1 TITLE PAGE

A prospective, multicenter, randomized, comparator-controlled, evaluator-blinded study to evaluate the safety and effectiveness of Belotero® Intense Lidocaine for lip augmentation

Study Identifier:	M930041001 / NCT05773066
Version Date:	14-NOV-2022, Amendment 1 Version 2.0 21-JUL-2022, Version1.0
Investigational Medical Device:	Belotero Intense Lidocaine Model IMD1-3 Lido US Class III Medical Device
+Sponsor:	Merz North America, Inc. See additional information in CCI
Contract Research Organization:	PPD

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Changes to Previous Versions of this Report

Version and Date	Change
Version 2.0, 14-NOV-2022	• Updated language for primary effectiveness endpoint based on FDA's interactive Review Feedback (section 7.2.1.1 & 7.2.1.2) • Removed minimum injection volume based on FDA's interactive Review Feedback (section 10.5.1.6) • Updated statistical section (13) based on FDA's interactive Review Feedback • Updated Vendor list and Contact information (section 16.13) • Corrected minor typographical errors throughout the protocol

2 SYNOPSIS

Title of Study	A prospective, multicenter, randomized, comparator-controlled, evaluator-blinded study to evaluate the safety and effectiveness of Belotero® Intense Lidocaine for lip augmentation
Study Identifier	M930041001
Number of Sites and Countries	This study will be conducted at 12 to 14 investigational sites in the United States.
Investigational Medical Device	Belotero Intense Lidocaine Model ID: IMD1-3 Lido US Class of Medical Device: Class III
Comparator Device	Restylane® Silk
Objectives	Primary objective – To confirm the effectiveness of Belotero Intense Lidocaine (BIL) for lip augmentation by demonstrating its non-inferiority versus an approved hyaluronic acid dermal filler following submucosal and/or subcutaneous injection. Secondary objective – To demonstrate safety of BIL for single and repeat use in lip augmentation.
Effectiveness Evaluation	Primary effectiveness endpoint – Subject's mean change of treated lips from baseline to Visit V3, according to the Merz Lip Fullness Assessment Scale (MLFAS), as assessed live by a blinded evaluator (mean is calculated at the subject level). Co-primary effectiveness endpoint – Responder rates at Visit V3, according to the MLFAS, as assessed live by a blinded evaluator, where response is defined as ≥ 1-point improvement on subject's treated lips compared to baseline. Secondary effectiveness endpoints – Global Aesthetic Improvement Scale (GAIS) scores for treated subject at Visit V3 as completed by the treating investigator. – GAIS scores for treated subject at Visit V3 as completed by the subject. – Change from baseline to Visit V3 in Rasch-transformed score of the FACE-Q Satisfaction with Lips (absolute scores and change from baseline) as assessed by the subject.

Safety Evaluation	Secondary endpoint – Incidence of related serious or related delayed-onset treatment emergent adverse events (TEAEs with onset > 21 days after last treatment), as reported by the investigators until Week 48 post last treatment.
Study Design Overview and Methodology	This is a prospective, multicenter, randomized, comparator-controlled, evaluator-blinded study to evaluate the safety and effectiveness of BIL for lip augmentation in subjects with upper and/or lower lip deficit on the MLFAS. A total of 220 subjects with a grade of 0 (very thin), 1 (thin), or 2 (medium) on the MLFAS on each lip will be enrolled at 12 to 14 sites in the US.[22] For this study, randomization will be block-stratified by investigational site. Enrolled subjects will be randomized at a 3:1 ratio to treatment with: o BIL: n=165 or o Restylane Silk (RS): n=55. A minimum of 20% of randomized subjects will be Fitzpatrick Skin Type (FST) IV, V, or VI. In this subset, subjects will be distributed as follows: ≥ 22 subjects of FST IV and ≥ 22 subjects of FST V or VI. Approximately 5% of the subjects enrolled will be male. Subjects enrolled will have a screening period of up to 10 days; thereafter, they will participate for up to 64 weeks after baseline depending on the treatment group. Subjects randomized to BIL will have the option of retreatment at 48-weeks post last injection (i.e., either baseline treatment or touch-up, if applicable). All BIL subjects, irrespective of retreatment status, will be followed for a total study duration of up to 64 weeks. Subjects treated with RS will be followed for 48-weeks post last injection, for a total study duration of up to 52 weeks.
Number of Study Subjects	Approximately 220 evaluable subjects are planned for this study. Given the estimated screen failure rate of 8%, approximately 240 subjects will be screened; 220 subjects will be randomized in a 3:1 ratio; 165 subjects will be randomized to BIL and 55 subjects will be randomized to RS.
Main Inclusion/ Exclusion Criteria	• Key inclusion criteria are as follows: – Healthy male, female, or transgender ≥21 and ≤65 years of age at the time of screening. – Subject who desires lip augmentation to correct volume and has upper and/or lower lip deficit of 0 (very thin), 1 (thin), or 2 (medium) on the MLFAS as determined independently by the treating investigator and blinded evaluator.

	• Key exclusion criteria are as follows: – Any previous surgery, including plastic surgery or permanent implant or graft. – Any previous treatment with fat injections or permanent and/or semi-permanent dermal fillers. – Any treatment with porcine-based collagen fillers or with Juvéderm® Voluma XC, Restylane® Lyft Lidocaine, CaHA within the past 24 months and/or other dermal fillers within the past 12 months in the lips, in the lower third part of the face, and/or the nose. – Any previous treatment with dermal therapies within the past three months. – Has undergone oral surgery in the past 30 days. – Lip volume deficit due to medical conditions. – Known history of allergic/ anaphylactic reactions/ hypersensitivity to lidocaine or any of the device components.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation/Term	Definition
ADE	Adverse device effect
AE	Adverse event
AEI	Adverse event of interest
ANCOVA	Analysis of covariance
ASADE	Anticipated serious adverse device effect
ATC	Anatomical Therapeutic Chemical classification system of the World Health Organization
BDDE	1,4-butanediol diglycidyl ether
BIL	Belotero® Intense Lidocaine
CaHA	Calcium hydroxyapatite
CD	Compact disc
CFR	Code of Federal Regulations
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CRO	Contract research organization
CSP	Clinical study protocol
CTR	Common treatment response
DVD	Digital versatile disc
eCRF	Electronic case report form
EDC	Electronic data capture
EOS	End of study
FACE-Q™	Set of subject reported questionnaire modules
FAST	Facial drooping, Arm weakness, Speech difficulties and Time to call emergency services
FCS	Fully Conditional Specification
FDA	Food and Drug Administration, US
FST	Fitzpatrick skin type
GAIS	Global Aesthetic Improvement Scale
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HA	Hyaluronic acid

Abbreviation/Term	Definition
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICF	Informed consent form
IFU	Instructions for use
iGAIS	Investigator Global Aesthetic Improvement Scale
IMD	Investigational medical device
IPR	Independent Panel Reviewer
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputations
MLFAS	Merz Lips Fullness Assessment Scale
n	Number of values analyzed
PHI	Protected health information
PLLA	Poly L-Lactic Acid
PPS	Per-protocol set
PT	Preferred term
RS	Restylane® Silk
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis Software®
SES	Safety evaluation set
sGAIS	Subject Global Aesthetic Improvement Scale
SOC	System organ class
SSED	Summary of Safety and Effectiveness Data
TEAE	Treatment emergent adverse event
UADE	Unanticipated adverse device effect
UDI	Unique Device Identifier code
US	United States

5 ETHICS

5.1 Ethical Conduct of the Study

This study will be performed in accordance with the principles outlined in the Declaration of Helsinki and in compliance with International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use's Good Clinical Practice (ICH-GCP), International Organization for Standardization of the Clinical Investigation Medical Devices for Human Subjects – Good Clinical Practices (ISO 14155:2020), the United States Food and Drug Administration Code of Federal Regulations (US FDA CFR) Title 21 Part 812 – Investigational Device Exemptions (21 CFR Part 812), 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 Institutional Review Board (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 clinical study protocol (CSP). 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.

In the event of a pandemic disease outbreak (e.g., COVID-19 public health emergency) procedures that prioritize the reporting of protocol deviations that could impact subject safety will be defined and communicated to the appropriate IRB. In addition, changes in protocol conduct necessary to promptly ensure subject safety, such as conducting telephone or virtual visits for safety monitoring rather than on-site visits, can be implemented immediately with subsequent communication and review by the appropriate IRB and notification to regulatory authorities.

5.2 Informed Consent

Verbal and written informed consent must be obtained from every subject 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, local-language translation of the informed consent form (ICF) will be provided.

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 IRB and use of the amended form. Ongoing subjects will be required to re-confirm consent by signing the amended form.

The original and any amended signed and dated ICF must be retained at the investigational site, and a copy of the signed and dated ICF(s) must be given to the subject.

During the study, the subject will be informed if information becomes available that may be relevant to the subject's willingness to continue participation in the study.

Each ICF will include contact information (with a phone number) the subject should use to communicate any medical concerns 24 hours a day. Each ICF will also include the contact information for an ophthalmologist, who is identified by the investigator, for instances in which a subject requires evaluation by an ophthalmologist (e.g., subject experiences sudden visual changes following treatment injections). However, the subject is free to withdraw consent at any time and for any reason, whether expressed or not.

In the event of a pandemic disease outbreak (e.g., COVID-19 public health emergency), if re-confirming subjects' consent is deemed necessary due to significant changes made to the CSP and/or monitoring plan that could impact subjects, then:

- Alternative ways of obtaining consent will be defined as subjects should not visit sites for the sole purpose of re-confirming consent. For example, subjects will be contacted via phone or video calls and verbal consent will be obtained, supplemented with written confirmation (e.g., via email).
- IRB-approved updated subject information sheets and ICFs will be provided to subjects by email, mail, or courier when re-confirming consent.
- All instances of re-confirming consent that are obtained through alternative ways will be documented.

The subjects' consent will be re-confirmed through regular consent procedures at the earliest opportunity once/if the subjects are able to return to the sites, if applicable.

5.3 Subject Privacy

The subject will be informed of procedures to protect subject privacy. Under US federal law (the Privacy Rule), any protected health information (PHI) that is created or obtained during this study cannot be used or disclosed without permission. The currently designated statistical contract research organization (CRO) processes subject data in accordance with the data protection provisions set forth in the German Federal Data Protection Act (Bundesdatenschutzgesetz), specifically in the version applicable as of 25-MAY-2018, and in the European-focused General Data Protection Regulation law (GDPR). Informed consent on data processing will be obtained in writing directly from the subject before recording of any data. Authorization to use and disclose PHI will be obtained in writing directly from the subject before recording of any data. Recorded data will be pseudonymized before transferring to authorized individuals. The investigator will

maintain source documents that link unique subject numbers with subject names (e.g., in case of emergencies).

At the conclusion of the study, subject photographs will be stored and archived electronically by the sponsor and the investigational site. Photographs allowing identification of the subject will be published only if the subject has given written permission.

5.4 Confidentiality of Subject Information

Subject pseudoanonymity is to be maintained during the study. Subjects will be identified by a unique subject number on all study documentation. Health information that could identify the subject (i.e., PHI) must be maintained in strict confidence by the investigator to the extent permitted by applicable laws and regulations. Subjects must sign an authorization to allow PHI to be disclosed to the sponsor and anyone working on behalf of the sponsor, the IRB, or regulatory authorities.

Confidentiality will also be maintained for any medical information obtained from the subject during study participation. At a subject's request, the subject's medical information may be provided to the subject's personal physician or other appropriate medical personnel.

If the results of the investigation are published, the subject's identity will remain confidential.

