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Clinical Study Protocol

Evaluation of Pain with Belotero® Balance with Integral Lidocaine for Correction of the Nasolabial Folds

Study protocol number:	M930021001
Protocol amendment date:	24-JUL-2017 (replaces Version 1.0, 26-APR-2017)
Development phase:	Device Pre-Market
Investigational product:	Belotero® Balance with integral lidocaine
Indication:	Injection into the mid-to-deep dermis for correction of moderate-to-severe facial wrinkles and folds, such as nasolabial folds
Sponsor:	Merz North America, Inc. 6501 Six Forks Road Raleigh, NC 27615 Telephone: (919) 582-8000
Authors:	Clinical Project Director: [redacted] Medical Expert: [redacted] Medical Writer: [redacted] Biostatistician: [redacted]

Signature Page

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

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

[redacted] 07-25-2017

[redacted] Signature Date

Statement of Compliance and Investigator Signature

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

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

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

Furthermore, I understand that:

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

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

PROTOCOL SYNOPSIS

Protocol Title	Evaluation of Pain with Belotero® Balance with Integral Lidocaine for Correction of the Nasolabial Folds
Protocol Number	M930021001
Active Product	Belotero® Balance with integral lidocaine
Comparator Product	Belotero® Balance
Study Phase	Device Pre-Market
Indication	Injection into the mid-to-deep dermis for correction of moderate-to-severe facial wrinkles and folds, such as nasolabial folds (NLF)
Number of Sites and Countries	This study will be conducted at up to three (3) study centers in the United States.
Number of Study Subjects	Approximately fifty-two (52) subjects will be enrolled and treated. Each NLF (i.e., right and left NLFs) will be analyzed separately for the primary and secondary endpoints, resulting in approximately 104 discrete units of measure.
Objectives	Effectiveness • Demonstrate the effectiveness of Belotero Balance with lidocaine (Test group) for the reduction of injection-related pain in comparison to Belotero Balance without lidocaine (Control group) for the correction of NLFs. Safety • Identify and describe adverse events (AEs) and serious adverse events (SAEs) during the course of the study. Additionally, common treatment site responses (CTRs) will be assessed.
Key Endpoints	Primary • Demonstrate a statistically significant, mean reduction in pain, measured using a 10-cm visual analogue scale (VAS), in the Test NLF compared to the Control NLF immediately after split-face NLF treatment (i.e., at time zero) on Day 1. Time zero will be defined as the time the last injection needle is removed from each NLF, separately, after a full correction on Day 1. Secondary • Compare the responder rates between the Test and Control NLFs, separately, at Week 6, as assessed live by the blinded evaluator and according to the Merz NLF Scale. Response is defined as ≥ 1-point improvement on the Merz NLF Scale for each NLF compared to baseline. Each NLF is to be assessed separately. 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 CTRs will be evaluated using subject diaries.
Study Design Overview	This is a 6-week, prospective, randomized, split-face, double-blind, multicenter, pre-market study to demonstrate the effectiveness of Belotero Balance with integral lidocaine (Test) for reduction of injection-related pain when compared to Belotero Balance without lidocaine (Control) for the correction of NLFs. The split-face study consists of two treatment arms. Approximately 52 subjects will be randomized to receive treatment with Belotero Balance with integral lidocaine (Test product) in one NLF and Belotero Balance without lidocaine (Control product) in the contralateral NLF on Day 1. Randomization will also determine which NLF (subject's right or left) will be injected first. Subjects will be eligible for an optional touch-up treatment, at the investigator's discretion and to achieve optimal correction, at Week 2. Subjects will be followed for at least 4 weeks after the last injection. Subjects enrolled will have a baseline rating of moderate to severe (i.e., rating of 2 or 3) on the Merz NLF Scale. Subjects must have the same Merz NLF Scale rating in both NLFs at the time of enrollment. A minimum of 20% of the enrolled subjects will be Fitzpatrick skin type IV, V, or VI. Subjects from the Fitzpatrick skin type IV, V, and VI group will be approximately evenly distributed within the IV, V, and VI categories. The planned duration of participation for individual subjects is 6 weeks. For all subjects randomized at baseline, the study will consist of three office visits and a 72-hour post-treatment phone call. Additional effectiveness assessments include the blinded-evaluator Global Aesthetic Improvement Scale (GAIS), the subject GAIS, and two (2) FACE-Q assessments.
Key Inclusion/ Exclusion Criteria	To be eligible for the study, each subject must meet all of the following criteria: 1. Has right and left NLF ratings of 2 or 3 (moderate or severe) on the Merz NLF Scale, as determined by the blinded evaluator. 2. Has the same Merz NLF Scale rating on both NLFs (i.e., symmetrical NLFs). 3. Is at least 18 years of age. 4. Understands and accepts the obligation not to receive any other procedures (i.e., dermal fillers, toxin treatments, facial ablative or fractional laser, microderm abrasion, chemical peels, non-invasive skin-tightening [e.g., Ultherapy, Thermage], or surgical procedures) below the orbital rim on the face during study participation. Patients meeting any of the following criteria are not eligible to participate in the study: 1. Had prior surgery in the mid- and/or lower-face area, including the nasolabial fold(s), or has a permanent implant or graft in the mid- and/or lower-face area that could interfere with effectiveness assessments. (**NOTE**: Rhinoplasty is permitted if the procedure

	was ≥ 12 months prior to study enrollment.) 2. Has skin or fat atrophy, beyond typical for the subject's age, in the mid- to lower-facial region or has been diagnosed with a connective tissue disorder. 3. Has unphysiological skin laxity or sun damage, beyond typical for the subject's age, or subject plans to tan during the study period. 4. Has undergone oral surgery (e.g., orthodontia, extraction, implants) in the past 30 days or plans to receive such surgery during participation in the study. 5. Has received mid- and/or lower-facial region treatments with porcine-based collagen fillers, Belotero® Volume, JUVÉDERM VOLUMA®, Restylane® Lyft, RADIESSE®, poly L-lactic acid (PLLA), or mesotherapy within the past 24 months and/or with other hyaluronic acid (HA) products within the past 12 months or plans to receive such treatment during participation in the study. 6. Has ever been treated with fat injections or permanent and/or semi-permanent dermal fillers in the mid- and/or lower-facial region or plans to receive such treatment during participation in the study. 7. Has received immunosuppressive medications or systemic steroids (except intranasal/inhaled steroids) in the past 2 months or plans to receive such treatment during participation in the study. 8. Has an acute inflammatory process or infection at the injection site (e.g., skin eruptions such as cold sores, cysts, pimples, acne, eczema, hives, streptococcus infections) or history of chronic or recurrent infection or inflammation with the potential to interfere with study results or increase the risk of AEs. 9. Has a history of allergic/anaphylactic reactions, including hypersensitivity to lidocaine or anesthetics of the amide type, hyaluronic acid preparations, gram positive bacterial proteins, or any of the device components. 10. Has a known bleeding disorder or has received or is planning to receive anti-coagulation, anti-platelet, or thrombolytic medications (e.g., warfarin), anti-inflammatory drugs (oral/injectable corticosteroids or NSAIDs [e.g., aspirin, ibuprofen]), or other substances known to increase coagulation time (e.g., vitamins or herbal supplements, i.e., Vitamin E, garlic, gingko) from 10 days before injection to 3 days after injection. 11. Has any other medical condition with the potential to interfere with study outcome assessments or compromise subject safety (i.e., increase the risk of adverse events).

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List of Abbreviations

Abbreviation/Term	Definition
ADE	Adverse device effect
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
BDDE	Butanediol diglycidyl ether
BMI	Body mass index
CFR	Code of Federal Regulations
CI	Confidence interval
cm	Centimeter
CRF	Case report form
CRO	Contract research organization
CTM	Clinical trial material
CTR	Common treatment site response or common treatment response
eCRF	Electronic case report form
EDC	Electronic data capture
[redacted]	[redacted]
FAS	Full analysis set
FDA	Food and Drug Administration, US
[redacted]	[redacted]
GCP	Good clinical practice
IB	Investigator's brochure
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IFU	Instructions for use
IP	Investigational product
IRB	Institutional review board
kg	Kilogram
LD50	Lethal dose that kills 50% of a test sample
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MI	Multiple imputation
mL	Milliliter
N	Number of non-missing observations
NLF	Nasolabial fold
pH	Potential of hydrogen (quantitative measure of the acidity or basicity)
PI	Principal investigator
PLLA	Poly-L-lactic acid
PMA	Premarket approval

Abbreviation/Term	Definition
PPS	Per protocol set
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SES	Safety evaluation set
SOC	System organ class
UADE	Unanticipated adverse device effect
US	United States
UV	Ultraviolet
VAS	Visual analogue scale
WHO	World Health Organization

1 INTRODUCTION

1.1 Background

Belotero Balance (Control product) was approved by the U.S. FDA in November 2011 (PMA Number: P090016) to help smooth moderate-to-severe facial wrinkles and folds, such as nasolabial folds (NLF), by temporarily adding volume to facial tissue and restoring a smoother appearance to the face. At present, the approved Belotero Balance formulation does not contain lidocaine hydrochloride. The investigational device (Test product) is a change to the approved Belotero Balance formulation to integrate 0.3% lidocaine hydrochloride for the purpose of pain reduction.

