturbance (including, but not limited to, any loss of vision, blurry vision, double vision, pain in or around eye (other than typical injection-induced pain), blind spot or shadow in the visual field, trouble moving eyes, etc.) will be reported. The investigator will be instructed to report any AE of visual disturbance within 24 hours. The incident will then be reported to the Agency within 10 business days of receipt by the sponsor. These reports will be generated by the sponsor or designee and will include injection volume, symptoms observed, time to onset and resolution, and any interventions implemented.

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 or designee 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, 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 the end of the observational period would need to be reported if the investigator considers the event to be related to investigational medical device. These reports generally will not be entered into the investigation database. 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 their 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.

- A Device Technical Complaint form must be completed and submitted by the investigative site, irrespective of whether the complaint led to an AE.

- 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 [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. Each pregnancy has to be reported on the AE CRF.

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]

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

In order to assess the ability of the planned sample size to provide power for a statistical comparison of the treatment and control groups success proportions (based on a ≥ 1-point improvement on both IOHs using the MIHAS from baseline to Month 2), a power calculation using a Fisher's exact test with a binomial distribution was performed using the following assumptions:

- Type I error rate: 0.05 (two-sided)
- Control group success proportion: 0.20
- Treatment group success proportion: 0.60
- Allocation ratio (control: treatment): 1:2
- Total N (number of evaluable subjects): 60 (40 subjects in the treatment group and 20 subjects in the control group).

Based on the above assumptions, the study power is approximately 80%. To account for possible missing data, attrition, and/or study deviations (up to 10%), a total of 66 subjects will be enrolled (44 subjects in the treatment arm and 22 subjects in the no treatment control arm).

Approximately 70% of the total sample size will consist of subjects with a Fitzpatrick skin type of I, II, or III, and approximately 30% of the subjects will consist of subjects with a Fitzpatrick skin type IV, V, or VI. Subjects from the Fitzpatrick skin type IV, V, and VI group will be distributed as follows: ≥ 6 subjects will be enrolled in the Fitzpatrick skin type group IV and ≥ 12 subjects will be enrolled in the Fitzpatrick Skin Type group V and VI. Each clinical site will enroll a minimum of 6 subjects with Fitzpatrick skin types IV, V, VI. At least 5 males will be enrolled into the study.

In the event that the sample size accounting for missing data, attrition, and/or deviations is attained (i.e., 44 treated subjects and 22 untreated/control subjects), using the assumptions above, the study power would be approximately 84%.

nQuery Advisor 7.0 was used for the power calculation.

8.2 Randomization

The randomization procedure for this study will be a block randomization stratified per site which will be computer-generated independently of the study team. Block randomization will control for potential deviations from the intended allocation ratio between treated and control subjects. Accordingly, a 2:1 allocation ratio will be utilized with approximately 44 subjects randomized to treatment and 22 subjects to control.

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. All effectiveness endpoints will be analyzed as randomized.
- The Per Protocol Population (PP) 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 Safety Population (SP) will consist of all enrolled/randomized subjects who received at least one study treatment.

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 SP. 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

The sponsor will finalize the formal SAP prior to database lock. Deviations from the analyses outlined in this protocol will be documented in the SAP.

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

Adequate descriptive statistics will be provided for each endpoint. Continuous variables will be summarized by number of observations, number of missing, mean, standard deviation, minimum, median, maximum. Categorical data will be summarized by counts (n) and percentages (%). Ordered categorical data will be summarized by both.

[redacted]

8.4.1 Effectiveness analysis

8.4.1.1 Primary effectiveness endpoint

The primary effectiveness endpoint, the proportion of subjects with ≥ 1-grade improvement of both IOHs on the MIHAS from baseline to Month 2 will be summarized as percentages for the treatment ($p_{treatment}$) and control ($p_{control}$) subjects and inferentially compared according to the following hypothesis:

H_0 (null): $p_{treatment} \leq p_{control}$

H_a (alternate): $p_{treatment} > p_{control}$

For this hypothesis testing, the Fisher's exact test will be used to compare both proportions in order to test for the superiority of treatment over control. If the two-sided p-value obtained from this test statistic is < 0.05 H_0 will be rejected in favor of H_a.