6 INTRODUCTION

6.1 Background

Aging is a natural process that causes changes to the skin and supporting tissue. Factors that contribute to aging of the skin are lifestyle, diet, genetics, smoking, stress, and exposure to the sun and pollution; these effects weaken the natural collagen support layer, causing loss of subcutaneous support, and resulting in wrinkles and fine lines of the skin.[1, 2]

The lips and the mouth play an indispensable role in vocalization, mastication, and face aesthetics.[3] In addition, the lips are the key aesthetic features of the lower face and contribute significantly to the overall impression of a person.[1, 4] Fullness and delineation of the lips are associated with attractiveness, sensuality, and youth.[4] A number of noxious and hereditary factors contribute to the deterioration of the perioral tissues with age.[3] Aging signs of the lips are characterized by thinning of the upper and/or lower lip bodies, loss of projection in the lips, lengthening of the upper lip, hanging or drooping corners of the mouth, and formation of mentolabial wrinkles.[2] In many instances, social pressure or fear of exclusion leads one's desire to stop the aging process, resulting in cosmetic correction of unwanted attributes.[2]

Theoretically, there is a wide range of possible reconstructive methods that can be applied to rebuild damaged tissues such as tissue engineering using stem cells [5-7], gene therapy [8, 9] and artificial biocompatible scaffolds [10, 11], but their use has been not well-established in routine clinical settings. Among the non-surgical regenerative and reconstructive procedures, hyaluronic acid (HA)-based dermal filling is one of the most frequently used treatments.[12, 13] Its advantages over other filling materials include its natural occurrence, which provides non-immunogenic properties.[12] Lip augmentation is the current treatment used to correct the signs of aging in this anatomical area. According to Fischer et al., 2016, "The objective of lip augmentation is a natural, three-dimensional increase in volume with a well delineated redness of the lips that fits in with the entire face."[2]

Anti-aging and aesthetic markets are rapidly advancing to accommodate the growing demand for fuller and more-defined lips. In addition to various consumer or over-the-counter products, the US FDA has approved several dermal fillers for use in filling perioral lines (small wrinkles in the skin around the mouth and lips) and for increased lip volume.

Clinical studies show that HA dermal fillers are effective and safe for lip augmentation. In a study of HA with lidocaine, subjects (83.6%) reported being extremely satisfied, very satisfied, or satisfied with the improvement in their lips after the first injection.[4] Physicians also reported being extremely satisfied or very satisfied with lip improvement in 100% of study subjects.[4] Patients have reported satisfaction with their HA filler results

and their overall satisfaction met their goals.[14, 15] Patients also reported their willingness to repeat the treatment and recommend to their friends and family.[14]

Regarding safety a recent meta-analysis of lip studies revealed that the five most common reported adverse events were tenderness (n = 1,320, 88.7%), injection site swelling (n = 1,105, 74.3%), contusion (n = 725, 48.7%), injection site mass (n = 406, 27.3%), and injection site pain (n = 293, 19.7%).[3] The reported severity of those AEs was mostly mild or moderate. In other studies, physicians reported little, light, or moderate discomfort during the first lip injection or immediately after injection.[2, 4, 14] In one study, pain scores during injection was reported higher in sensitive areas. The addition of lidocaine to reduce procedural-associated discomfort or pain is well justified in the clinical literature.

The current protocol introduces the investigational medical device (IMD) Belotero® Intense Lidocaine (BIL), as a new dermal HA filler option for lip augmentation. HA is a naturally occurring polysaccharide (glycosaminoglycan) in the skin found in all organs of the body, and it is an essential component of the extracellular matrix that supports the collagen and elastin fibers.[1, 2] Unmodified HA decomposes rapidly when injected into the skin because of hyaluronidase and free radicals.[2] Thus, through chemical crosslinking, HA forms an extensive hydrogel matrix that is resistant to degradation and can remain in the skin for a long time.[2] New filler materials and technologies have simplified the application and have led to longer lasting results, combined with a fewer side effects and minimal failure rates.[2]

BIL is a sterile, non-pyrogenic, viscoelastic, colorless, transparent cross-linked sodium hyaluronate gel of non-animal origin, in a physiological phosphate buffer. It has a HA concentration of 25.5 mg/mL and contains 0.3% of lidocaine hydrochloride. The presence of lidocaine aims to reduce local pain associated with the injection of the gel and to improve subject comfort. It is indicated for submucosal or subcutaneous injection into the lips. BIL is a CE-marked dermal filler and marketed in the European Union and multiple other countries, including Canada.

The comparator device, Restylane® Silk (RS), is a gel of HA generated by *Streptococcus* species of bacteria, chemically cross-linked with 1,4-butanediol diglycidyl ether (BDDE), stabilized, and suspended in phosphate buffered saline at pH = 7 and concentration of 20 mg/mL with 0.3% lidocaine. It is currently indicated for submucosal implantation for lip augmentation and dermal implantation for correction of perioral rhytids in patients over the age of 21(P040024/S072).

6.2 Study Rationale

This clinical study is designed to demonstrate the safety and effectiveness of BIL for lip augmentation in subjects with upper and/or lower lip deficit.

Published scientific [3, 16], pre-clinical [5, 17], and clinical studies using HA dermal fillers with lidocaine have demonstrated the effectiveness and safety of these products.[2, 4, 14] Studies also showed that patients and physicians have high satisfaction ratings when using these products for lip augmentation.[1, 2, 4, 14, 15]

Due to growing interest among clinicians for use of HA fillers with lidocaine in lip augmentation, the current clinical study has been designed to collect data for FDA approval of a new HA filler. A total of 220 subjects, with upper and/or lower lip deficit and desiring lip augmentation, will be enrolled at 12 to 14 sites in the US. Enrolled subjects will be randomized 3:1 at baseline to the IMD or to the comparator device: BIL (n = 165) and RS (n = 55). Depending on their assigned treatment group, enrolled subjects will participate in the study for up to 64 weeks after their baseline visit.

The primary objective of this clinical study is to confirm the effectiveness of BIL in lip augmentation by demonstrating non-inferiority of BIL versus an approved HA dermal filler following submucosal and/or subcutaneous injection. The secondary objective is to demonstrate the safety of BIL for single and repeat use in lip augmentation.

Although subjects of all FSTs are eligible for study enrollment, the current CSP proposes that the group of subjects with FST V or VI must have the required MLFAS lip thinness score only for at least one lip (either upper or lower) to be enrolled. This adaptation has been added as the African-American population shows morphological differences in the lip anatomy compared to White or Asian population. Lips are more protrusive and fuller in this population; therefore, the likelihood of seeking treatment for lip augmentation is reduced in this population.[6]

6.3 Potential Benefits and Risks

6.3.1 Anticipated Clinical Benefits

The potential benefit of BIL and the comparator device RS is to add or restore and enhance lip volume of subjects with volume deficit of upper and/or lower lip and thus an improved overall aesthetic impression and quality-of-life. The potential benefit of lidocaine incorporated in BIL is the reduction of injection-related pain when using dermal fillers for lip augmentation.

In addition,

- HA is a biodegradable material; undesirable effects such as overcorrection of the treated area or dissatisfaction with the outcome of the corrective procedure subside spontaneously after a few months or can be enzymatically degraded (use of hyaluronidase has been described in scientific publications, if necessary).[7, 18]

- Allergies and immunological reactions against components of the gel (e.g., sodium hyaluronate, lidocaine) occur very rarely compared to other filler materials. The probability of occurrence is assessed as $<10^{-6}$ according to the product risk analysis report. The risk to develop an allergic reaction to lidocaine is also considered low.[9]
- For the past two decades, subject satisfaction with HA filler injections is increasing as more and more subjects are being treated. A large majority of treated subjects reported that they would recommend dermal fillers to their peers.[8]
- HA is a very soft, viscoelastic material which can be shaped manually immediately after the injection treatment to optimize its distribution and by this obtaining an optimal cosmetic result.
- Treatment with injectable devices is performed on an ambulatory basis. No special preparations for the procedure are required.
- Injection with HA products is less invasive and less permanent than available invasive treatment options via plastic surgery.

6.3.2 Anticipated Adverse Device Effects

The following anticipated adverse device effect may occur with the use of BIL:

- A transient slight bleeding may occur during injection that resolves as soon as the injection is finished.
- One or more of the following may occur either immediately or as a delayed reaction (list not exhaustive): Injection site reactions may occur. These are generally mild or moderate in intensity and usually resolve within a few days. These include swelling, nodule or lump/bump, bruising, hematoma, ecchymosis, induration, erythema/redness, tenderness, pain, discoloration, pruritus/itching, tingling, paresthesia, numbness, hypoesthesia, scabbing, needle marks, and discomfort or irritation.
- Use of BIL at specific sites in which an active inflammatory process (skin eruptions such as cold sores, cysts, pimples, acne, eczema, rashes, or hives) or infection is present should be deferred until the underlying process has been controlled.[19]
- Introduction of BIL into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction. 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.[19]

Clinical data on BIL in the lip indication were previously collected in a post-market clinical follow-up study conducted in the European Union.[11] One hundred and eighty-four subjects (178 female and six male) were treated in the indication upper and lower lip

volume. Related treatment-emergent adverse events (TEAEs) occurred with a frequency of 65.2% in subjects treated with BIL for upper and lower lip volume.

The majority of non-serious TEAEs occurred at the injection site and were recorded for the system organ class (SOC) General disorders and administration site conditions. Overall, 124 subjects (67.4%) experienced 313 non-serious TEAEs occurring at the injection site. Within this SOC, the most frequently reported non-serious TEAEs were injection site hematoma and injection site swelling. Overall, injection site hematoma was reported in 96 subjects (52.2%) and injection site swelling was reported in 85 subjects (46.2%).

Further frequently reported non-serious TEAEs were recorded for the SOC Infections and infestations. Overall, 45 subjects (24.5%) experienced 53 non-serious TEAEs of the SOC Infections and infestations of which the most frequently reported non-serious TEAE was nasopharyngitis reported in 23 subjects (12.5%).

Most subjects experienced TEAEs of mild intensity (48.4%), followed by TEAEs of moderate intensity (25.5%) of subjects TEAEs of moderate intensity, and TEAEs of severe intensity (2.2%) and 2.2% of subjects TEAEs of severe intensity. Only four (4) subjects (1.8%) experienced a total of six (6) severe TEAEs (preferred terms [PTs]: injection site hematoma, intervertebral disc protrusion, breast cancer, cystocele, and uterine prolapse).

TEAEs that occurred in the treatment area most commonly affected both lips (25.0% of subjects), followed by the upper lip (14.1% of subjects), and the lower lip (5.4% of subjects). Further 31.5% of subjects experienced TEAEs that occurred outside the treatment area or in treatment areas of other indications. Of the TEAEs that affected the treatment area (upper and/or lower lip), the PTs injection site swelling (both lips: 19.6% of subjects, upper lip: 8.2% of subjects, lower lip: 1.6% of subjects), injection site hematoma (both lips: 5.4% of subjects, upper lip: 10.3% of subjects, lower lip: 4.9% of subjects), injection site pain (both lips: 2.2% of subjects, upper or lower lip: no subject), and angioedema (both lips: no subject, upper lip: 1.6% of subjects, lower lip: no subject) were the most common. All other PTs that affected the treatment area of upper and lower lip volume were single occurrences only.

One hundred twenty (120) subjects (65.2%) experienced 245 related TEAEs and 117 subjects (63.6%) experienced 238 related TEAEs occurring at the injection site. The most frequently reported related TEAEs were injection site hematoma (46.2% of subjects) and injection site swelling (40.2% of subjects). Further related TEAEs were injection site pain (2.2% of subjects) and injection site nodule (1.6% of subjects). Injection site erythema, injection site bruising, injection site hypoesthesia, injection site induration, and injection site pruritus were experienced as related TEAEs by 0.5% of subjects each. Furthermore, three (3) subjects (1.6%) experienced angioedema and one subject (0.5%) experienced hematoma as related TEAE.

All related TEAEs were resolved. Most of them were resolved after 15 days. One subject experienced a related injection site reaction with a duration of more than 30 days (PT: injection site nodule, affecting the lower lip). This related TEAE of injection site nodule was non-serious and of mild severity. All related TEAEs affected the injection site, except for angioedema (6 events in three subjects, all occurred at the upper lip), which all were non-serious and of mild or moderate intensity. None of the related TEAEs were serious.

All serious TEAEs were assessed as not related to BIL or the procedure by the investigator. None of the subjects discontinued the study due to a TEAE. There were no fatal TEAEs.