Notably, a formulation similar to Belotero Balance with lidocaine has been registered in approximately 32 countries worldwide since 2013 (brand names: Esthelis Basic Lidocaine, Belotero Basic Lidocaine).

1.2 Study rationale

During the administration of dermal fillers, pain is one of the most consistent patient complaints [1]. To mitigate patient pain and discomfort, lidocaine hydrochloride ($C_{14}H_{23}ClN_2O$ x H_2O, herein, lidocaine) is frequently used by healthcare providers prior to dermal filler injection or alternatively lidocaine is mixed directly into the product [2][3][4].

Lidocaine is one of the most widely used anaesthetic drugs in the world. Although its activity as a membrane-stabilizing agent has made it useful as an anti-arrhythmic drug, the most common application of lidocaine is as a local anaesthetic. It is available as injectable solution and in topical formulations. The compound was first synthesized in 1943 and commercialized by Astra AB in 1948; this amide type anaesthetic has a long history of safe and effective use [5].

The safety profile of lidocaine is well characterized [6]. Toxicity is modest, with cited LD50 values from 159-773 mg/kg in rats and 105 mg/kg (intraperitoneal injection) in mice. The recommended maximum dosage in adults or children is 4.5 mg/kg or 300 mg/session. While serious side effects, including respiratory failure and cardiac arrest, have been observed at high doses, especially following intravenous administration, side effects following peripheral injection at the recommended dosage are modest and include dizziness, tinnitus, drowsiness, and sensation of heat, cold, or numbness. Although allergic reactions to lidocaine have been documented, they have been reported as being “extremely rare”. Buffering the pH of lidocaine solutions near physiological pH, but below pKa of ~7.85, improves both safety and efficacy, since lidocaine hydrochloride is more soluble than lidocaine base, and buffered lidocaine solutions are less painful at injection than unbuffered solutions [7][8].

The pharmacokinetics profile of lidocaine has been extensively studied in both humans and animal models. In humans, the majority (up to 70%) of lidocaine is metabolized in the liver, with the metabolites excreted in the urine. Lidocaine levels in the blood follow a biphasic exponential curve, with an initial half-life of 8 to 17 minutes in the first 10 to 15 minutes after intravenous injection followed by a half-life of 87 to 108 minutes for the remainder of the degradation time in humans. Lidocaine diffuses rapidly through tissue, reaching peak plasma concentration only 17 minutes after intranasal administration in rats.

Pairing its efficacy with an extensive physician experience, lidocaine is frequently the anaesthetic of choice in facial aesthetic applications and has been incorporated into products such as Artefill®, Prevelle® Silk, Restylane-L®, Radiesse® (+), and JUVÉDERM® Ultra, all at the 0.3% concentration.

Literature on the effectiveness and safety of lidocaine in various facial aesthetic applications, accompanied by its use in other similar products, justifies the need for Merz North America, Inc. to conduct a robust randomized clinical trial to demonstrate the effectiveness of Belotero Balance with lidocaine (Test product) for reduction of injection-related pain when compared to FDA-approved Belotero Balance without lidocaine (Control product) for the correction of nasolabial folds. The investigational device (Test product) is a change to the approved Belotero Balance formulation to integrate 0.3% lidocaine hydrochloride for the purpose of pain reduction.

1.3 Potential benefits and risks

The potential benefit of Belotero Balance with integral lidocaine (Test product) is the reduction of injection-related pain when using dermal fillers to correct the NLFs.

Adverse events have been identified during post-approval use of Belotero Balance (Control product); 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 adverse events associated with the use of Belotero Balance Lidocaine (Test product) include: induration (transient or permanent); bump (transient or permanent); nodule (transient or permanent); lump (transient or permanent); blister; edema/swelling; erythema/redness; rash; bleeding; hematoma; pain; itching/pruritus; tingling; numbness;

burning sensation; hyperpigmentation; hypopigmentation; Tyndall effect; inflammation; Type I allergy; Type IV allergy; superficial local infection; severe deep local infection; severe systemic infection; chronic infection; necrosis; scarring; severe vascular compromise; transmissible severe systemic disease; fever; granuloma; cardiovascular compromise (e.g., loss of consciousness, palpitations, nausea, vomiting); embolization; sweating; nausea; paralysis; organ damage; nervous system impairments (e.g., dizziness, paraesthesia); worsening of a pre-existing condition; headache/cephalgia; severe visual impairment/blindness; nonthrombotic embolism; discoloration; scarring; transient vascular compromise; and/or death.

For both the test and control products, an additional harm or risk, which is not an adverse event, includes disappointment due to lack of or reduced performance and/or undesirable aesthetic effect.

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

Lidocaine is commercially available and frequently used as a local and regional anesthetic agent. Potential side effects anticipated with its use include: lightheadedness; nervousness; apprehension; euphoria; confusion; dizziness; drowsiness; ringing noise in the ears; blurred or double vision; vomiting; sensations of heat, cold or numbness; twitching; tremors; convulsions; unconsciousness; respiratory depression and arrest; slow heartbeat; hypotension; and/or cardiovascular collapse, which may lead to cardiac arrest.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Effectiveness

The primary objective of the study is to demonstrate the effectiveness of Belotero Balance with lidocaine (Test product) for the reduction of injection-related pain in comparison to Belotero Balance without lidocaine (Control product) for the correction of NLFs.

2.1.2 Safety

The safety objective includes the identification and description of adverse events (AEs) and serious adverse events (SAEs) during the course of the study. Additionally, common treatment site responses (CTRs) will be assessed.

2.2 Endpoints

2.2.1 Primary endpoint

Demonstrate a statistically significant, mean reduction in pain, measured using a 10-cm visual analogue scale (VAS), in the Test NLF compared to the Control NLF immediately after split-face NLF treatment (i.e., at time zero) on Day 1. Time zero will be defined as the time the last injection needle is removed from each NLF, separately, after a full correction on Day 1.

2.2.2 Secondary endpoint

Compare the responder rates between the Test and Control NLFs, separately, at Week 6, as assessed live by the blinded evaluator according to the Merz NLF Scale. Response is defined as ≥ 1-point improvement on the Merz NLF Scale for each NLF compared to baseline. Each NLF is to be assessed separately. The blinded evaluator is a qualified healthcare practitioner, delegated by the treating investigator.

- [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 an 6-week, prospective, randomized, split-face, double-blind, multicenter, pre-market study to demonstrate the effectiveness of Belotero Balance with integral lidocaine (Test product) for reduction of injection-related pain when compared to Belotero Balance without lidocaine (Control product) for the correction of NLFs. Approximately 52 subjects will be enrolled at approximately 3 investigational sites in the United States; a minimum of 20% of the enrolled subjects will be Fitzpatrick skin type IV, V, or VI. Subjects from the Fitzpatrick skin type IV, V, and VI group will be approximately evenly distributed within the IV, V, and VI categories. Subjects enrolled will have right and left NLF ratings of 2 or 3 (i.e., moderate or severe) on the Merz NLF Scale, as determined by the blinded evaluator. Both NLFs must have the same rating (i.e., symmetrical NLFs) at baseline.