8.4.1.2 Secondary effectiveness endpoint

- For the FACE-Q satisfaction with eyes, sum scores and the equivalent Rasch-transformed scores will be analyzed descriptively for baseline and Month 2 for treatment and control groups. The FACE-Q scale will be scored using a look-up conversion table approach. The scale ranges from 0 to 100 with higher numbers indicating greater satisfaction. The FACE-Q user manual is included in Appendix 10.4, and additional information related to the scoring of the FACE-Q satisfaction with eyes scale will be included in the SAP.

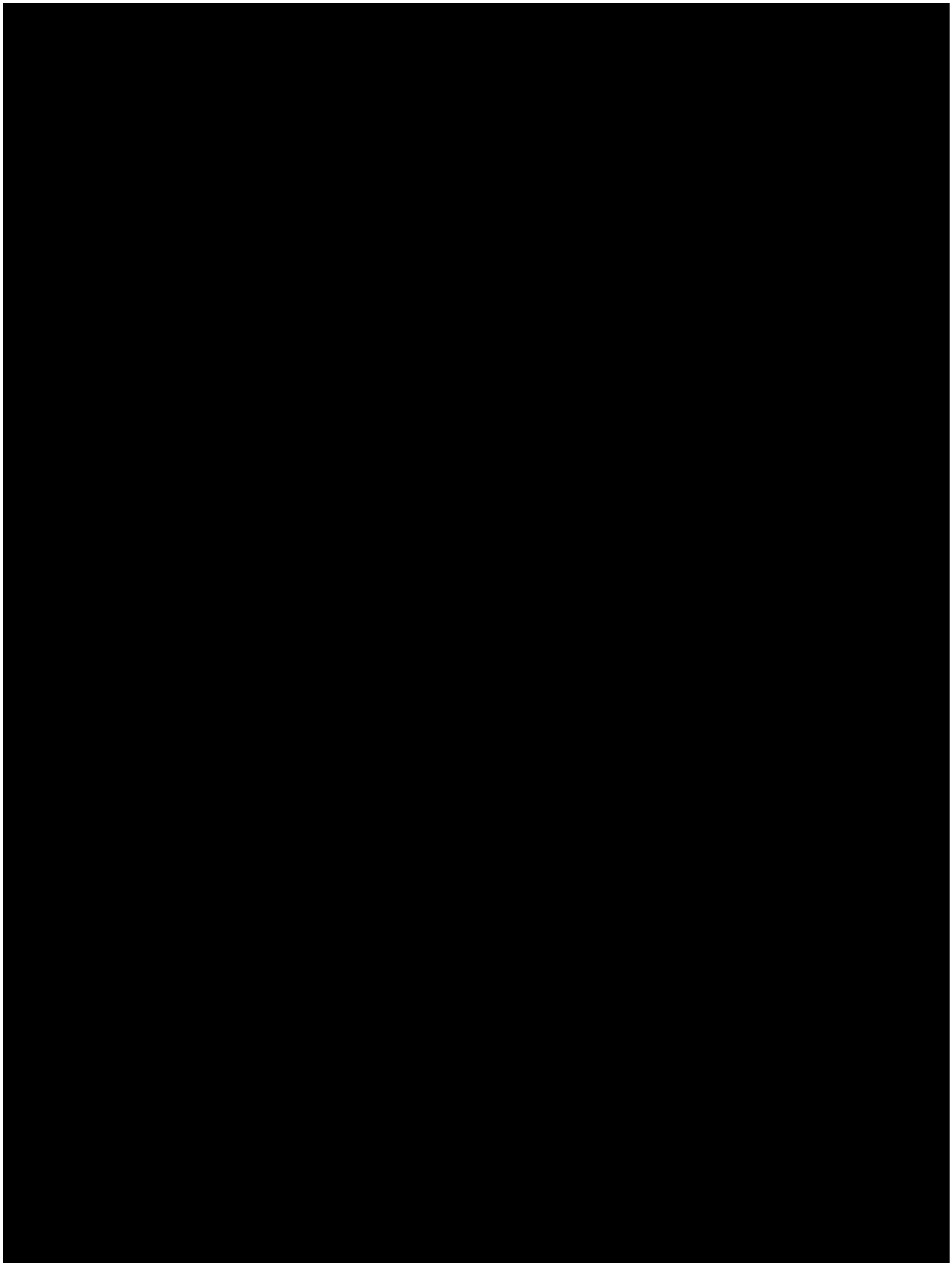
- The investigator GAIS categories will be analyzed descriptively at Month 2 post last injection (i.e., either baseline treatment or touch-up, if applicable) among treated subjects using counts (n) and percentages (%) for each GAIS category