Further, clinical studies have shown that HA dermal lip fillers achieved the natural look and feel of the lips.[2, 4] Patients with lip deficit, who received lip augmentation through HA dermal filler, increased their self-confidence and returned to socialize among their peers.[4]

In clinical studies, mild to moderate adverse events (AE) have been reported.[1, 2, 10, 14, 15] Some studies reported AEs as a side effect, injection site reaction, or treatment-related AEs. Most studies reported the degree of severity as mild or moderate, and events resolve without sequalae.[1, 2, 10, 14, 15]

In a clinical study that used purified porcine collagen, purified bovine collagen, and a cross-linked HA gel; an unexpected finding was the recorded adverse events. Two-thirds of the recorded adverse events were not related to the injected material (e.g., right knee replacement and tooth extracted). These events were reported because it happened during the course of the study. However, the most common adverse events reported was cold sore, which was a direct trauma caused by the injection and may have contributed to the tissue being more vulnerable to the viral infection.[1]

In a clinical study that used Belotero Balance Lidocaine and BIL, swelling was the most frequently reported adverse events occurring immediately after injection (e.g., swelling, erythema, hematoma, hardening, Tyndall effect).[2] In another clinical study using HA dermal filler with lidocaine reported bruising and swelling as the most common adverse event. However, physicians in this clinical study reported little to no bruising or swelling.[4]

In a clinical study using multiple HA fillers with lidocaine based on cohesive polydensified matrix technology (Belotero and Esthélis [i.e., Soft-L, Basic-L, Extra/Intense-L, and Modélis-L]) the investigators found that pain was the most common adverse events (228 times). A visual analog scale of 11-points, where 0 represents no pain and 10 represents extreme pain was used. Pain scores were higher during injection in sensitive areas. However, the mean overall pain scores were very low (< 1.0).[14]

The following serious AEs (SAEs) were reported in published clinical studies:

– One study reported an SAE of angioedema that occurred during injection of the device. The subject was treated with antihistamine and hyaluronidase injections with a 6-day course of prednisone, and the event resolved without sequalae.[10]

– In another study, two SAEs were reported: one subject had a urinary tract infection that required hospitalization, and the other subject miscarried. Both SAEs were reported as unrelated to the study treatment/device.[1]

Additional risks that may arise in the event of a pandemic disease outbreak (e.g., new COVID-19 public health emergency) may affect clinical study conduct.

Investigators must be informed that, as with any injectable medical device, the following device deficiencies may occur:

- Needle breakage
- Leakage of material from syringe
- Resistance during injection, needle jamming.

7 STUDY OBJECTIVES AND ENDPOINTS

7.1 Objectives

7.1.1 Primary Objective

To confirm the effectiveness of Belotero Intense Lidocaine (BIL) for lip augmentation by demonstrating its non-inferiority versus an approved HA dermal filler following submucosal and/or subcutaneous injection.

7.1.2 Secondary Objective

To demonstrate safety of BIL for single and repeat use in lip augmentation.

7.2 Endpoints

Note: Endpoint analyses, including comparisons made, are described in Section 13.4.

7.2.1 Effectiveness Endpoints

7.2.1.1 Primary Effectiveness Endpoint

Primary effectiveness endpoint:

– Subject's mean change of treated lips from baseline to Visit V3, according to the MLFAS, as assessed live by a blinded evaluator.[1] (mean is calculated at the subject level)

Co-primary effectiveness endpoint:

[1] Assessments conducted at screening will be used as baseline values during analysis. If a single lip was treated, only its MLFAS values will be used for analysis. For each subject the primary effectiveness endpoint will be derived as follows: First, the change from baseline to Visit V3 for individual lips will be calculated. Secondly, for subjects treated in both lips, the average of change for upper and lower lip will be calculated. For subjects treated in only one lip, the change for the treated lip will be considered as primary effectiveness endpoint. In the co-primary effectiveness endpoint subjects treated in both lips need to have a ≥ 1-point improvement in both lips in order to qualify as responder.

- Responder rate at Visit V3, according to the MLFAS, as assessed live by a blinded evaluator, where response is defined as ≥ 1-point improvement on subject's treated lips compared to baseline.[1]

7.2.1.2 Secondary Effectiveness Endpoints

- Global Aesthetic Improvement Scale (GAIS) scores for treated subject at Visit V3 as completed by the treating investigator.
- GAIS scores for treated subject at Visit V3 as completed by the subject.
- Change from baseline to Visit V3 in Rasch-transformed score of the FACE-Q Satisfaction with Lips (absolute scores and change from baseline) as assessed by the subject.

Table 1: Primary and Secondary Effectiveness Endpoints Overview

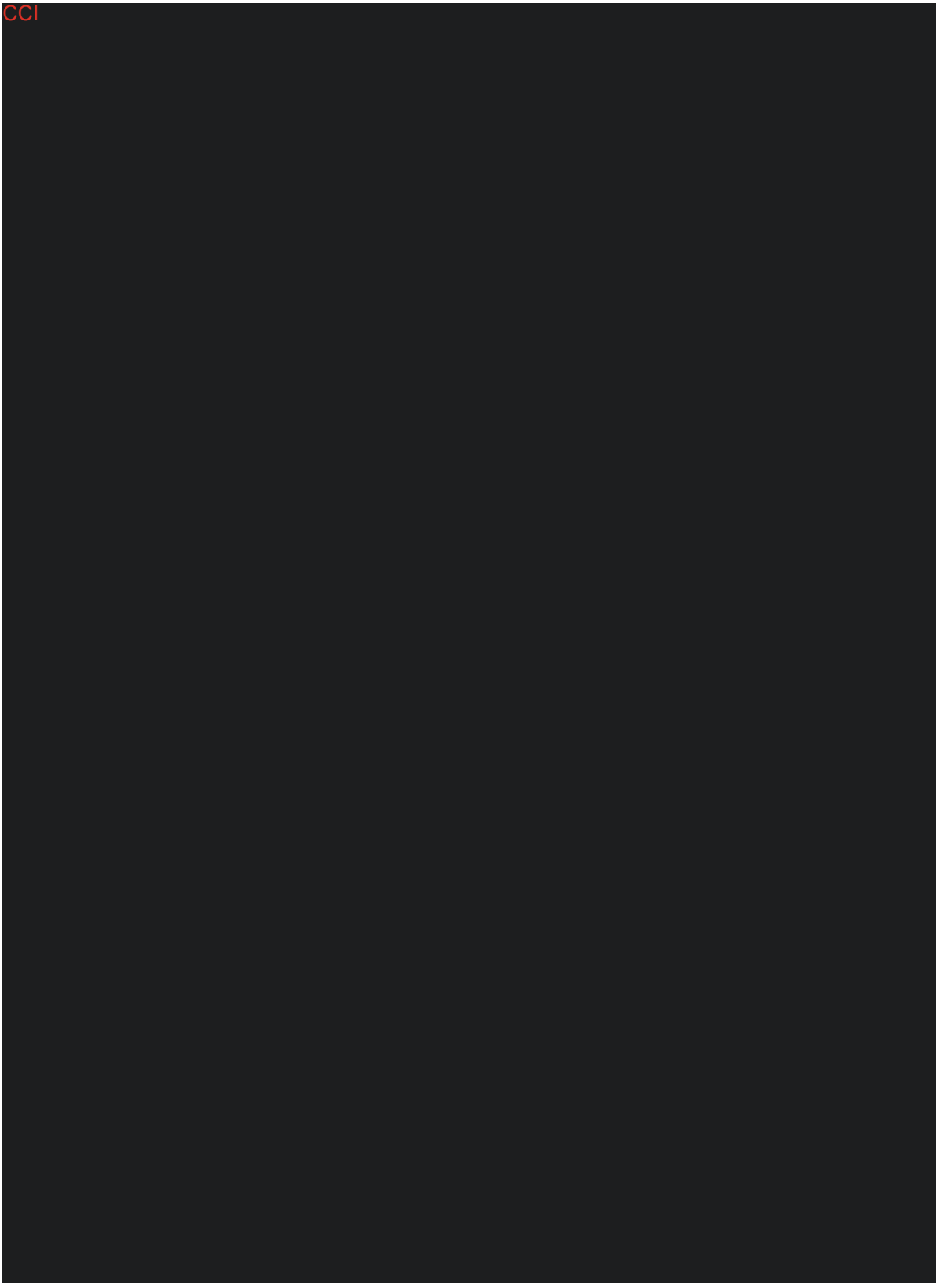
Effectiveness endpoints	Description	Evaluator	Time point	Assessment
Primary	Subject's mean change from baseline of treated lips on the MLFAS[1]	Blinded evaluator	Visit V3	Live
Co-primary	Responder rate, according to MLFAS, where response is defined as ≥ 1-point improvement from baseline on MLFAS of subject's treated lips[1]	Blinded evaluator	Visit V3	Live
Secondary	Investigator's Global Aesthetic Improvement Scale (iGAIS) scores	Treating investigator	Visit V3	Live
Secondary	Subject's Global Aesthetic Improvement Scale (sGAIS) scores	Subject	Visit V3	Live
Secondary	FACE-Q - Satisfaction with Lips	Subject	Visit V3	Live

[1] Assessments conducted at screening will be used as baseline values during analysis. If a single lip was treated, only its MLFAS values will be used for analysis. For each subject the primary effectiveness endpoint will be derived as follows: First, the change from baseline to Visit V3 for individual lips will be calculated. Secondly, for subjects treated in both lips, the average of change for upper and lower lip will be calculated. For subjects treated in only one lip, the change for the treated lip will be considered as primary effectiveness endpoint.

In the co-primary effectiveness endpoint subjects treated in both lips need to have a ≥ 1-point improvement in both lips in order to qualify as responder.

CCI

CCI



7.2.2 Safety Endpoints

7.2.2.1 Secondary Safety Endpoint

– Incidence of related serious or related delayed-onset TEAEs > 21 days after last treatment, as reported by the investigators until Week 48 post last treatment.



7.2.3 Other Data Collected

– Subject disposition (including number of subjects enrolled, number of discontinuations, and reason for discontinuation).

– Demographic data and baseline characteristics (sex, age, race, FST).

– Previous and concomitant therapies (medications and non-drug therapies).

– Relevant medical history and concomitant diseases.

– Injection technique, depth of injections, number of injection points, and injection volume.

8 CLINICAL INVESTIGATION PLAN

8.1 Overview of Study Design

This is a prospective, multicenter, randomized, comparator-controlled, evaluator blinded study to evaluate the safety and effectiveness of BIL for lip augmentation in subjects with upper and/or lower lip deficit on the MLFAS.

Subjects enrolled in the study will have a screening period of up to 10 days. Thereafter, they will be participating for up to 64 weeks after baseline depending on the treatment group. A total of 220 subjects with a grade of 0 (very thin), 1 (thin), or 2 (medium) on the MLFAS on each lip will be enrolled at 12 to 14 sites in the US.[2] For this study, randomization will be block-stratified by investigational site. Enrolled subjects will be randomized using a 3:1 ratio to one of two treatment groups:

- BIL – n=165 or
- Restylane Silk (RS) – n=55.

A minimum of 20% of the randomized subjects will be FST IV, V, or VI. In this subset, subjects will be distributed as follows: ≥ 22 subjects of FST IV and ≥ 22 subjects of FST V or VI (CCI [redacted]). Approximately 5% of the subjects enrolled into the study will be male.

As shown in CCI [redacted], the current study design includes two randomized treatment arms. Subjects treated with RS will be followed for 48-weeks post last injection for a total study duration of up to 52 weeks.

Subjects randomized to BIL will have the option of retreatment, of up to 1.5 mL per lip, 48-weeks post last injection (i.e., either baseline treatment or touch-up, if applicable) upon agreement between the subject and the investigator. Subjects who receive such retreatment will be followed for additional 12 weeks for a total study duration of up to 64 weeks. In addition, BIL subjects who do not receive retreatment will remain in the study for up to 64 weeks to assess long-term effectiveness and safety.

In addition, three IPRs will assess all enrolled subjects' pre-treatment baseline photographs, as well as photographs taken eight (8) weeks after last injection (i.e., either baseline treatment or touch-up, if applicable), using the MLFAS. Standards photographs of the lips will be captured to serve as reference pictures/comparison for the treating investigator, subject, and IPRs.

[2] Subjects with FST V or VI must have the required MLFAS lip thinness score for at least one lip (either upper or lower) to be enrolled.

Please reference CCI [redacted] for the Schedule of Events and CCI [redacted] for an overview of the visit schedule and the study design.

8.2 Discussion of Study Design, Including the Choice of Control Groups

The prospective, multicenter, randomized, comparator-controlled, evaluator blinded study design was chosen to adequately investigate the effectiveness and safety of BIL following submucosal or subcutaneous injection into the lips for lip volume augmentation and to assess non-inferiority against an FDA-approved comparator in the indication.

In general, prospective designs can achieve a higher data quality as compared to retrospective designs due to the standardization of treatment application and assessments as well as monitoring of the data.

Using several study sites increases the representativeness of the study results and decreases study site-related biases.

Randomization prevents selection bias in allocating interventions to enrolled subjects. Blinding of the blinded evaluator reduces the risk of the knowledge of which intervention has been assigned to the enrolled subject; since, the blinded evaluator should not have access to the enrolled subject's study records.