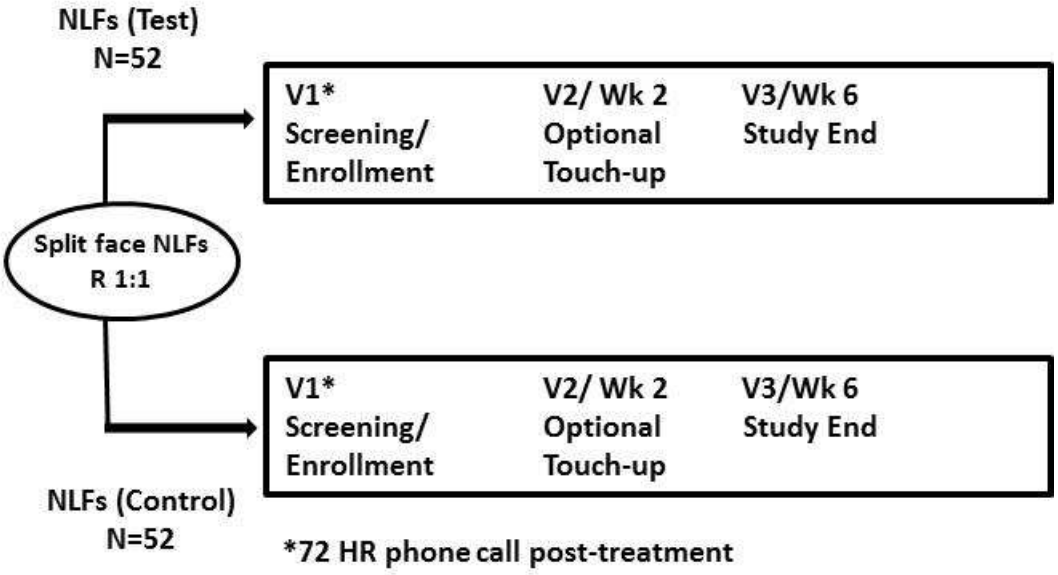
In this split-face design, a single randomization scheme will determine which NLF (subject's right or left) will be assigned to Test product or Control product and which NLF (subject's right or left) will be injected first. The treating investigator, the Merz NLF Scale evaluator, and the subject will be blinded to which NLF is randomized to Test and which NLF is randomized to Control.

Study subjects will receive treatment with Belotero Balance with integral lidocaine in one NLF (Test) and Belotero Balance without lidocaine in the contralateral NLF (Control) on Day 1. All subjects without ongoing, treatment-related, investigator-reported AEs will be eligible for an optional touch-up treatment, at the investigator's discretion and to achieve optimal correction, at Week 2. Each treatment session will consist of multiple mid- to deep-dermal injections of 0.1 to 0.2 milliliters (mL) Belotero Balance with and without lidocaine (up to a maximum of 3 mL per NLF over the two treatment sessions) into the left or right NLF according to the randomization assignment and the instructions for use. Subjects not receiving the optional, touch-up injection will be followed for six (6) weeks after their initial injection, while touch-up subjects will be followed for four (4) weeks after their last injection. Subjects will be evaluated at screening/enrollment, by phone at 72 hours after treatment, at Week 2 (optional touch-up treatment), and Week 6 (end of study). If subjects report a safety concern at the 72-hour phone call, an unscheduled visit will be scheduled to address safety concerns. Of the 52 estimated subjects enrolled, each NLF will be analyzed as a separate unit of measure (i.e., either Test or Control NLF) for the primary and secondary effectiveness endpoints, resulting in approximately 104 evaluable NLFs (52 Test, 52 Control). Pain levels, between the Test NLF and Control NLF, will be compared using a 10-cm VAS. Pain assessments will be evaluated at time zero (i.e., time the last injection needle is removed from each NLF, separately, after a full correction) [redacted].

Standard safety endpoints, including documentation of AEs and SAEs, will be assessed. Furthermore, several, pre-defined common treatment site responses (CTRs) will be evaluated via subject diaries.

Figure 1 illustrates the visit schedule associated with the split-face design. Section 5.1 and Appendix 11.1 detail a full schedule of study events and a schedule of events for each visit.

Figure 1: Study design



NLFs: Nasolabial folds; N: sample size; V: Visit; Wk: Week; R: Randomization; HR: hour

3.2 Study assessments and definitions

3.2.1 Effectiveness assessments

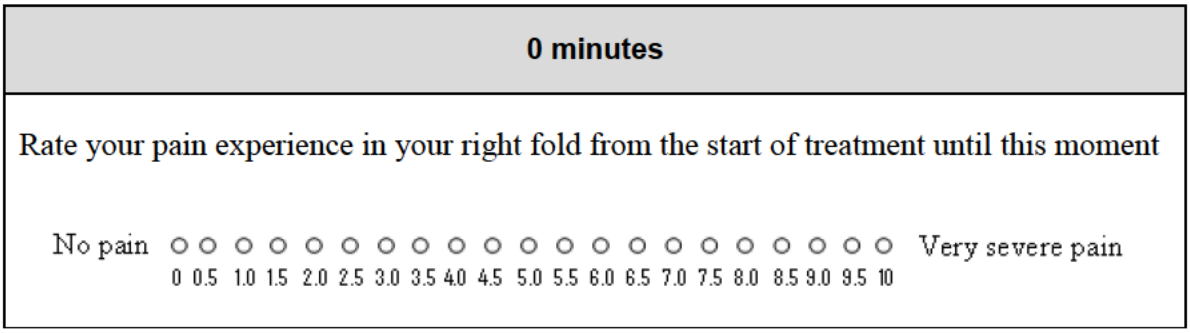
3.2.1.1 Evaluation of pain

Pain will be assessed using a visual analog scale (VAS) [9][10][11]; this VAS includes 21-numbered circles at 0.5 cm increments, spanning 10 cm total, and is anchored by word descriptors (see Figure 2). The level of pain will be evaluated for each NLF independently immediately upon completion of injection (time zero) [redacted] on Day 1. Time zero will be defined as the time the last injection needle is removed from each NLF, separately, after a full correction on Day 1. At time zero, the subject will be asked to rate the pain experienced throughout the injection

procedure in a given NLF. For all other intervals, subjects will be asked to rate the pain experienced at that specific time point.

At the specified Day 1 assessment times, subjects will be presented with the VAS and asked to circle the one (1) number that best describes their pain level. Subjects will have access to their previous scores during the rating process.

Figure 2: Example of a visual analog scale (VAS) for the right NLF at time zero on Day 1



Immediately after administration of the time-zero pain VAS, subjects will be asked to assess their treatment preference with respect to pain. The Subject Pain-Preference Assessment will include questions similar to the following:

1. Was one treatment less painful than the other? (yes or no)
2. If answered yes, which side was less painful? (right or left)
3. If answered yes to question 1: Based on the difference in pain you felt between the two sides, would you choose one treatment over the other in the future? (yes, no, or no preference).

The treating investigator or study coordinator will verbally query the subject and subsequently record the Subject Pain-Preference Assessment responses in the source documents and enter in the eCRF.

3.2.1.2 Evaluation of aesthetic effectiveness

3.2.1.2.1 Merz Nasolabial Fold Scale (assessed by blinded evaluator)

The Merz NLF Scale (see Figure 3) will be used to measure aesthetic effectiveness of the study products. The Merz NLF Scale is an outcome measure with a 5-point ordinal rating

for the assessment of NLF severity. In this study, the left and right NLFs of each subject are assessed independently with the Merz NLF Scale.

Study subjects will be evaluated at the screening/enrollment visit and at Week 6 with the Merz NLF Scale; the scale assessor is a trained evaluator who is blinded to the subject's treatment assignment and who will perform the scale assessment independently from any study staff. In addition to the Merz NLF Scale assessment, the blinded evaluator will evaluate the subject using a GAIS at Week 6 (see Section 3.2.1.2.3). The blinded evaluator should not be present for any study procedures other than the Merz NLF Scale assessment (at baseline and Week 6) and the Week 6 GAIS assessment, and he/she should not have access to subject study records. Further, subjects will be instructed not to discuss aspects of their treatment with the blinded evaluator.

Prior to study enrollment, at least one blinded evaluator at each site will be trained by the study sponsor to perform NLF ratings using the Merz NLF Scale. Training will consist of an instructional session, followed by the blinded-evaluator trainees scoring two sets of photographs, at least 2 weeks apart for inter- and intra-evaluator weighted Kappa analyses prior to study enrollment. Any blinded evaluator who does not achieve the minimal weighted Kappa point estimate value of ≥ 0.70 will be retrained and requalified. If sites have multiple blinded evaluators identified, the evaluator with the highest Kappa statistics will be chosen as the primary blinded evaluator. In the event the primary blinded evaluator is unavailable, the qualified backup evaluator may be used. Efforts will be made to maintain the same evaluator for all assessments throughout the study. If evaluator retention (e.g., change in personnel) becomes an issue during the study, new blinded evaluators must be qualified by the sponsor and the Kappa analyses must be re-run according to the criteria above. The qualification and training of the evaluators will be documented.