[redacted]

[redacted]

- The responder rates at Month 2 according to the MIHAS, [redacted] using subject photographs will be summarized. Treatment response is defined as ≥ 1-point improvement on both IOHs compared to baseline. [redacted]

[redacted]



[redacted]

8.4.2 Safety analysis and endpoints

Nature, frequency, and severity of AEs will be recorded. All AEs, SAEs, and device effects will be stratified by treatment and summarized descriptively including type, duration, severity, relationship to study device.

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 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.

Treated subjects will be asked to record any CTRs that may occur in a subject diary. CTR results from the subject diaries will be summarized descriptively. The treating investigator will review all CTRs; he/she will determine whether any CTR qualifies as an AE and needs to be added to the CRF. CTRs that are deemed AEs will be presented in the AE tables and coded.

[redacted]

8.5 Timing of statistical analyses

The time from the baseline visit to the end of study is thirteen months. The primary effectiveness endpoint is at Month 2 post last injection (i.e. either baseline treatment or touch-up, if applicable); however, treated subjects will continue to be followed for safety via in clinic visits at Months 3, 6, 9, and 12 after the last injection (i.e., either baseline treatment or touch-up, if applicable). For the purposes of the clinical study report (CSR), statistical analyses will be performed after all subjects have completed the Month 2 post last injection visit. At this time, the data will be cleaned and the database temporarily locked for all effectiveness and safety analyses corresponding to the Month 2 primary effectiveness endpoint. A CSR will be written for these data and an addendum will be made to the report based on additional safety analyses associated with the safety monitoring for treated subjects up to 12 months after the last injection (i.e., either baseline treatment of touch-up, if applicable).

8.6 Special statistical/ analytical issues

8.6.1 Subject discontinuation and missing effectiveness data

To account for missing effectiveness data for the primary endpoint, missing MIHAS data will be imputed as no change (i.e. subject is considered as non-responder). This approach is conservative because it assumes that missing values are attributable to lack of treatment benefit. Furthermore, given that the primary effectiveness is only performed at baseline and Month 2 post last injection (i.e., either baseline treatment or touch-up, if applicable), the only observation that can be imputed for a missing Month 2 after the last injection time point is the baseline value, which assumes no change. Additionally, analyses will also be performed using the observed case (OC) method where no missing value imputations will be conducted. All other effectiveness and safety data will be analyzed as observed.

8.6.2 Imputation of safety data

Details regarding imputation rules and analyses of safety data (i.e., CTRs) will be provided in the statistical analysis plan and finalized prior to database lock.

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/EC, 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 contain contact information with a phone number the subject should contact if they have medical concerns 24 hours a day. Each ICF will also include the

contact information for a retinal specialist, who is identified by the Investigator, for instances in which a subject requires evaluation by a retinal specialist (e.g., subject experiences sudden visual changes following treatment injections).

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 in accordance with the currently approved protocol and all applicatory regulatory requirements and guidelines.

Investigators agree to grant direct 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). Standardized photography methods are detailed in the separate photography user manual.

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 case report forms should be derived from source documents and must be consistent with the sources from which they derive. Investigators will sign and date the case report forms 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 electronic case report forms (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.

Subjects will enter data into their electronic diaries and site staff will review the diary as required per protocol Sections 3.2.2.1 and 5.1.

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

- Copies of any photographs
- 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 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.

10 APPENDICES