Use of the validated MLFAS to assess the upper and lower lip of subjects with lip deficit, prior to lip augmentation, will be used as a reference to compare pre-treatment data to the last post-treatment assessment. The result of the comparison between visits will show if there is improvement and/or clinical benefit on how the subject feels with regards to appearance, function, and sensitivity.

The observational period of 64 weeks (if touch-up has been performed) was chosen to assess the long-term safety of subjects treated with BIL in the lips.

RS was selected as the comparator because it is an FDA-approved dermal HA filler to correct lip volume deficit. Like BIL, its composition is based on a BDDE-crosslinked dermal HA filler containing 0.3% lidocaine hydrochloride.

9 STUDY POPULATION AND RESTRICTIONS

9.1 Number of Subjects and Sites

Approximately 220 evaluable subjects are planned for this study. Given the estimated screen failure rate of 8%, approximately 240 subjects will be screened; 220 subjects will be randomized in 3:1 ratio; 165 subjects will be randomized to BIL and 55 subjects will be randomized to RS.

Subjects will be enrolled at 12 to 14 investigational sites in the US.

To ensure a reasonable number of evaluable subjects per investigational site, the maximum number of subjects randomized at each investigational site is planned to be approximately 40, and the intended minimum number of subjects to be included for each site is eight (8).

In general, subjects who are enrolled; randomized; received study treatment; and who do not complete the study will not be replaced. In case of more than 10% missing primary effectiveness data due to a public health emergency (e.g., COVID-19), additional subjects can be randomized.

A minimum of 20% of the randomized subjects will be FST IV, V, or VI. In this subset, subjects will be distributed as follows: ≥ 22 subjects of FST IV and ≥ 22 subjects of FST V or VI. Approximately 5% of the subjects enrolled into the study will be male.

Additional information regarding subject enrollment is provided within the sample size justification in Section 13.1.

9.2 Selection of Subject Population

The inclusion and exclusion criteria have been chosen to identify a suitable population of subjects to investigate the study objectives and to minimize safety concerns in this population.

9.2.1 Inclusion Criteria

To be eligible for study participation, the treating investigator will ensure each subject meets all study inclusion criteria at the screening visit as follows:

1. A) Subject of FST **I to IV** who desires lip augmentation to correct volume deficit and has upper and lower lip deficit with a rating of 0 (very thin), 1 (thin), or 2 (medium) on the MLFAS on each lip, as determined independently by the treating investigator and the blinded evaluator.

B) Subject of FST **V or VI** who desires lip augmentation to correct volume deficit and has upper and/or lower lip deficit with a rating of 0 (very thin), 1 (thin), or 2 (medium) on the MLFAS on at least one lip, as determined independently by the treating investigator and the blinded evaluator.

Note: The blinded evaluator and the treating investigator must each have the same MLFAS ratings assigned for lips to be treated.

2. CCI [redacted] age at the time of screening.
3. Subject has an adequate understanding (reading, speaking, and writing) of the English language.
4. Willingness and ability to provide written informed consent and Health Insurance Portability and Accountability Act of 1996 (HIPAA) authorization prior to performance of any study-related procedure.
5. Understands and accepts the obligation not to undergo any elective surgeries, procedures or skin treatments involving the treatment area for the duration of the study.
6. Willingness to adhere to study-required photography and its associated procedures (e.g., removal of jewelry and make-up).
7. Willingness and ability to comply with all protocol requirements, including compliance with all protocol-specified instructions and restrictions, receiving pre-treatment medications, following post-treatment care instructions, completing the subject electronic diary (eDiary), returning for follow-up visits, and abstaining from exclusionary procedures for the duration of the study.
8. Willingness to refrain from use of moisturizers or any other emollients in the area to be treated on the day of any study-related visit.
9. Willingness to avoid excessive or prolonged exposure to sunlight, tanning booths, sun lamps, or UV-light sources for the duration of the study.

9.2.2 Exclusion Criteria

Subjects meeting any of the following criteria either at screening or baseline will not be eligible to participate in the study:

1. Had prior surgery, including facial plastic surgery, or has a permanent implant or graft in the lower third part of the face including the nose that could interfere with effectiveness assessments.
2. Has ever been treated with fat injections or permanent (e.g., silicone, polymethylmethacrylate (PMMA)) and/or semi-permanent (e.g., polycaprolactone, poly L-lactic acid (PLLA)) dermal fillers in the face or plans to receive such treatments during participation in the study.

3. Has received treatments with porcine-based collagen fillers or with Juvéderm® Voluma XC, Restylane® Lyft Lidocaine, calcium hydroxyapatite (CaHA), within the past 24 months and/or with other dermal HA fillers within the past 12 months in the lips, in the lower third part of the face and/or the nose or plans to receive such treatments in the face during participation in the study.
4. Permanent make-up in the treatment area.
5. Prior treatment with dermal therapies (e.g., facial ablative or fractional laser, microdermabrasion, chemical peels, and non-invasive skin-tightening) within the past three months in the lower third part of the face including the nose that could interfere with effectiveness assessments.
6. Has undergone oral surgery (e.g., orthodontia, extraction, implants) in the past 30 days or plans to undergo oral surgery during participation in the study.
7. Facial hair (i.e., beards, sideburns, etc.) that would interfere with study assessments and/or create inconsistency in required study photography.
8. Facial nerve palsy or history of facial nerve palsy.
9. Lip volume deficit due to medical conditions such as congenital defect, trauma, abnormalities in adipose tissue related to immune-mediated diseases such as generalized lipodystrophy (i.e., juvenile dermatomyositis), partial lipodystrophy (i.e., Barraquer-Simons-Syndrome), inherited disease, or HIV-related disease.
10. Has abnormal lip function, with inability to effectively suck water through a straw.
11. Has abnormal lip sensation, with inability to feel a 0.4 g monofilament or a cotton wisp at any site on the lip
12. Has moderate or severe abnormal lip asymmetry.
13. Known history of allergic/anaphylactic reactions including hypersensitivity to lidocaine or anesthetics of the amide type, BDDE, HA preparations, gram positive bacterial proteins, or any of the device components.
14. Has an acute inflammatory process or active infection at the injection site (e.g., skin eruptions such as cold scores, cysts, pimples, acne, eczema, rashes, hives, abscess, or *Streptococcus* infection) or history of chronic or recurrent infection or inflammation with the potential to interfere with the study results or increase the risk of AEs.
15. Any current or history of uncontrolled retinal disease or detached retina or any other condition with the potential to cause a decline of visual acuity (e.g., uncontrolled diabetes, glaucoma).
16. Has monocular vision and/or best corrected visual acuity of 20/50 or less in either eye.
17. Has constriction of visual field on the confrontation exam in any quadrant in either eye.
18. Has asymmetry or abnormal ocular motility.

19. A history of recurrent herpetic eruption in the mid or lower facial region, including the lips, within the past 12 months.
20. A known bleeding disorder or has received or is planning to receive anticoagulation, anti-platelet, or thrombolytic medications (e.g., clopidogrel, apixaban, heparin, phenprocoumon, warfarin), anti-inflammatory drugs (e.g., aspirin, ibuprofen, diclofenac), or other substances known to increase coagulation time (vitamins or herbal supplements, e.g., vitamin E, fish oil garlic, gingko St. John's Wort), from 10 days before to three (3) days after injection.
21. Scarring, tattoos, piercings, current acute sun damage, open wounds, or lesions in area to be treated.
22. Any open wounds or lesions in the areas to be treated, including active herpes simplex.
23. History or documented evidence of an active autoimmune disease (e.g., scleroderma, systemic lupus erythematosus, rheumatoid arthritis). Subjects with Hashimoto thyroiditis (chronic lymphocytic thyroiditis) can be included.
24. History of streptococcal diseases (e.g., chronic recurrent angina) or known allergy against gram positive bacterial proteins.
25. History of hyper- or hypopigmentation, keloid formation, or hypertrophic scarring.
26. Present or uncontrolled malignant disease.
27. Evidence of recent excessive or prolonged exposure to sunlight, tanning booths, sun lamps, or UV-light sources on the lips/face.
28. History of drug or alcohol abuse within 12 months prior to screening.
29. History of psychiatric drug use that, in the investigator's opinion, would impair the subject's understanding of the protocol requirements or understanding and signing of the informed consent.
30. Has any other medical condition with the potential to interfere with study outcome assessments or compromise subject safety (i.e., increase the risk of AEs; symptoms associated to COVID-19 or any other public health emergency according to investigators' judgement).
31. Subjects who, in the treating investigator's opinion, have a history of poor cooperation, noncompliance with medical treatment, or unreliability.

32. Subject of childbearing potential[3] and not using medically effective birth control[4] or is pregnant or lactating or plans to become pregnant during the study. (Note: Urine pregnancy tests will be used in subjects of childbearing potential.)
33. Participated in an investigational device or drug study in the last 30 days, or is enrolled or plans to enroll in any other interfering investigational study during participation in this study.
34. Employee or direct relative of an employee of the CRO, the investigational site, or the sponsor (Merz).

9.2.3 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 their participation in the study:

- Application of any new over-the-counter or prescription, oral or topical, skin products in the lower third part of the face.
- Cosmetic facial plastic surgery or oral surgery procedures (i.e., orthodontia, extraction, implants).
- Facial treatments with permanent and/or semi-permanent dermal fillers (e.g., collagen, fat, HA products, calcium hydroxyapatite products, etc.).
- Additional dermal therapies other than the investigational treatment (i.e., dermal fillers, toxin treatments, facial ablative or fractional laser, microdermabrasion, chemical peels, non-invasive skin-tightening [2] or surgical procedures) on the face.
- Anticoagulation, anti-platelet, or thrombolytic medications (i.e., clopidogrel, apixaban, heparin, phenprocoumon, warfarin), anti-inflammatory drugs (e.g., aspirin, ibuprofen, diclofenac), or other substances known to increase coagulation time (vitamins or herbal supplements, e.g., vitamin E, garlic, gingko) for three (3) days after treatment.
- Using skin-irritating agents (e.g., keratolytic, antiseborrheic, anti-acne agents) on the face for at least three (3) days after treatment.
- Waxing and/or shaving the treated area three (3) days after treatment.
- Touching/pressing the treatment area for 12 hours after treatment.

[3] 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).

[4] 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 throughout the duration of the study, such as implants, injectables, combined oral contraceptives, intrauterine devices (IUDs), sexual abstinence, or vasectomized partner. Hormonal methods and the 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, and vasectomy must be completed 3 months prior to first study product administration; or in the alternative that a 0 sperm count will suffice.

- Applying make-up (e.g., lipstick / lip gloss) or lip balm to the treatment area for 24 hours after treatment.
- Exercising strenuously for 24 hours after treatment.
- Consuming alcoholic beverages for 24 hours before and after treatment.
- Exposure of the treated area to extensive sun or heat exposure or sauna for 48 to 72 hours after treatment. Finally, if the subject is a female of childbearing potential, she must commit to not becoming pregnant during the study.
- Finally, if the subject is a female of childbearing potential, she must commit to not becoming pregnant during the study and to continue using medically effective birth control for the duration of the study (i.e., until the end of their study participation).

9.2.4 Subject Enrollment and Randomization

All subjects who provide informed consent will be assigned a subject identification number.

Subjects are considered enrolled when they meet all eligibility criteria, provide informed consent (i.e., sign the ICF), and are randomized via the centrally interactive electronic data capture (EDC) system. Eligible subjects with signed consent form in place will be randomized at the Visit V1-a, Baseline, Day 1.

Screen failures are defined in Section 9.2.5.

9.2.5 Screen Failures

Subjects, who sign the ICF but do not meet eligibility criteria or withdrew consent prior to being randomized, 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 EDC system for screen failures, such as date of informed consent, demographics, and reason for failure. Individuals, who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

9.2.6 Removal of Subjects from Therapy or Assessment

9.2.6.1 Treatment Discontinuation

If study treatment is discontinued at any time during the study or during administration, the investigator will record the reason for treatment discontinuation in the study records. Potential reasons for discontinuation of treatment may include refusal by the subject to receive additional treatment or physician's decision. The investigator should request that a

subject discontinuing treatment continue to participate in the study and complete all remaining visits and assessments. For subjects who decline to continue study participation after treatment discontinuation, additional information regarding subject withdrawal is provided in Section 9.2.6.2.