The treating investigator will also attend a Merz NLF Scale instructional session to ensure understanding of the subject-eligibility criteria of moderate-to-severe nasolabial folds, defined as a Merz NLF Scale rating of 2 or 3 at study entry.

Figure 3: Merz Nasolabial Fold Scale: At rest

[redacted]

3.2.1.2.2 Photographs

Standardized photographs will be taken at the screening/enrollment visit and at Week 6. [redacted] Every effort should be made to have the same study personnel take photographs at every visit. Photography procedures will be described in a separate user manual.

3.2.1.2.3 [redacted]

[redacted]

[redacted]

[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 the last study visit will be recorded. Events will be recorded regardless of causality.

A subject diary will be dispensed on the day of treatment (Day 1). Diaries will be reviewed by study staff at the Week 2 visit and re-dispensed for final collection at the Week 6 visit. Completed diaries will also be reviewed by study staff at the Week 6 visit. For subjects receiving an optional touch-up treatment at Week 2, the initial diary will be collected with only two (2) weeks of diary entries completed and a second diary will be dispensed and collected at Week 6. Subjects will be asked to record daily on the diary any pre-defined Common Treatment Site Responses (CTRs) that may occur. These CTRs will include: swelling; firmness; lumps/bumps; bruising; pain; tenderness upon pressing; redness; discoloration (not redness or bruising); itching; stinging/burning; and numbness. The treating investigator will review and initial the subject diary and determine if any entries should be reported as AEs. The investigator may also determine that a CTR will not be reported as a physician-reported AE.

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

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, and completed all visits defined in the Schedule of Events (see Section 5.1 and Appendix 11.1).

3.2.3.3 End of study

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

3.3 Duration of study

Subjects are screened and enrolled at the baseline visit. Treatment will occur at the screening/enrollment (baseline) visit. The time between baseline and end of study is 42 days (+ 3 day window).

4 STUDY POPULATION AND RESTRICTIONS

4.1 Number of subjects and sites

Approximately fifty-two (52) subjects will be enrolled and treated. Each NLF (i.e., right or left NLF) will be analyzed separately, resulting in approximately 104 discrete units of measure for the primary and secondary effectiveness endpoints. Subjects will be enrolled from up to 3 sites in the United States. A minimum of 20% of the enrolled subjects will be Fitzpatrick skin type IV, V, or VI. Subjects from the Fitzpatrick skin type IV, V, and VI group will be approximately evenly distributed within the IV, V, and VI categories. 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:

1. Has right and left NLF ratings of 2 or 3 (moderate or severe) on the Merz NLF Scale, as determined by the blinded evaluator (i.e., a qualified healthcare practitioner delegated by the treating investigator).
2. Has the same Merz NLF Scale rating on both NLFs (i.e., symmetrical NLFs).
3. Is a candidate for bilateral NLF treatment with Belotero Balance.
4. Is at least 18 years of age at the time of screening.
5. Has an adequate understanding (reading, speaking, and writing) of the local/ regional language.
6. Is willing and able to give written informed consent after having been informed of the requirements and the restrictions of the study.
7. Understands and accepts the obligation not to receive any other procedures (i.e., dermal fillers, toxin treatments, facial ablative or fractional laser, microderm abrasion, chemical peels, non-invasive skin-tightening [e.g., Ultherapy, Thermage], or surgical procedures) below the orbital rim on the face during study participation.
8. Is willing to comply with all requirements of the study, including being photographed, following post-treatment care instructions, and attending all study visits.

4.3 Exclusion criteria

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

1. Has skin or fat atrophy, beyond typical for the subject's age, in the mid- to lower-facial region or has been diagnosed with a connective tissue disorder.
2. Has unphysiological skin laxity or sun damage, beyond typical for the subject's age, or subject plans to tan during the study period.
3. Has an acute inflammatory process or infection at the injection site (e.g., skin eruptions such as cold sores, cysts, pimples, acne, eczema, hives, streptococcus infections) or history of chronic or recurrent infection or inflammation with the potential to interfere with study results or increase the risk of AEs.
4. Had prior surgery in the mid- and/or lower-face area, including the nasolabial fold(s), or has a permanent implant or graft in the mid- and/or lower-face area that could interfere with effectiveness assessments. (**NOTE**: Rhinoplasty is permitted if the procedure was ≥ 12 months prior to study enrollment.)
5. Had lower-lid blepharoplasty within 6 months prior to enrollment.
6. Has ever been treated with fat injections or permanent and/or semi-permanent dermal fillers in the mid- and/or lower-facial region or plans to receive such treatment during participation in the study.
7. Has received mid- and/or lower-facial region treatments with porcine-based collagen fillers, Belotero® Volume, JUVÉDERM VOLUMA®, Restylane® Lyft, RADIESSE®, poly L-lactic acid (PLLA), or mesotherapy within the past 24 months and/or with other hyaluronic acid (HA) products within the past 12 months or plans to receive such treatment during participation in the study.
8. Has undergone oral surgery (e.g., orthodontia, extraction, implants) in the past 30 days or plans to receive such surgery during participation in the study.
9. Has begun use of any new over-the-counter or prescription, oral or topical, skin products on the face within 90 days prior to enrollment or is planning to begin use of such products during participation in the study.

   NOTE: Use of sunscreens and continued therapy with some cosmeceuticals (e.g., alpha hydroxyl acids, glycolic acids, skin-bleaching agents, retinol, or retinoic acids) are allowed if the regimen was established > 90 days prior to enrollment and the subject agrees to continue the same regimen throughout the study.
10. Has used any prescription topical steroids or skin-irritating preparations on the face in the past 2 weeks or plans to receive such treatment during participation in the study.

11. Had prolonged exposure to natural or artificial sources of UV radiation (e.g., sunlight or tanning booth) on the face in the past 7 days or plans for prolonged UV-radiation exposure during participation in the study.
12. Has received facial dermal therapies (e.g., facial ablative or fractional laser, microderm abrasion, chemical peels, non-invasive skin-tightening [e.g., Ultherapy, Thermage], or surgical procedures) in the mid-face region within the past 12 months or plans to receive such treatment during participation in the study.
13. Has received neurotoxin treatment in the midface within the past 4 months or plans to receive such treatment during participation in the study.
14. Has received immunosuppressive medications or systemic steroids (except intranasal/inhaled steroids) in the past 2 months or plans to receive such treatment during participation in the study.
15. Has a history of allergic/anaphylactic reactions, including hypersensitivity to lidocaine or anesthetics of the amide type, hyaluronic acid preparations, gram positive bacterial proteins, or any of the device components.
16. Has facial nerve palsy or a history of facial nerve palsy.
17. Has volume deficit in the mid- and/or lower-face area due to medical conditions such as congenital defect, trauma, and abnormalities in adipose tissue related to immune-mediated diseases such as generalized lipodystrophy (e.g., juvenile dermatomyositis), partial lipodystrophy (e.g., Barraquer-Simons-Syndrome), inherited disease, or HIV-related disease.
18. Has active or a history of recurrent or chronic edema or rosacea in the mid- and/or lower-face area.
19. A history or documented evidence of an autoimmune disease (e.g., scleroderma, lupus erythematosus, rheumatoid arthritis).
20. Has a known bleeding disorder or has received or is planning to receive anti-coagulation, anti-platelet, or thrombolytic medications (e.g., warfarin), anti-inflammatory drugs (e.g., oral/injectable corticosteroids or NSAIDs [e.g., aspirin, ibuprofen]), or other substances known to increase coagulation time (e.g., vitamins or herbal supplements, e.g., Vitamin E, garlic, gingko) from 10 days before injection to 3 days after injection.
21. Has a propensity toward pigmentary skin changes, such as hyper- or hypo-pigmentation in the face, keloid formation, or hypertrophic scarring.
22. Has lost $\geq$ 2 body mass index (BMI) units within the previous 90 days or has the intention to lose a significant amount of weight during the course of the study.
23. Has a history of recurrent herpetic eruption in the midfacial region, excluding the lips, within 12 months.

24. Is a female of childbearing potential[1] and not using medically effective birth control[2] or is pregnant or lactating. (**NOTE**: Urine pregnancy tests will be used in female subjects of childbearing potential.)
25. Has facial hair (i.e., beards, sideburns, etc.) that would interfere with study assessments and/or create inconsistency in required study photography.
26. Has congenital methemoglobinemia, with glucose-6-phosphate dehydrogenase deficiencies, or is receiving concomitant treatment with methemoglobin-inducing agents.
27. Has any other medical condition with the potential to interfere with study outcome assessments or compromise subject safety (i.e., increase the risk of adverse events).
28. Refusal to refrain from any anesthesia or other methods to minimize pain (e.g., Tylenol®, ice or ice compress, topical anesthetic, local nerve block) before NLF injection on Day 1. That is, no pre-treatment forms of facial pain reduction are allowed on Day 1.