9.2.6.2 Subject Withdrawal or Discontinuation

Each subject will be followed to the EOS, or until the sponsor decides to terminate the study, whichever comes first. Reasons a subject will not be followed for all scheduled visits include withdrawal of consent, continuous non-compliance with protocol requirements, or loss to follow-up (e.g., moving away from investigational site; unresponsive to attempts to contact the subject). Additionally, the investigator can discontinue any subject, at any time, if medically necessary.

Subjects have the right to withdraw from the study at any time at their own request without prejudice. In cases of withdrawn consent, data collected until the date consent was withdrawn will be analyzed as recorded.

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 discontinued from the study.

The reason for the subject's discontinuation should be documented in the electronic case report form (eCRF). The investigator should make every attempt to complete the recommended follow-up assessments specified for the End of Study/Early Termination visit specified in the Schedule of Events (Section 11.1 and CCI) while fully respecting the subject's rights. If a subject decides to withdraw from the study during a planned study visit, assessments specified for the End of Study/Early Termination visit specified in the Schedule of Events (Section 11.1 and CCI) should be completed and documented in the eCRF.

In the case of a reported vascular embolic event leading to skin necrosis, vision loss, or stroke, enrollment and treatment at the investigational site will be suspended and a root-cause investigation will be conducted to determine the cause and whether the outcome was anticipated (the investigator did not properly follow the treatment instructions) or unanticipated (the investigator did properly follow the treatment instructions). The investigator and the sponsor will conduct a thorough evaluation of the event. The sponsor will then immediately decide if the study should be suspended (Section 9.2.8).

If a non-serious AE is unresolved at the time of the subject's final study visit, an effort will be made to follow the subject until the AE is resolved or stabilized, the subject is lost to follow-up, or some other resolution of the event occurs. The investigator should make every attempt to follow all SAEs and unanticipated adverse device effects (UADEs) to resolution. Information on pregnancy and the outcome for any female who becomes pregnant during the study will be collected.

9.2.6.3 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 the end of the study or after subject discontinuation, 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.

9.2.7 Suspension or Premature Termination of an Investigational Site

Study participation by individual sites may be suspended or prematurely terminated by the sponsor. Reasons for the premature discontinuation of investigational sites include, but are not limited to, the following:

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

The sponsor will provide the investigational site written notification documenting the reason for suspension or premature termination. The sponsor will inform the responsible regulatory authority, as appropriate, and ensure the IRB is notified. If the suspension or premature termination was in the interest of safety, the sponsor will inform all other principal investigators.

In cases of temporary suspension at an investigational site, the sponsor will conduct an analysis of the reason(s) for suspension. After completing this analysis and implementing necessary corrective actions, a temporary site suspension may be lifted. The sponsor will inform the principal investigators, the IRB, and, where appropriate, the regulatory authority of the rationale, providing relevant data supporting this decision. Concurrence must be obtained from the IRB and, where appropriate, regulatory authorities before the investigational site resumes trial activities. If subjects were informed of the suspension, the

principal investigator or authorized designee will inform them of the reasons for resumption.

In cases of premature termination, the investigator will conduct site-closure activities in accordance with all applicable sponsor, local, and international guidelines and regulations.

In the event of a pandemic disease outbreak (e.g., COVID-19 public health emergency), it may not be feasible for an investigational site to continue study participation. In this scenario, consideration will be given to the impact of investigative site-closure on the safety and well-being of participating subjects.

9.2.8 Suspension or Premature 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.

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 IRB to suspend or terminate approval/favorable opinion for the study;
- Sponsor decision;
- The risks and benefits of continuing the investigation have been reassessed, and the risks outweigh any potential benefits;
- The incidence of AEs constitutes a potential health hazard to the subjects;
- New scientific data on the IMD does not justify a continuation of the investigation; and/or
- The investigator or investigational site exhibit serious and/or persistent non-adherence to the CSP, Declaration of Helsinki, ISO14155:2020, and/or applicable regulatory requirements.

- If suspicion of an unacceptable risk to subjects arises during the trial or if instructed by the IRB or regulatory authorities, the sponsor will suspend the trial while the risk is assessed. If the analysis determines that implementing necessary corrective actions is sufficient, a temporary trial suspension may be lifted. If an unacceptable risk is confirmed, the sponsor will terminate the trial.

In the event of study suspension or premature termination for any reasons, the sponsor will inform all investigators and relevant regulatory authorities promptly of the study suspension/termination and reason for the action, as detailed in Section 9.2.7. The investigator will conduct site-closure activities in accordance with all applicable sponsor and local/international guidelines and regulations.

In the event of a public health emergency the sponsor will inform all investigators, the IRB, and the relevant regulatory authorities promptly of any planned mitigations to protect the safety and well-being of subjects. This can include but is not limited to putting the study recruitment on hold, stopping or postponing further treatments, or changing on-site visits to visits by phone or at another clinical site (e.g., if the primary site is closed due to quarantine).

9.2.9 End of Study

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

10 STUDY DEVICES AND TREATMENT OF SUBJECTS

10.1 Description of Study Devices

10.1.1 Belotero Intense Lidocaine

The investigational medical device under evaluation in the current study is Belotero Intense Lidocaine (BIL). It is a sterile, non-pyrogenic, viscoelastic, colorless, transparent cross-linked sodium hyaluronate gel of non-animal origin, in a physiological phosphate buffer. BIL has an HA concentration of 25.5 mg/mL and contains 0.3% of lidocaine hydrochloride. The presence of lidocaine aims to reduce local pain associated with injection and improve subject comfort.

In the current study, the intended use of BIL is for lip augmentation, by submucosal or subcutaneous injection, in subjects with upper and/or lower lip deficit.

The BIL product is presented in a pre-filled glass syringe sterilized by moist heat and designed for single use only. BIL has a clear, colorless (transparent) appearance. In the event the material in the syringe is not clear, **do not use** and notify the sponsor immediately. Likewise, if the package is opened or damaged, **do not use** and notify the sponsor immediately.

Manufacturer: CCI

Model ID: CCI

Classification: Class III, per US FDA product code LMH

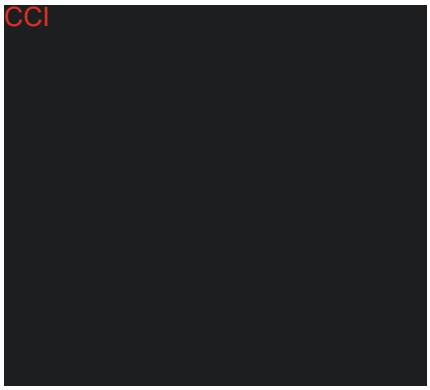
For further information, please see BIL's package insert provided by the sponsor.

10.1.2 Restylane Silk

The comparator device in the current study is Restylane Silk (RS). It is a gel of HA generated by *Streptococcus* species of bacteria, chemically cross-linked with BDDE, stabilized, and suspended in phosphate buffered saline at pH = 7 and concentration of 20 mg/mL with 0.3% lidocaine.

The product is indicated for submucosal implantation for lip augmentation and dermal implantation for correction of perioral rhytids in patients over the age of 21.

RS is supplied in a disposable glass syringe with a Luer Lock® fitting and is for single use only. RS is a clear and colorless gel without particulates. In the event the contents of a syringe show signs of separation and/or appears cloudy, do not use the syringe and notify the manufacturer (see Section 10.1.2 for the manufacturer's information).

Manufacturer:	
Manufactured for:	
Model ID/Version No.:	1.0 mL Syringe
Unique Device Identifier (UDI):	
Classification:	Class III, per US FDA product code LMH (approved under PMA #P040024, S121)

For additional information, please see RS's Instructions for Use (IFU).

10.2 Instructions for Use and Administration

BIL and RS should be used in the lip treatment region according to the information and instructions presented in Section 10.5. As provided by the sponsor, additional information on product usage is provided in BIL's package insert or in RS's IFU.

Both products should only be administered by the treating investigators. All treating investigators that will participate in the study are board-certified dermatologists and/or plastic surgeons.

10.3 Methods of Assigning Subjects to Treatment Groups

Subjects who provide informed consent, complete all screening assessments, meet all eligibility criteria, and are accepted for enrollment into the study will be randomized at the baseline visit.

Treatment-group assignments will be made based on the study randomization scheme; this planned multicenter investigation will use a balanced randomization (Section 13.2).

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10.5 Study Treatment

All protocol-specific criteria for the administration of study treatments must be met and documented prior to administration of any study treatment. All treatments will be performed on-site by the treating investigator. Subjects will not be dispensed any clinical trial materials.

Prior to treatment, investigational site personnel should:

- Ensure each subject meets all study inclusion criteria and no exclusion criteria;
- Perform a review of the subject's medical history; and
- Have the subject sign the ICF prior to treatment.

10.5.1 Planned Treatment Regimen

10.5.1.1 Lip Treatment Region

The investigator will use BIL and RS and all investigational materials only within the framework of the clinical investigation and in accordance with this CSP.

BIL and RS are designed to be injected submucosally; in addition, BIL can be injected subcutaneously by the treating investigator. Location (upper and/or lower lip), injection volumes (per lip), depth, techniques, and number of injection points will be recorded. Figure1 illustrates that the injection of the filler takes place laterally from the midline.



Note:

- **Pay attention** to the path of the arteries in the midline area, as changes in the path often occur here.
- **Do not** overfill with BIL or RS because this might change the proportion of the lips.
- As with other indications, knowledge about the course and location of important anatomical structures is essential for safe tissue augmentation with few side effects. **The lips are very well vascularized, and care should be taken as vessels are always near to the injected material**. With regard to the lip area, the superior labial artery and the inferior labial artery should primarily be noted.

10.5.1.2 Preparation of the Treatment Region

- The subject's face should be washed with soap and water, dried with a clean towel and the area to be treated should be cleansed with alcohol or another suitable antiseptic solution.
- Any make-up in the lip area should be removed.
- As with all transcutaneous procedures, BIL and RS injection carry a risk of infection and should be conducted with aseptic technique. Sterile gloves are recommended while injecting.

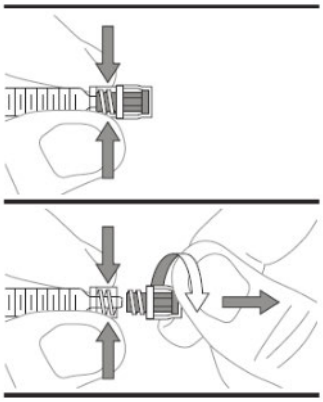
– Only topical anesthetic, at the preference of the treating investigator, or ice may be applied to anesthetize the injection site. Any medication or therapy used must be recorded in the eCRF.

10.5.1.3 Investigational Medical Device: Belotero Intense Lidocaine

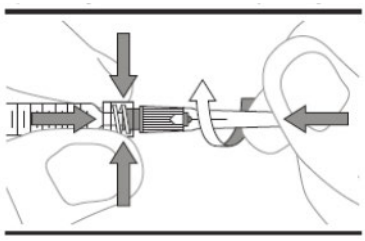
10.5.1.3.1 Needle Attachment

To assure proper attachment, use the needles provided with the clinical trial material.

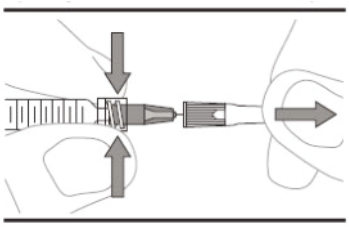
a) To attach the needle to the syringe, open the needle packaging to expose the needle hub. Remove the Luer syringe cap from the distal end of the syringe prior to attaching the needle.



b) Holding the Luer-lock fitting of the syringe, twist the needle onto the syringe. The needle must be tightened securely to the syringe. Do not over-tighten as this may break the needle and/or dislodge the syringe.



c) Pull off the needle guard to expose needle.



d) Prime the needle with BIL gel.

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

10.5.1.3.2 Treatment Procedure and Injection Techniques

– BIL is administered only using a thin gauge needle (27 G x ½").

- The following two injection techniques can be used during the clinical study:

A. Tunneling Technique

When using the tunneling technique, multiple linear threads are placed adjacent to each other. In addition, cupid's bow peaks can be further enhanced by adding a small bolus injection (Figure 2).



– Inject BIL **slowly**, applying even pressure on the plunger rod in retrograde technique. It is important that injection is stopped just before the needle is pulled out of the skin to prevent material from leaking out or ending up too superficially in the skin.

– **Do not** inject too superficially.

– When injection is completed, the treatment site should be firmly held for 15 to 20 seconds to ensure that all linear threads have coalesced to form a confluent subdermal filler deposition so that it conforms to the contour of the surrounding tissues. If an overcorrection has occurred, massage the area firmly between your fingers or against an underlying area to obtain optimal results. Ensure even deposition of product and symmetrical proportions of the lip before finishing the treatment.

B. Fanning Technique

When using the fanning technique, small linear threads are implanted subcutaneously, in a shape of a fan, with a sharp needle, starting from the medial portion on both sides of the midline in a retrograde direction. Optionally, the lateral portions may also be slightly augmented, with less material injected toward the puncture site to prevent overfilling of the injection site. These injection patterns are a foundational guide, individual subjects may require more application sites depending on individual lip variations (Figure 3).



10.5.1.3.3 Post-injection Massage

When injection is complete, the injection site may be gently massaged, if necessary.

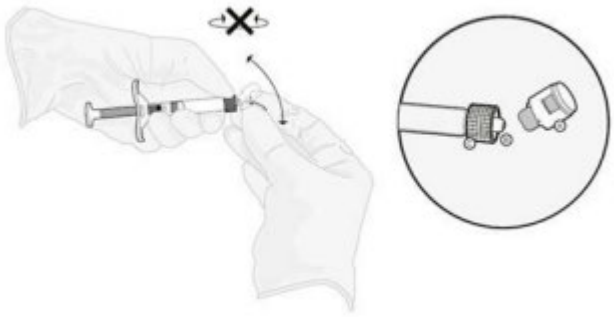
10.5.1.4 Comparator Medical Device: Restylane Silk

10.5.1.4.1 Needle Attachment

For safe use of RS, it is important that the needle is properly assembled.

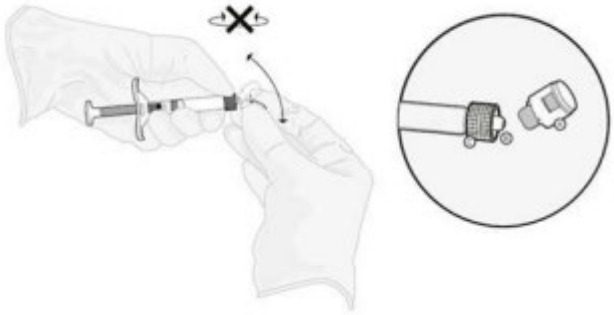
RS is administered using only a thin gauge needle (30 G x ½") in this study.

- Hold the syringe on the ribbed part (C) of the white closure system (Luer-lock adapter).
- With your other hand, take hold of the white cap (A) at the end of the closure system and gently tilt back and forth carefully until cap disconnects and can be pulled off (seal will be broken).
- Do not rotate.
- Do not touch the syringe tip (B) to keep it sterile.



-

Use the thumb and forefinger to hold firmly around both the glass syringe barrel and the Luer-lock adapter. Grasp the needle shield with the other hand. To facilitate proper assembly, both push and rotate firmly.



10.5.1.4.2 Treatment Procedure and Injection Techniques

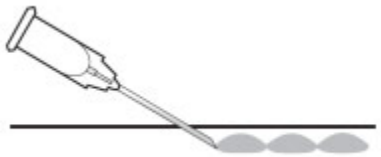
- When using needle, after insertion, and just before injection, the plunger rod should be withdrawn slightly to aspirate and verify that the needle is not intravascular.
- RS is administered only using a thin gauge needle (30 G x ½").
- When using a needle, the needle is inserted at an approximate angle of 30° parallel to the length of the wrinkle, fold, or lip. RS should be injected into the submucosal layer

for lip augmentation, care should be taken to avoid intramuscular injection. If RS is injected too superficially this may result in visible lumps and/or bluish discoloration. Inject slowly.

- Inject RS applying even pressure on the plunger rod. It is important that the injection is stopped just before the needle is pulled out of the skin to prevent material from leaking out or ending up too superficially in the skin.
- RS can be injected by a number of different techniques that depend on the treating physician's experience and preference, and patient characteristics.
- Serial puncture (A) involves multiple, closely spaced injections along wrinkles or folds. Although serial puncture allows precise placement of the filler, it produces multiple puncture wounds that may be undesirable to some patients.
- Linear threading (includes retrograde and antegrade) (B) is accomplished by fully inserting the needle into the middle of the wrinkle or fold and injecting the filler along the track as a "thread." Although threading is most commonly practiced after the needle has been fully inserted and is being withdrawn, it can also be performed while advancing the needle ("push-ahead" technique). To enhance the vermilion of the lip, the retrograde linear threading technique is the most advisable.
- Serial threading is a technique that utilizes elements of both approaches.

- Note! The correct injection technique is crucial for the final result of the treatment.

A. Serial Puncture



B. Linear Threading (includes retrograde and antegrade)



- Dissection of the sub-epidermal plane with lateral movement of the needle, rapid flows (> 0.3 mL/min), rapid injection or high volumes may result in an increase in short-term episodes of bruising, swelling, redness, pain, or tenderness at the injection site.
- When the injection is completed, the treated site should be gently massaged so that it conforms to the contour of the surrounding tissues. If an overcorrection has occurred,

massage the area firmly between your fingers or against an underlying area to obtain optimal results.

10.5.1.5 In-Procedure Warnings

If immediate blanching occurs (i.e., the overlying skin turns into a whitish color with reticular pattern), 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 American Society for Dermatologic Surgery guidelines, **which include** possible hyaluronidase injection.[13]

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; and/or
- Unusual pain during or shortly after the procedure.

Subjects should receive prompt medical attention and possible evaluation by an appropriate healthcare practitioner specialist should an intravascular injection occur.

Correct to 100% of the desired volume effect. Do not overcorrect. The degree and duration of the correction depend on the character of the defect treated, the tissue stress at the implant site, the depth of the implant in the tissue, and the injection technique. Markedly indurated defects may be difficult to correct.

10.5.1.6 Maximum Injection Volume

For both BIL and RS, the volume to achieve optimal aesthetic correction is at the treating investigator's discretion. The maximum recommended dose per treatment is 1.5 mL per lip. Do not overcorrect.

10.5.2 Selection and Timing of Treatment for Each Subject

10.5.2.1 Treatment Allocation Schedule

Treatment allocation to subjects will be done in a randomized manner. Randomization will be performed on Day 1 (Visit V1-a) before treatment using the electronic interactive EDC system (for details see Section 13.2).

Injections for subjects randomized to BIL will occur at baseline (V1-a), at the touch-up visit (V2-a), if applicable, and at the retreatment visit (V7-a) 48-weeks after the last injection (i.e., either initial treatment or touch-up), if applicable.

Injections for subjects randomized to RS will occur at baseline (V1-a) and at the touch-up visit (V2-a), if applicable.

In case of a public health emergency, further treatments may be halted or postponed.

10.5.2.2 Eligibility Criteria for Touch-up or Additional Treatment

A touch-up injection is **required** when the subject fails to show a 1-point improvement in one or both lip(s) on the MLFAS, as assessed by the blinded evaluator four (4) weeks post-treatment compared to baseline in at least one of the lips.

If a 1-point improvement is reached, but the subject does not achieve optimal aesthetic correction, according to the treating investigator, a touch-up / retreatment injection **may be** performed at the discretion of the investigator.

A touch-up will only be administered if there are no medical contraindications or existing AEs of concern, as determined by the treating investigator. A rationale should be recorded in the eCRF when the subject fails to achieve a 1-point improvement, but no touch-up is performed.

10.6 Prior and Concomitant Therapies

Medical history and concomitant therapies that are deemed relevant for study conduct by the investigator (e.g., chronic diseases, previous aesthetic treatments) should be documented in the eCRF.

Restrictions regarding concomitant therapy are discussed in detail in Section 9.2.2 and Section 9.2.3 (Exclusion Criteria and Subject Restrictions, respectively).

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[redacted]

10.7.1 Belotero Intense Lidocaine

IMD package contains one BIL blister pack, each containing the following supplies:

- One 1-mL pre-filled glass syringe of BIL with an ergonomically shaped injection plunger and finger grip;
- Two sterile needles (27G UTW x ½"); and
- Two subject labels.

BIL is packaged with peel-off subject labels that can be placed on the subject's medical records for traceability of the IMD. Recording of the following information regarding the IMD during and after the study is another method to provide IMD traceability.

- Receipt date,
- Quantity received,
- Unique subject identification,
- Lot number or serial number (if applicable),
- Expiration date,
- Procedure date,
- Names of person who received the IMD, and
- Return date with reason for return of damaged IMD.

BIL is clear, colorless, and transparent in appearance. In the event that the syringe contains material that is not clear, **do not use** the syringe and notify the sponsor.

BIL gel is for single use only and it is ready for injection. Do not re-sterilize the needle of the BIL syringe. Do not use if package is opened or damaged. **Do not use** the syringe if the package is opened or damaged and notify the sponsor immediately.

In the event of a pandemic disease outbreak (e.g., COVID-19 public health emergency), considerations may be made to supply investigational sites with sufficient study supplies to prevent supplying disruptions during the outbreak.

10.7.2 Restylane Silk

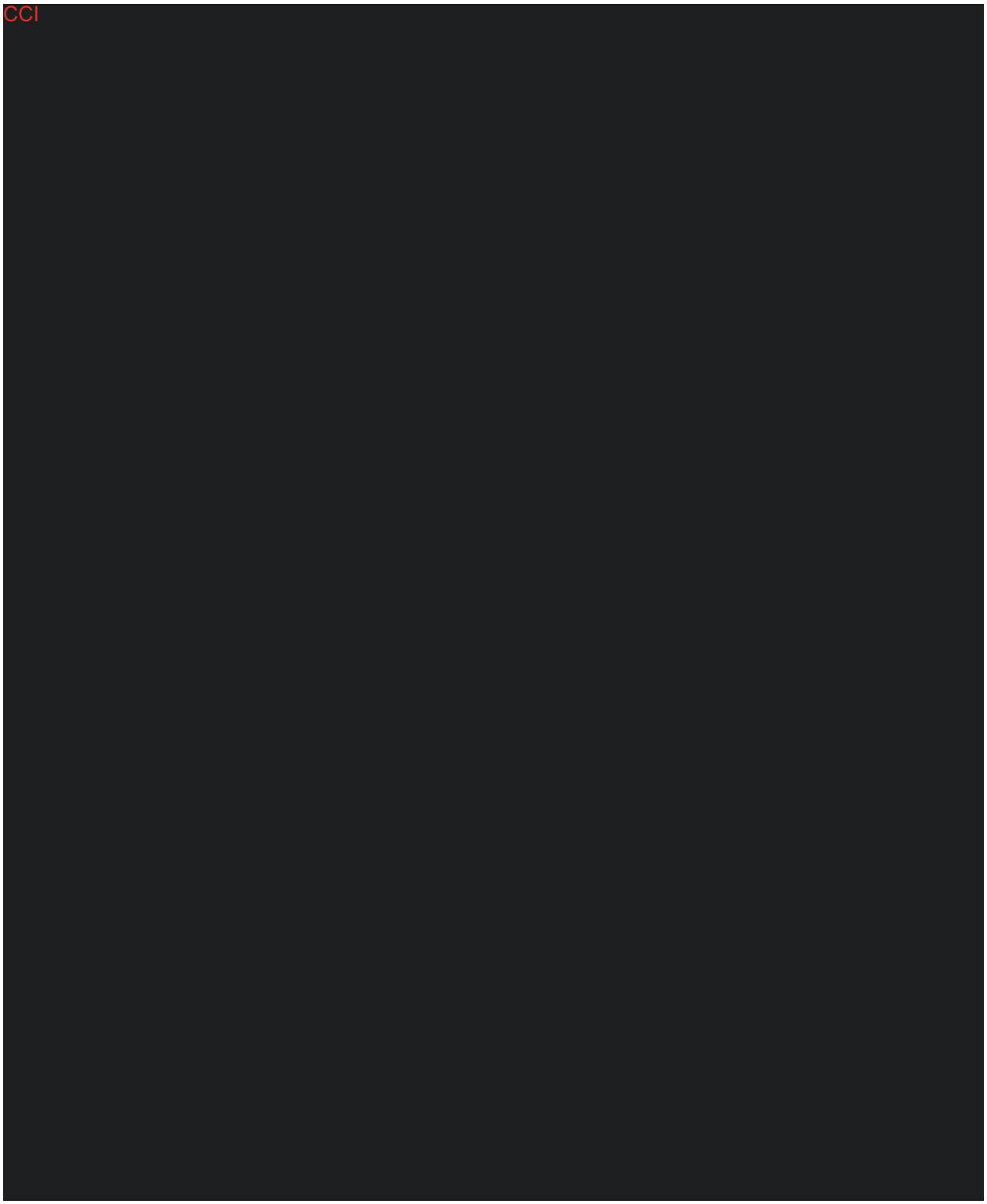
RS is supplied in a disposable glass syringe with a Luer-lock fitting. RS is co-packed with sterilized needle(s) 30 G x ½" as indicated on the carton. A patient record label is a part of the syringe label. Remove it by pulling the flap marked with three small arrows. This label is to be attached to the patient's records to ensure traceability of the product.