    NOTE: After completion of the 60-minute VAS pain assessment (see Section 3.2.1.1), ice, cold compresses, and/or other medication(s) to minimize swelling and bruising are permitted at the discretion of the treating investigator.
29. Has participated in a study in the last 30 days or is enrolled or plans to enroll in any other interfering investigational study during participation in this study.
30. Is an employee or direct relative of an employee of the investigational department of the site or of the study sponsor.

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:

- Application of any new over-the-counter or prescription, oral or topical, skin products in the mid- or lower-facial region.

[1] Childbearing potential is defined as NOT premenarche, permanently sterilized, bilateral tubal ligation, or postmenopausal (i.e., 12 months with no menses without an alternative medical cause).

[2] Defined as a highly effective method that results in a low-failure rate (i.e., less than 1% per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, IUDs, sexual abstinence, or vasectomized partner. Hormonal methods and IUD must be in use at least 30 days prior to first study product administration; barrier methods must be in use at least 14 days prior to study product administration; vasectomy must be completed 3 months prior to first study product administration, or as an alternative, a zero (0) sperm count will suffice.

  - **NOTE:** Use of sunscreens and continued therapy with some cosmeceuticals (e.g., alpha hydroxyl acids, glycolic acids, skin-bleaching agents, retinol, or retinoic acids) are allowed if the regimen was established > 90 days prior to enrollment.

- Cosmetic facial plastic surgery or oral surgery procedures (e.g., orthodontia, extraction, implants).
- Facial treatments with permanent and/or semi-permanent dermal fillers (e.g., collagen, fat, hyaluronic-acid products, calcium-hydroxylapatite products, etc.).
- Additional dermal therapies other than the investigational treatment (e.g., dermal fillers, neurotoxin treatments, facial ablative or fractional laser, microderm abrasion, chemical peels, non-invasive skin-tightening [e.g., Ultherapy, Thermage], or surgical procedures) on the face.
- Prescription topical steroids or skin-irritating preparations on the face.
- Immunosuppressive medications or systemic steroids (except intranasal/inhaled steroids).
- Prolonged exposure to natural or artificial sources of UV radiation (e.g., sunlight or tanning booth) on the face.
- Exposure to extreme cold or heat (e.g., sauna, Turkish bath).
- Loss of a significant amount of body weight (i.e., ≥ 2 BMI units).

Subjects are also prohibited from the following activities post treatment:

- Touching/pressing treated parts of the face for 12 hours post treatment.
- Applying makeup to treated parts of the face for 12 hours post treatment.
- Exercising strenuously for 24 hours after treatment.
- Consuming alcoholic beverages for 24 hours after treatment.
- Taking anti-coagulation, anti-platelet, or thrombolytic medications (e.g., warfarin), anti-inflammatory drugs (e.g., oral/injectable corticosteroids or NSAIDs [e.g., aspirin, ibuprofen]), or other substances known to increase coagulation time (e.g., vitamins or herbal supplements, e.g., Vitamin E, garlic, gingko) for 3 days after treatment.

Finally, if the subject is a female of childbearing potential, she must commit to not becoming pregnant during the study.

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, and reason for screen failure.

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

4.6 Subject withdrawal criteria

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

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

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

5 STUDY PROCEDURES

5.1 Schedule of events by visit

The Schedule of Events is presented in Appendix 11.1.

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

The following procedures will be performed at Visit 1:

Pre-treatment assessments:

- Obtain written informed consent. A subject must be informed of the study requirements, including the risks and benefits of participation. An IEC/IRB-approved informed consent must be signed and dated by the subject prior to any study-related activities or procedures being performed, including discontinuation of any prohibited medications.
- Record demographics/medical history.
- Review and record concomitant medications/procedures.
- Perform urine pregnancy test (if female of childbearing potential). Negative test required prior to randomization.
- Have blinded evaluator (i.e., a qualified healthcare practitioner delegated by the treating investigator and trained by the sponsor) independently perform the Merz Nasolabial Fold (NLF) Scale assessment.
    - **NOTE**: Every effort should be made to ensure that the same blinded evaluator perform the NLF scale assessment at each visit.
- Take standardized NLF baseline photographs.
- Treating physician confirms that the subject meets all eligibility criteria prior to randomization.
- Recall that no anesthesia or other methods to minimize pain (e.g., Tylenol®, ice or ice compress, topical anesthetic, local nerve block) are allowed before NLF injection. *That is, no pre-treatment forms of facial pain reduction are allowed on Day 1.*
- Randomize subject to Belotero Balance injections (Test or Control product by NLF, Subject's right or left NLF injected first). All subject randomization codes will be generated by an electronic system.
- [redacted]

Injection and accompanying assessments:

- Administer treatment injections**, not to exceed the maximum allowable injection volume of 3 mL per NLF over the two treatment sessions (initial injection on Day 1 and optional touch-up injection at Week 2).**
  - Document volume injected into each fold (right and left) in the eCRF.
  - Document injection technique (i.e., serial puncture and/or linear threading) in the eCRF.
    - **NOTE**: The same injection technique must be used for both NLFs on Day 1.
- Administer VAS pain assessment for each NLF at time zero (i.e., the time the last injection needle is removed from each NLF, separately, after a full correction).
- Administer Subject Pain-Preference Assessment (three questions) after treatment of both NLFs (i.e., immediately after the time-zero pain VAS assessment).

Additional visit 1 assessments:

- Record any AEs.
- Dispense subject diary and discuss completion instructions.
- Schedule 72-hour follow-up phone call.
- Schedule Visit 2.

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

- Review and record changes in concomitant medications/procedures.
- Review and record any AEs reported by the subject.
- If subject reports a safety concern, arrange an unscheduled visit to address.
- Remind subject to record CTRs in the subject diary.
- Schedule and/or confirm Visit 2.

Visit 2 (Week 2): Day 14 (+ 3 days)

- Review and record any changes in concomitant medications/procedures.
- Review and record any adverse events.
- Review and collect subject diary. Record subject-reported CTRs in the eCRF. The investigator will review and initial the diary and determine if any entries should also be recorded as AEs on the AE eCRF.

For subjects receiving a touch-up injection at Week 2:

All subjects without ongoing, treatment-related, investigator-reported AEs are eligible for an optional touch-up treatment, at the investigator's discretion and to achieve optimal correction, at Week 2.

- Perform urine pregnancy test (if female of childbearing potential).
- Administer touch-up injection**, not to exceed the maximum allowable injection volume of 3 mL per NLF over the two treatment sessions (initial injection on Day 1 and optional touch-up injection at Week 2).**
- Dispense subject diary and discuss completion instructions.

Visit 3 (Week 6): Day 42 (+ 3 days)

- Review and record any changes in concomitant medications/procedures.
- Review and record any adverse events.
- Perform urine pregnancy test (if female of childbearing potential).
- Take standardized NLF photographs.
- Have blinded evaluator independently perform the Merz Nasolabial Fold (NLF) Scale assessment.
    - **NOTE**: Every effort should be made to ensure that the same blinded evaluator perform the NLF scale assessment at both visits.
- [redacted]
- [redacted]
- Re w and collect subject diary. Record subject-reported CTRs in the eCRF. The investigator will review and initial the diary and determine if any entries should also be recorded as AEs on the AE eCRF.

5.1.1 Scheduled visits

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

5.1.2 Unscheduled visits

To ensure subject safety during the study, any subject who requires additional follow-up during the study for any reason (that does not fall on a scheduled study visit) should have that visit recorded as an unscheduled visit; additionally, all applicable eCRFs for that unscheduled visit should be completed (e.g., AEs, concomitant medications/ procedures).

5.2 Stopping rules

5.2.1 Criteria for treatment discontinuation

If study treatment is discontinued at any time during the treatment administration, the investigator will record the reason for treatment discontinuation in the study records. The investigator may request that a subject discontinuing treatment continue to participate in the study and complete all remaining visits and assessments. If a subject declines to continue study participation, the investigator will make every effort to perform the appropriate assessments specified in the Schedule of Events (Section 5.1 and Appendix 11.1).