The contents of the syringe are sterile. The volume in each syringe and needle gauge is as stated on the syringe label and on the carton.

RS is an FDA-approved medical device. A patient record label is part of the syringe label. The investigator or designated study personnel should remove this label by pulling the flap

marked with three small arrows and attach the label to the subject's study records to ensure traceability of the product.

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10.9 Device Accountability Procedures

The sponsor will provide the investigator with all necessary study supplies after approvals of the CSP and ICF have been received from the IRB. Accountability for study supplies at the investigational site is the responsibility of the investigator.

Access to the study supplies will be controlled, and the study supplies will be used only in the clinical investigation and according to the CSP. The sponsor will keep records to document the physical location of all study supplies from shipment to the investigational sites until return to the sponsor. The investigator or an authorized designee is responsible for ensuring that accurate records of receipt, use, and return of the study supplies are maintained and include:

- The date of receipt and quantity of units received.
- Identification of each study supply (BIL and RS batch number/serial number or unique code).
- Expiration date.
- Date or dates of use.
- Unique subject number.
- Date of return of unused, expired, or malfunctioning study supplies (if applicable).
- Reason for return of malfunctioning study supplies.

All unused investigational products must be returned to the sponsor or designee immediately after the study is completed. Products accidentally destroyed during shipment or at an investigational site should be accounted for and documented. All clinical supplies must be accounted for at the termination of the study and a written explanation provided for discrepancies.

In the event of a pandemic disease outbreak (e.g., COVID-19 public health emergency), performing study-accountability procedures remotely should be considered and return of unused supplies may be delayed until return procedures can be safely performed by study-site personnel.

10.10 Treatment Compliance

Treatment is administered by the treating investigator or by delegated and qualified study personnel; therefore, assessment of compliance is unnecessary. Variations from the defined study treatment administration will be reported as protocol deviations.

10.11 Duration of Study

Study subjects will have a screening period of up to 10 days. Thereafter, subjects will participate for up to 64 weeks after baseline depending on the treatment group.

Enrolled subjects will be randomized 3:1 at baseline (Day 1) to BIL or RS.

Subjects, irrespective of treatment group, can have an optional touch-up injection four (4) weeks after the initial injection, to achieve optimal aesthetic outcome.

Subjects treated with RS will be followed for 48-weeks post last injection, for a total study duration of up to 52 weeks.

Subjects randomized to BIL treatment will have the option of a retreatment with BIL 48-weeks post last injection (i.e., either baseline treatment or touch-up, if applicable) upon agreement between the subject and the investigator. Subjects who receive such retreatment will be followed for an additional 12 weeks, for a total study duration of up to 64 weeks. In addition, BIL subjects who do not receive a retreatment will remain in the study for up to 64 weeks to assess long-term effectiveness and safety.

CCI provides an overview of the visit schedule and the study design. etails a Schedule of Events for each visit.

In the event of a public health emergency, the study might be halted, recruitment interrupted, and/or study processes and flow might be modified impacting the study duration and/or visit schedule depending on the study status at the time of the event. Mitigations may include, but are not limited to, extending visit windows, performing visits by phone or video, and/or performing effectiveness assessments remotely (Section 11.1.3).

11 STUDY PROCEDURES

11.1 Visit Schedule

11.1.1 Scheduled Visits

The purpose of the screening visit is to determine subject eligibility for investigation participation. Subjects who are diagnosed with a medical condition during the screening process will be notified and referred for medical care. The screening evaluation must be completed no earlier than 10 days and no later than three (3) days prior to baseline.

Baseline is defined as Day 1, which is the day of randomization and first implantation of the IMD (BIL).

During the active treatment period, subjects will receive BIL at Day 1 (V1-a), Week 4 (V2-a), if applicable, and optionally at Week 48 (V7-a) post last injection. Subjects will receive the comparator (RS) at Day 1 (V1-a) and Week 4 (V2-a), if applicable. The investigation activities and Schedule of Events are shown in CCI [redacted]

On days when treatments are scheduled, the IMD or the comparator device should be administered at the investigational site by the treating investigator. Following implantation of IMD or comparator device, subjects will be observed for a minimum of 30 minutes. Visual safety and lip function assessments will be performed to ensure subject safety (Section 11.2.2.5).

The primary outcome visit will occur at Week 8 (V3) post last injection, irrespective of the randomized treatment arm.

The End of Study visit will occur at Week 60 (V8) post initial injection or touch-up for subjects randomized to BIL and at Week 48 (V7-a) post last injection for subjects randomized to RS.

Safety follow-up visits will occur post implantation. Subjects will be contacted by telephone at 72 hours (+1 day) and will have a clinic visit if indicated by AEs. Otherwise, subjects will have safety follow-up visits two (2) weeks following implantation of the IMD or comparator device. For subjects being retreated at Week 48 (V7-a) an additional safety follow-up visit four (4) weeks after retreatment will be conducted.

All effectiveness assessments (e.g., MLFAS, GAIS, FACE-Qs; Section 11.2.1) and photography must be completed prior to administering any form of treatment (e.g., initial, touch-up, and/or retreatment). Please reference CCI [redacted] for the Schedule of Events and CCI [redacted] for an overview of the visit schedule and the study design.

Note: Make-up must be removed at the beginning of each visit in which effectiveness assessments, treatment, and/or photography are performed.

- *Note: Subjects should use the study-specific, standardized mirror when answering the FACE-Q questionnaires and the lip hydration and appearance questionnaires.*

11.1.1.1 Screening Day

- Obtain written informed consent.
- Perform urine pregnancy test (if female of childbearing potential). Negative test required prior to randomization.
- Record demographics (including FST as assigned by the treating investigator).
- Record height and weight for body mass index (BMI) calculation.
- Review and record medical history including prior medications and procedures.
  - *Note: Subject-reported medical history is acceptable.*
- Review and record concomitant medications and procedures.
- Have blinded evaluator (i.e., a qualified healthcare practitioner delegated by the treating investigator and trained by the sponsor) **and** the treating investigator independently perform the MLFAS assessments (i.e., they must not collaborate or discuss their MLFAS ratings). The MLFAS ratings from the blinded evaluator and the treating investigator must match for the subject to qualify for the study.
  - *Note: Every effort should be made to ensure the same blinded evaluator performs MLFAS assessment at all visits.*
- Have treating investigator or qualified delegate conduct lip symmetry and movement assessments.
- Administer lip hydration and appearance questionnaires to subject.
- Administer **two** FACE-Q assessments to subject:
  - Satisfaction with Lips and
  - Psychological Function Scale.
- The subject will complete an assessment to test their lip function and active lip sensation
- Have treating investigator or qualified delegate perform visual safety assessments **on both eyes**.
  - Visual acuity test (using a Snellen chart);
  - Confrontation visual field test; and
  - Ocular motility exam.

- Have treating investigator and/or study personnel take standardized photographs.
  - *Note: Make-up must be removed prior to photography.*
- Review and record any AEs (since the time of signing the ICF).
- Have treating investigator confirm the subject meets all inclusion criteria and no exclusion criteria.

11.1.1.2 Treatment Phase

Visit V1-a: Baseline / Initial Treatment (Day 1)

- Perform urine pregnancy test (if female of childbearing potential). Negative test required prior to randomization.
- Review and record changes in any concomitant medications/procedures. Confirm subject remains compliant with any applicable study restrictions.
- Review and record any AEs (since the time of signing the ICF).
- **Re-take** standardized lip photographs **ONLY if issues were detected with the screening photographs** and a reshoot is deemed necessary by the central photography vendor prior to treatment.
  - *Note: Make-up must be removed prior to photography.*
- Have treating investigator or qualified delegate perform pre-treatment visual safety assessments **on both eyes**:
  - Visual acuity test (using a Snellen chart);
  - Confrontation visual field test; and
  - Ocular motility exam.
- Have treating investigator confirm the subject meets all inclusion criteria and no exclusion criteria prior to randomization.

Randomization

- Subjects will be randomized via interactive EDC system to either the investigational device (BIL) or the comparator (RS).

Treatment (injection upper and/or lower lip(s)):

- Per randomization assignment, administer BIL or RS according to the injection instructions in Section 10.5.
- Have treating investigator or qualified delegate perform post-treatment visual safety assessments **on both eyes** within 30 minutes following injection of the last lip:
  - Visual acuity test (using a Snellen chart);

  - Confrontation visual field test; and
  - Ocular motility exam.

- Have treating investigator or qualified delegate perform FAST (Facial drooping, Arm weakness, Speech difficulties and Time to call emergency services) test 30 min post-treatment.
- Initiate web-based eDiary, perform training, and discuss eDiary completion instructions. Subject should be reminded to start their first diary entry on the day of treatment.
- Schedule 72-hour post-treatment follow-up phone call.

Visit V1-b: Follow-up phone call (72-hours post-treatment) (+1 day)

- Discuss and record any changes in concomitant medications/procedures. Confirm subject remains compliant with any applicable study restrictions.
- Discuss and record any safety concerns reported by the subject. Assess whether safety concerns warrant escalation for investigator reporting on the AE eCRF.
- If subject reports a safety concern, arrange an unscheduled visit to address.
- Review diary and remind subject to complete the subject eDiary daily and discuss any areas of concern with the subject.
- Ask whether the subject is experiencing any new or unusual symptoms related to a vascular occlusion (e.g., signs of stroke, changes in vision, tissue necrosis) or visual disturbance (any loss of vision, blurry vision, double vision, pain in or around eye, blind spot or shadow in the visual field, trouble moving eyes).
- If the subject reports any such symptoms, they should be assessed and referred for immediate medical treatment, as deemed necessary per best medical practices. If any change to vision is reported, the subject may be asked to come in immediately for an examination or referred immediately to the site-identified ophthalmology practice for further evaluation.

Visit V1-c: 2 weeks post-treatment safety follow-up (± 3 days)

- Review and record changes in any concomitant medications/procedures. Confirm subject remains compliant with any applicable study restrictions.
- Review and record any AEs.
- Administer lip function and sensation questionnaires to subject.
- Have treating investigator or qualified delegate conduct lip symmetry and movement assessments.
- The subject will complete an assessment to test their lip function and active lip sensation

- Have treating investigator or qualified delegate perform vision function assessments on **both** eyes:
  - Visual acuity test (using a Snellen chart);
  - Confrontation visual field test; and
  - Ocular motility exam.
- Review subject eDiary (from the initial treatment). The treating investigator will acknowledge review of the eDiary and determine if any entries should also be recorded as AEs on the AE eCRF.
- Remind subject to continue eDiary data entries.

Visit V2-a: 4 weeks post-treatment follow-up (+ 5 days)

All subjects will present for Visit V2-a and may receive a touch-up, as applicable. If no touch-up is performed, some assessments are not needed, and Visits V2-b and V2-c are not required. **All effectiveness assessments and photographs must be completed prior to administering the touch-up.**

- Review and record changes in any concomitant medications/procedures. Confirm subject remains compliant with any applicable study restrictions.
- Review and record any AEs.
- Review subject eDiary (from the initial treatment). The treating investigator will acknowledge review of the eDiary and determine if any entries should also be recorded as AEs on the AE eCRF.
  - *Note: If subject returns greater than 28 days after the initial treatment (within the +5 day window), eDiary information is not required beyond 28 days.*
- Administer lip function and sensation questionnaires to subject.
- Have treating investigator or qualified delegate conduct lip symmetry and movement assessments.
- Administer lip hydration and appearance questionnaires to subject.
- The subject will complete an assessment to test their lip function and active lip sensation
- Have treating investigator or qualified delegate perform vision function assessments **on both eyes**:
  - Visual acuity test (using a Snellen chart);
  - Confrontation visual field test; and
  - Ocular motility exam.
- Have blinded evaluator independently perform the MLFAS assessment.