5.2.2 Premature suspension or termination of the study

Should the investigator, 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 reported 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 entire study will be immediately suspended and no subjects will be enrolled 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 or lost to follow-up (e.g., moving away from study site; unresponsive to attempts to contact the subject).

If a subject withdraws consent to continue in the study, the investigator should make every attempt to complete the 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 the event. The investigator should make every attempt to follow all SAEs/UADEs to resolution. Information on pregnancy and the outcome for any female who becomes pregnant during the study will be collected. Additional information on subject withdrawal criteria is provided in Section 4.6.

5.2.5 Provision of care for subjects after study discontinuation

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

6 STUDY DEVICE AND TREATMENT OF SUBJECTS

6.1 Description of the study devices

6.1.1 Test product

The investigational device is a change to the Belotero Balance formulation to integrate 0.3% lidocaine hydrochloride for the purpose of pain reduction. Belotero® Balance with integral lidocaine is a sterile, bioresorbable, non-pyrogenic, viscoelastic, clear, colorless, homogeneous gel device. It 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.

Belotero Balance with integral lidocaine injectable implant will be supplied by the study sponsor. This product should be stored at room temperature (up to 25°C/77°F), away from heat, and should not be refrigerated. The test product has a clear, colorless (transparent) appearance. In the event that the syringe contains material that is not clear, do not use the syringe and notify the study sponsor.

6.1.2 Control product

Belotero® Balance is a sterile, bioresorbable, non-pyrogenic, viscoelastic, clear, colorless, homogeneous gel device. It 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. Belotero® Balance is indicated for injection into the mid-to-deep dermis for correction of moderate-to-severe facial wrinkles and folds, such as nasolabial folds. The Belotero Balance Premarket Approval (PMA) submission (P090016) was approved November 14, 2011 by the Food and Drug Administration (FDA). Belotero filler had been previously approved for aesthetic use in the United Kingdom, Germany, Italy, Russia, Austria, and Switzerland. Currently, the approved Belotero Balance formulation does not contain lidocaine hydrochloride. The Belotero Balance package insert is included in Appendix 11.2.

Belotero Balance injectable implant will be supplied by the study sponsor. This product should be stored at room temperature (up to 25°C/77°F), away from heat, and should not be refrigerated. Belotero Balance has a clear, colorless (transparent) appearance. In the event that the syringe contains material that is not clear, do not use the syringe and notify the study sponsor.

6.2 Usage

Test and control products should be used in the NLF treatment region according to the information and injection instructions presented in Section 6.3. Test and control products are packaged and designed for single use only. Syringes are not to be re-sterilized. Products should not be used if the package is opened or damaged or beyond the expiration date provided to the investigational site. Please refer to the study-site binder for the expiry date memorandum from Anteis SA (manufacturer); this memo indicates the clinical trial material (CTM) lot number, the expiration date of the lot, and a statement indicating the product meets its release specifications. Do not use CTM lots beyond the expiration date indicated by the manufacturer.

6.3 Study treatment

All protocol-specific criteria for the administration of study treatment must be met and documented prior to administration of any study treatment. All device administration (injection) will be performed on site by the principal investigator (PI); only the PI can inject. The PI is also described as the treating investigator in this document. 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

Subjects will receive treatment with Belotero Balance with integral lidocaine (Test product) and Belotero Balance without lidocaine (Control product).

At baseline, approximately 52 subjects will be randomized in this split-face study. Prior to injection, one NLF will be randomized to receive Belotero Balance with integral lidocaine (Test), and the contralateral NLF will receive Belotero Balance without lidocaine (Control).

A single randomization scheme will determine which NLF (subject's right or left) will be assigned to Test product or Control product and which NLF (subject's right or left) will be injected first. Randomization will be provided by an electronic randomization system, which site personnel must access following confirmation that the subject meets all eligibility criteria.

Care must be taken to follow the subject's randomization assignment – ensuring the Test product and Control product syringes are injected according to their assigned order (Test first or Control first) and into the NLF that is randomly assigned to be injected first (subject's right NLF first or subject's left NLF first). Accurate documentation of (1) which product (Test or Control) is injected into which NLF (subject's right or left) and (2) in the order assigned by the randomization system

(subject's right NLF first or subject's left NLF first) is of critical importance in this study.

During the screening/enrollment visit, randomized subjects will receive Belotero Balance (Test and Control) in both NLFs per the administration instructions below. Each NLF of each subject will be treated until, in the agreement of the treating investigator and the subject, an optimal result is achieved, defined as "optimal cosmetic result" for the implant in that subject; however, treatment is **not to exceed the maximum allowable injection volume of 3 mL per NLF over two treatment sessions (Day 1 and optional touch-up at Week 2)**. The same injection technique (i.e., serial puncture and/or linear threading) must be used for both NLFs on Day 1. Subjects will be eligible for a single, optional touch-up treatment, at the investigator's discretion and to achieve optimal correction, at the Week 2 visit.

Color-coded subject labels, packaged in the kit tray with the syringe and needles, will be used to document which NLF was injected with which blinded product. After receiving the randomization assignment and preparing the products for injection, these labels should be affixed to the subject's source documents. The site personnel shall write the following on each label:

1. (R)ight or (L)eft (corresponding to the subject's right or left NLF) and
2. #1 or #2 (corresponding to which NLF was treated first or second).

This information will remain in the subject's source documents and made available for verification of the proper randomization sequence by the sponsor or designee during monitoring visits.

Injection volumes, depth, and technique will be recorded for each NLF injection location. Observed AEs will also be recorded.

The NLF region and treatment area are shown in Figure 5 and Figure 6, respectively.

Figure 5: Nasolabial fold region

Crease formed lateral to the mouth from the alar-tragus to the oral commissure

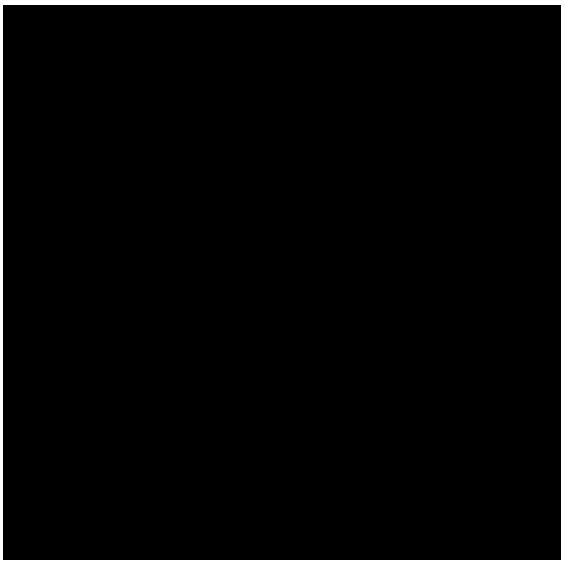


Figure 6: Treatment area

Injection in the nasolabial fold from the alar-tragus line to the oral commissure

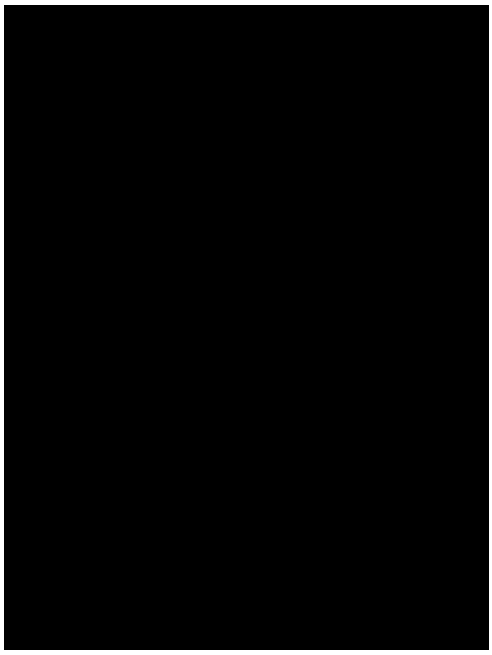
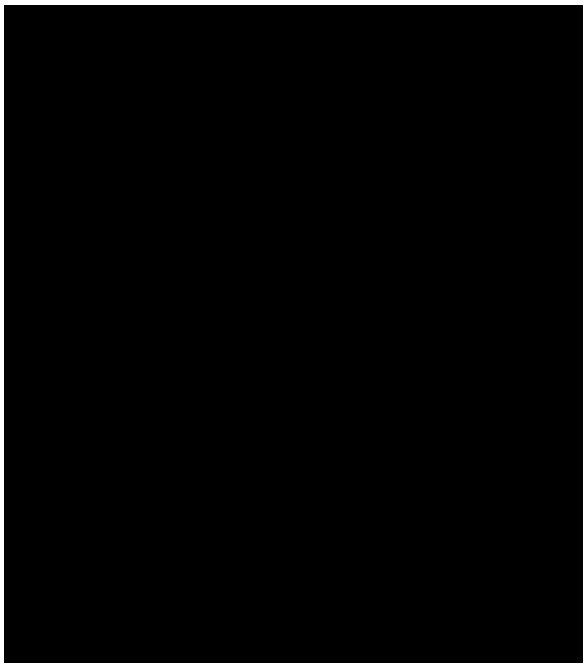


Figure 7: Alar-tragus line



6.3.1.1 Injection procedure

Injection occurs for all subjects at Visit 1 (baseline).

1. Prepare the pre-filled syringes of Belotero Balance (Test and Control) and the injection needle(s) before the percutaneous injection as described below. To assure proper needle attachment, use only needles provided with the clinical trial product.
2. To attach needle to syringe, open the needle packaging to expose the needle hub. Remove the Luer-syringe cap from the distal end of the syringe prior to attaching the needle.
3. Holding the Luer-lock fitting of the syringe, twist the needle onto the glass syringe provided in the kit, taking care not to contaminate the needle. Discard needle packaging. **The needle must be tightened securely to the syringe and primed with Belotero Balance (Test and Control) injectable implant. Do not over-tighten as this may break the needle and/or dislodge the syringe.**
4. Pull off the needle guard to expose needle. If excess implant is on the surface of the Luer-lock fittings, 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 needle.
5. If leakage is noted at the Luer fitting, it may be necessary to remove the needle, and clean the surfaces of the Luer fitting or, in extreme cases, replace both the pre-filled syringe and the needle.
6. Prepare subject for percutaneous injection using standard aseptic methods (e.g., alcohol, Betadine, chlorhexidine).

   NOTE: In this trial, no anesthesia or other methods to minimize pain (e.g., Tylenol®, ice or ice compress, topical anesthetic, local nerve block) are allowed in either NLF before device injection through the end of the 60-minute pain assessment on Day 1 (see Section 3.2.1.1).
7. According to the subject's randomization assignment (i.e., Test or Control product injected first and subject's right or left NLF injected first), Belotero Balance (Test and Control) is to be injected into the mid to deep dermis using a 30 gauge x ½ inch needle. The injection technique (i.e., angle and orientation of the bevel, depth of injection, and quantity administered) may vary. A linear-threading technique, tunneling technique, serial puncture injections, or a combination of these have been used to achieve optimal results. Care must be used to avoid intravascular injection, with particular attention given to the region superior to the alar-tragus line (see Figure 7), regardless of technique used.

NOTE: In this trial, the maximum allowable injection volume of Belotero Balance (Test or Control) is not to exceed 3 mL per NLF over the two treatment sessions. In addition, the same injection technique (i.e., serial puncture or linear threading) must be used for both NLFs at Day 1.

8. The number of NLF injection locations and volume (not to exceed 3 mL per NLF over the two treatment sessions) of dermal filler injected are at the discretion of the treating investigator until, in the agreement of the treating investigator and the subject, an optimal result is achieved, defined as "optimal cosmetic result" for the implant in that subject. Augment to optimal 1:1 correction. Do not overcorrect.
9. For the linear-threading technique and/or tunneling technique, the needle is inserted at an approximate angle of 30° parallel to the length of the NLF. The injection can be performed with a constant low-to-moderate pressure on the plunger while slowly and gradually withdrawing the needle.
10. For the serial puncture technique, the needle is inserted at multiple sites along the NLF as per the provider's clinical discretion.
11. With both injection techniques, 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 (Test and Control) into the superficial dermis when removing the needle.
12. If immediate blanching occurs, the injection should be stopped and the area massaged until it returns to a normal color. Blanching may represent a vessel occlusion. If normal skin coloring does not return, do not continue with the injection. Treat in accordance with the American Society for Dermatologic Surgery guideline, which includes **possible** hyaluronidase injection.
13. When the injection is complete, the site may be gently massaged, if necessary.

    NOTE: In this trial, after completion of the 60-minute VAS pain assessment (see Section 3.2.1.1), ice, cold compresses, and/or other medication(s) to minimize swelling and bruising are permitted at the discretion of the treating investigator.

14. Immediately stop the injection if a study subject exhibits any of the following symptoms: changes in vision; signs of a stroke; blanching of the skin; or unusual pain during or shortly after the procedure. Subjects should receive prompt medical attention and possibly evaluation by an appropriate healthcare practitioner specialist should an intravascular injection occur.

    Subjects must be also be informed that, at any time over the study interval, if they experience signs or symptoms of an intravascular injection, similar to those noted above, or symptoms listed on the first page of the study diary

card or within the informed consent form, they must seek immediate medical attention and notify the study doctor immediately. The study doctor must refer the subject to a specialist if additional medical attention is deemed necessary.

6.3.1.2 Maximum injection volume

In this study, the maximum injection volume of Belotero Balance (Test or Control) is not to exceed 3 mL per NLF over the two treatment sessions (Day 1 and optional touch-up injection at Week 2). Subjects should not receive more than 6 mL of Belotero Balance per year. The safety of injecting greater amounts has not been established.

6.4 Packaging of treatment supplies

Belotero Balance with integral lidocaine (Test product) and Belotero Balance without integral lidocaine (Control product) will be provided by the study sponsor. The sponsor will package study materials according to applicable regulatory requirements. The sponsor will provide all pertinent labeling information, as well as a description of the specific device-packaging conditions.

The sponsor will provide a blinded, bulk supply of both Test product and Control product. The product kits, including syringe and needles, will be distinguished only by different colored labels. Only the unblinded sponsor will have the product lot number key (i.e., code break).

Product kits will include:

- One sterile 1-mL prefilled glass syringe of Belotero Balance with integral lidocaine (Test) or
- One sterile 1-mL prefilled glass syringe of Belotero Balance without integral lidocaine (Control);
- Two sterile 30 gauge, ½ inch needle(s) with Luer-lock fittings; and
- Color-coded subject labels (provided in the kit tray) for appropriate source documentation.

6.5 Receipt, storage, dispensing, and return/disposal

Upon receipt, the site personnel will verify the contents of all study supplies received and promptly notify the appropriate contacts of any discrepancies or damages. The investigator is responsible for ensuring that an accurate record of inventory is maintained. The investigator will keep a current record of the study product delivery to the study site,

inventory, and dispensing, and this record will be made available to the sponsor upon request. Study sites will be queried about any discrepancies.

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

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

Any used syringes of Belotero Balance (Test and Control) and needles should be discarded per the appropriate handling and disposal procedures at the site. Any unused/unopened product, needles, and/or outer packaging (of used kits) should be retained so the monitor can 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 supplies, the following address shall be used:

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

Phone: (866) 862-1211
Fax: (866) 862-1212

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

6.6 Accountability procedures

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

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

1. The date of receipt.
2. Identification of each investigational medical device (batch number/serial number or unique code).
3. The expiry date (see Section 6.2 for additional information).
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).

6.7 Level and method of blinding

In this split-face design, the treating investigator, the Merz NLF Scale evaluator (i.e., person responsible for assessing aesthetic effectiveness), and the study subject will be blinded to treatment assignment. The blinded evaluator cannot be the treating investigator or the study coordinator.

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

7.1.4 Serious adverse event (SAE)

A SAE is any adverse event that results in:

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

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

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

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

7.1.5 Serious ADE (SADE)

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

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

7.1.6 Unanticipated adverse device effect (UADE)

A UADE is defined as:

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

7.1.7 Anticipated serious adverse device effect (ASADE)

An ASADE is defined as:

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

7.1.8 Common treatment site 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 diary cards provided to them. The treating investigator will review and initial the diary and determine if any entries should be reported 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, SAE, ADE, SADE, and/or UADE.

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 severity/intensity of an AE will be classified as follows:

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

The definitions above are difficult to apply for some data (e.g., clinically relevant laboratory values that are documented and evaluated on the 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
- Not recovered/not resolved
- Recovered/resolved with sequelae
- Fatal
- Unknown

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

7.2.4 Procedures for reporting specific events

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

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

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 eCRF. New AEs or ADEs reported to the investigator during the observational period (i.e., after the start of treatment with the investigational medical device) must also be documented, treated, and followed.

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

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

The investigator will assess and record any AE or ADE in detail in the subject's file (medical record) and in the 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
- AE resulting in subject discontinuation (yes or no)

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 7.2 and the site's IEC/IRB per their reporting guidelines.

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

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

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

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

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

SAEs/SADEs occurring after the end of the observational period would need to be reported if the investigator considers the event to be related to the 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 his/her standard of care.

7.2.4.3 Technical device complaints

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

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

- **A** Device Technical Complaint form must be completed and submitted by the investigative site, irrespective of the seriousness of the case.
- 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 using the following email address: complaints2@merz.com.

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 must be reported on the end of study eCRF.

7.3 Submission procedure

The investigator should complete and send any SAE forms or 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

Product Safety Fax: 336-458-5983
Product Safety Email: adverse.events@merz.com

7.4 Procedures for unblinding

Only the sponsor, the monitor, and the designee managing the electronic randomization system are unblinded in this study.

In the event of a medical emergency, where unblinding is determined to be necessary by the treating investigator, the medical monitor at the sponsor or designee will be contacted immediately to facilitate the identification of the Belotero Balance product (Test or Control) that was randomized to the NLF in question. In the event that unblinding becomes necessary, the treating investigator must adequately document the circumstances in the subject's source documents.

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 or unblinding, respectively, 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

Sample size calculation was performed using the nQuery+nterim version 4.0 statistical software. Based on a review of comparable clinical literature [2][3][4][12][13][14][15], it is assumed for this power calculation that a change of 3.8 cm on a 10-cm VAS represents a clinically meaningful difference in pain as experienced between lidocaine-treated and non-lidocaine-treated NLFs. Assuming a statistical power, 1–β of 95%, a one-sided level of significance of $\alpha = 0.025$, and a conservative estimate of standard deviation of difference of 7, a total of 47 subjects will be required. To account for possible subject dropout after randomization and prior to treatment (up to 10% attrition), a total of 52 subjects will be enrolled, yielding approximately 104 total NLFs (52 Test and 52 Control). Additionally, a minimum of 20% of the enrolled total sample size will consist of subjects in the Fitzpatrick Skin Types IV, V, or VI group. Subjects from the Fitzpatrick skin type IV, V, and VI group will be approximately evenly distributed within the IV, V, and VI categories.

8.2 Randomization

Randomization will be performed within blocks using a random allocation schedule that will assign one side of each subject's NLF to Belotero Balance with integral lidocaine (Test product) and the contralateral NLF to Belotero Balance without lidocaine (Control product) or vice versa. The blocks will be created in such a way that the proportion of subjects in both sequences (Test/Control – L/R or Control/Test – L/R) will be approximately equally distributed within each site.

8.3 Populations for analysis

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

- The Safety Evaluation Set (SES) will comprise subjects who are enrolled into the study, randomized, and receive an injection.

- The Full Analysis Set (FAS) is the subset of subjects in the SES for whom the primary effectiveness variable is available (i.e., all subjects who have a VAS assessment value for both left and right NLFs at time zero on Day 1).

- The Per Protocol Set (PPS) is a subset of subjects in the FAS without major protocol deviations. Final determination of what constitutes major or minor protocol deviations will be made prior to database lock.

The usage of the analysis populations as it pertains statistical analyses of study results will be described in the SAP.

8.4 Statistical analyses

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

Statistical tests will be two-sided at $\alpha = 0.05$ except for the primary effectiveness analysis where a one-sided $\alpha = 0.025$ will be used. Two-sided confidence limits (95%) and p-values associated with the appropriate test statistic will be provided where necessary. Primary and secondary effectiveness data will be summarized using the FAS and PPS. Other effectiveness endpoints will be summarized using only the FAS. All safety data will be summarized using the SES.

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.

8.4.1 Effectiveness analyses

8.4.1.1 Primary effectiveness endpoint

The assessment of a statistically significant, mean reduction in pain, measured using a 10-cm VAS, in the Test NLF compared to the Control NLF at time zero on Day 1 will be analyzed using a paired t-test to test the one-sided hypothesis that the mean of the differences in VAS scores between Test (μ_T) and Control (μ_C) folds is either greater than/equal to zero (≥ 0) or less than zero (< 0), as equivalently assessed using the following hypothesis-testing notation(s):

H_0 (null): $\mu_R \leq \mu_T$, (i.e. $\Delta = \mu_T - \mu_R \geq 0$) versus

H_a: (alternate): $\mu_R > \mu_T$, (i.e. $\Delta = \mu_T - \mu_R < 0$)

For testing this hypothesis using the t distribution, H_0 will be rejected if the upper limit of the 95% confidence interval (CI) around Δ is < 0 using a one-sided p-value $< (\alpha = 0.025)$, otherwise H_0 will not be rejected.

8.4.1.2 *Secondary effectiveness endpoint*

The Merz NLF Scale responder rates at Week 6 for the Test and Control NLF sides will be summarized separately as count (n) and percent (%). The McNemar's test will be used to compare both percentages.

8.4.1.3 [redacted]

[redacted]

[redacted]

8.4.2 Safety analyses

8.4.2.1 Safety endpoints

Nature, frequency, and severity of AEs will be recorded. All AEs and SAEs, designated by right or left NLF, will be stratified by Test and Control groups and summarized descriptively including type, duration, severity, and 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 Test and Control groups (as applicable) by the incidence of at least one event, the number of events, and the incidence using MedDRA preferred terms within the system organ classes (SOCs). AEs will be coded according to Medical Dictionary for Regulatory Activities (MedDRA).

Subjects will be asked to record any pre-defined CTRs that may occur in a subject diary; CTRs will be reported by fold (i.e., right NLF or left NLF). CTRs and other subject-diary

data will be summarized descriptively and separately by left or right NLF. 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.

8.4.3 Other variables

Subject disposition, demographic characteristics and baseline characteristics will be presented using standard descriptive statistics for continuous variables (i.e., n, mean, SD, median, minimum, and maximum) and for qualitative variables (absolute and percent frequencies (i.e., n, %). Demographic and baseline characteristics will be summarized for the SES, the FAS, and the PPS.

Prior and concomitant treatments as well as non-pharmacological concomitant procedures will be listed. Prior and concomitant medications will be coded using WHO Drug Dictionary.

Frequencies of concomitant medications will be given based on different ATC code levels as well as by generic name for the SES. Indications for concomitant procedures will be coded and only listed. Medical history and concomitant diseases will be summarized based on MedDRA system organ class (SOC) and preferred term (PT) levels for the SES.

8.5 Subject discontinuation and missing data

8.6 Imputation of effectiveness data

Observed Cases (OC)

- For the OC method, there will be no missing value imputations conducted. All effectiveness data will be analyzed as observed data.

Last Observation Carried Forward (LOCF)

- For the LOCF, in the analysis of the secondary effectiveness variable the subjects who have a missing score on the Merz NLF scale at Week 6, as well as who have an Early Discontinuation of unscheduled assessments will have their latest available post-baseline assessment carried forward and imputed into the missing Week 6 assessment.

8.7 Imputation of safety data

Details regarding imputation rules and analyses of safety data will be provided in the statistical analysis plan and finalized prior to data base 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, 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 (ICF) 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 the 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 interest. The subject, however, is free to withdraw consent at any time and for any reason, whether expressed or not.

Each ICF will include contact information (with phone number) the subject should use to communicate any medical concerns 24 hours a day.

9.3 Confidentiality of subject information

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

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

9.4 Study monitoring

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

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

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

9.5 Data quality assurance

9.5.1 Standardization procedures

Standardization procedures will be implemented to ensure accurate, consistent, complete, and reliable data, including methods to ensure standardization among sites (e.g., training, newsletters, investigator meetings, monitoring, centralized evaluations, and validation methods).

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

9.5.2 Data management

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

9.5.3 Data review and clarification procedures

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

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

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

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

- Subject files
- Subject identification code list
- A copy of the study protocol and any amendments
- Investigator's copies of the eCRFs and any associated subject-related source data
- Signed ICFs
- Copies of all direct correspondence with the IEC/IRB and with the regulatory authority(ies), and with the sponsor
- 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, or sponsor's designee, 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 U.S. FDA Financial Disclosure by Clinical Investigators (21 CFR 54) regulations require sponsors to obtain certain financial information from investigators participating in covered clinical studies. By participating in the study, the investigator agrees to provide the required financial information and to promptly update the sponsor with any relevant changes to this financial information throughout the course of the study and for up to one (1) year after its completion if necessary.

9.9 Investigator compliance

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

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

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

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