- *Note: Every effort should be made to ensure the same blinded evaluator performs MLFAS assessment at all visits.*

- Have treating investigator assess whether a touch-up injection is required (Section 10.5.2.2).
- Have treating investigator and/or study personnel take standardized photographs.

Pre-Touch-up Assessments (only for subjects receiving touch-up injections with BIL or RS):

- Perform urine pregnancy test (if female of childbearing potential). Negative test required prior to touch-up.

- **Touch-up injection (upper and/or lower lip(s)):**
  - Per randomization assignment, administer BIL or RS according to the injection instructions in Section 10.5.
  - Have treating investigator or qualified delegate perform post-treatment visual safety assessments **on both eyes** within 30 minutes following injection of the last lip:
    - Visual acuity test (using a Snellen chart);
    - Confrontation visual field test; and
    - Ocular motility exam.
  - Have treating investigator or qualified delegate perform FAST test 30 min post-treatment.
  - Initiate web-based eDiary, perform training, and discuss eDiary completion instructions. Subject should be reminded to start their first diary entry on the day of touch-up.
  - Schedule 72-hour post-treatment follow-up phone call.

Visit V2-b: Follow-up phone call (72-hours post-treatment) (+1 day)

Note: This visit is only for subjects who received a touch-up at Visit V2-a.

- For assessments, please refer to Visit V1-b: Follow-up phone call (72-hours post-treatment) (+1 day).

Visit V2-c: 2 weeks post-touch-up safety follow-up (± 3 days)

Note: This visit is only for subjects who received a touch-up at Visit V2-a.

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

- Administer lip function and sensation questionnaires to subjects.
- Lip symmetry and movement assessments to be conducted by treating investigator or qualified delegate.
- The subject will complete an assessment to test their lip function and active lip sensation
- Treating investigator or qualified delegate perform vision function assessments on **both** eyes.
    - Visual acuity test (using a Snellen chart);
    - Confrontation visual field test; and
    - Ocular motility exam.
- Review subject eDiary (from the touch-up treatment). The treating investigator will acknowledge review of the eDiary and determine if any entries should also be recorded as AEs on the AE eCRF.
- Remind subject to continue eDiary data entries.

Visit V2-d: 4 weeks post- touch-up safety follow-up (+7 days)

Note: This visit is only for subjects who received a touch-up at Visit V2-a.

- Review and record changes in any concomitant medications/procedures. Confirm subject remains compliant with any applicable study restrictions.
- Review and record any AEs.
- Review subject eDiary (from the touch-up treatment). The treating investigator will acknowledge review of the eDiary and determine if any entries should also be recorded as AEs on the AE eCRF.
    - *Note: If subject returns greater than 28 days after the touch-up (within the + 7 day window), eDiary information is not required beyond 28 days.*
- Administer lip function and sensation questionnaires to subject.
- Have treating investigator or qualified delegate conduct lip symmetry and movement assessments.
- The subject will complete an assessment to test their lip function and active lip sensation
- Have treating investigator or qualified delegate perform vision function assessments **on both eyes**:
    - Visual acuity test (using a Snellen chart);
    - Confrontation visual field test; and
    - Ocular motility exam.

11.1.1.3 Maintenance Phase

During the maintenance phase, Visits V3-V7 are scheduled based on the subject's last injection, which is either the initial injection or any applicable touch-up injection. For example, if a subject did not have a touch-up, Visit V3 is 8 weeks after Visit V1-a. If the subject received a touch-up, Visit V3 is 8 weeks after Visit V2-a.

Visit V3: 8 weeks post last treatment (+/-7 days)

- Review and record changes in any concomitant medications/procedures. Confirm subject remains compliant with any applicable study restrictions.
- Review and record any AEs.
- Record subject's weight.
- Have treating investigator and/or study personnel take standardized photographs.
    - *Note: Make-up must be removed prior to photography.*
- Have blinded evaluator independently perform the MLFAS assessment.
    - *Note: Every effort should be made to ensure the same blinded evaluator performs MLFAS assessment at all visits.*
- Have treating investigator complete the iGAIS.

  Note: Standardized photographs, previously taken during the screening/ baseline visit, will be available for the treating investigator to reference when completing the live GAIS assessment.
- Have subject complete the sGAIS.

  Note: Standardized photographs, previously taken during the screening/ baseline visit, will be available for the subject to reference when completing his/her GAIS assessment.
- Administer **three** FACE-Q assessments to subject:
    - Satisfaction with Lips;
    - Satisfaction with Outcome; and
    - Psychological Function Scale.
- Administer lip function and sensation questionnaires to subject.
- Have treating investigator or qualified delegate conduct lip symmetry and movement assessments.
- Administer lip hydration and appearance questionnaires to subject.
- The subject will complete an assessment to test their lip function and active lip sensation

- Treating investigator or qualified delegate perform vision function assessments on both eyes.
    - Visual acuity test (using a Snellen chart);
    - Confrontation visual field test; and
    - Ocular motility exam.

Visit V4: 16 weeks post last treatment (± 14 days)

- Review and record changes in any concomitant medications/procedures. Confirm subject remains compliant with any applicable study restrictions.
- Review and record any AEs.
- Have blinded evaluator independently perform the MLFAS assessment.
    - *Note: Every effort should be made to ensure the same blinded evaluator performs MLFAS assessment at all visits.*
- Have treating investigator complete the iGAIS.

  Note: Standardized photographs, previously taken during the screening/ baseline visit, will be available for the treating investigator to reference when completing the live GAIS assessment.
- Have subject complete the sGAIS.

  Note: Standardized photographs, previously taken during the screening/ baseline visit, will be available for the subject to reference when completing his/her GAIS assessment.
- Administer **three** FACE-Q assessments to subject:
    - Satisfaction with Lips;
    - Satisfaction with Outcome; and
    - Psychological Function Scale.
- Administer lip function and sensation questionnaires to subject.
- Have treating investigator or qualified delegate conduct lip symmetry and movement assessments.
- Administer lip hydration and appearance questionnaires to subject.
- The subject will complete an assessment to test their lip function and active lip sensation
- Treating investigator or qualified delegate perform vision function assessments on both eyes.
    - Visual acuity test (using a Snellen chart);
    - Confrontation visual field test; and

- Ocular motility exam.

Visit V5 and V6: 24 and 36 weeks post last treatment (± 14 days)

- Review and record changes in any concomitant medications/procedures. Confirm subject remains compliant with any applicable study restrictions.
- Review and record any AEs.
- **Only at V5:** Have treating investigator and/or study personnel take standardized photographs.
  - *Note: Make-up must be removed prior to photography.*
- Have blinded evaluator independently perform the MLFAS assessment.
  - *Note: Every effort should be made to ensure the same blinded evaluator performs MLFAS assessment at all visits.*
- Have treating investigator complete the iGAIS.

  Note: Standardized photographs, previously taken during the screening/ baseline visit, will be available for the treating investigator to reference when completing the live GAIS assessment.
- Have subject complete the sGAIS.

  Note: Standardized photographs, previously taken during the screening/ baseline visit, will be available for the subject to reference when completing his/her GAIS assessment.
- Administer **three** FACE-Q assessments to subject:
  - Satisfaction with Lips;
  - Satisfaction with Outcome; and
  - Psychological Function Scale.
- Administer lip function and sensation questionnaires to subject.
- Have treating investigator or qualified delegate conduct lip symmetry and movement assessments.
- Administer lip hydration and appearance questionnaires to subject.
- The subject will complete an assessment to test their lip function and active lip sensation
- Have treating investigator or qualified delegate conduct active lip function and active lip sensation assessments.

Visit V7: End of Study for RS subjects (48 weeks post last treatment) (± 14 days)

- Review and record changes in any concomitant medications/procedures.
- Perform urine pregnancy test (if female of childbearing potential).

- Review and record any AEs.
- Record subject's weight.
- Have treating investigator and/or study personnel take standardized photographs.
- Have blinded evaluator independently perform the MLFAS assessment.
    - *Note: Every effort should be made to ensure the same blinded evaluator performs MLFAS assessment at all visits.*
- Have treating investigator complete the iGAIS.

  Note: Standardized photographs, previously taken during the screening/ baseline visit, will be available for the treating investigator to reference when completing the live GAIS assessment.
- Have subject complete the sGAIS.

  Note: Standardized photographs, previously taken during the screening/ baseline visit, will be available for the subject to reference when completing his/her GAIS assessment.
- Administer **three** FACE-Q assessments to subject.
    - Satisfaction with Lips;
    - Satisfaction with Outcome; and
    - Psychological Function Scale.
- Administer lip function and sensation questionnaires to subject.
- Have treating investigator or qualified delegate conduct lip symmetry and movement assessments.
- Administer lip hydration and appearance questionnaires to subject.
- The subject will complete an assessment to test their lip function and active lip sensation
- Perform vision function assessments on **both** eyes.
    - Visual acuity test (using a Snellen chart);
    - Confrontation visual field test; and
    - Ocular motility exam.

11.1.1.4 Retreatment Phase

The following sections apply to BIL subjects only. All subjects will present for Visit V7-a and may receive a retreatment, as applicable. If no retreatment is performed, some assessments are not needed, and Visits V7-b, V7-c and V7-d are not required. **All effectiveness assessments and photographs must be completed prior to administering the optional retreatment.**

Visit V7-a: BIL retreatment (36 weeks post last treatment) (± 14 days)

- Review and record changes in any concomitant medications/procedures. Confirm subject remains compliant with any applicable study restrictions.
- Review and record any AEs.
- Record subject's weight.
- Have treating investigator and/or study personnel take standardized photographs.
- Have blinded evaluator independently perform the MLFAS assessment.
  - *Note: Every effort should be made to ensure the same blinded evaluator performs MLFAS assessment at all visits.*
- Have treating investigator complete the iGAIS.

  Note: Standardized photographs, previously taken during the screening/ baseline visit, will be available for the treating investigator to reference when completing the live GAIS assessment.
- Have subject complete the sGAIS.

  Note: Standardized photographs, previously taken during the screening/ baseline visit, will be available for the subject to reference when completing his/her GAIS assessment.
- Administer **three** FACE-Q assessments to subject:
  - Satisfaction with Lips;
  - Satisfaction with Outcome; and
  - Psychological Function Scale.
- Administer lip function and sensation questionnaires to subject.
- Have treating investigator or qualified delegate conduct lip symmetry and movement assessments.
- Administer lip hydration and appearance questionnaires to subject.
- The subject will complete an assessment to test their lip function and active lip sensation
- Perform vision function assessments on **both** eyes:
  - Visual acuity test (using a Snellen chart);
  - Confrontation visual field test and
  - Ocular motility exam.

Pre-BIL retreatment assessments:

- Perform urine pregnancy test (if female of childbearing potential). Negative test required prior to retreatment.

- **BIL retreatment injection (upper and/or lower lip(s)):**
  - Administer BIL according to assigned randomization and injection instructions in Section 10.5.
  - Have treating investigator or qualified delegate perform post-treatment visual safety assessments **on both eyes** within 30 minutes following injection of the last lip:
    - Visual acuity test (using a Snellen chart);
    - Confrontation visual field test; and
    - Ocular motility exam.
  - Have treating investigator or qualified delegate perform FAST test 30 min post-treatment.
  - Initiate web-based eDiary, perform training, and discuss eDiary completion instructions. Subject should be reminded to start their first diary entry on the day of treatment.
  - Schedule 72-hour post-treatment follow-up phone call.

Visit V7-b: Follow-up phone call (72-hours post-treatment) (+1 day)

Note: This phone call is only for subjects who received retreatment at Visit V7-a.

- For assessments, please refer to Visit V1-b: Follow-up phone call (72-hours post-treatment) (+1 day).

Visit V7-c: 2 weeks post-retreatment safety follow-up (± 3 days)

Note: This visit is only for subjects who received retreatment at Visit V7-a.

- Review and record changes in any concomitant medications/procedures. Confirm subject remains compliant with any applicable study restrictions.
- Review and record any AEs.
- Review subject eDiary. The treating investigator will acknowledge review of the eDiary and determine if any entries should also be recorded as AEs on the AE eCRF.
- Administer lip function and sensation questionnaires to subject.
- Have treating investigator or qualified delegate conduct lip symmetry and movement assessments.
- The subject will complete an assessment to test their lip function and active lip sensation.
- Have treating investigator or qualified delegate perform vision function assessments on **both** eyes:

  - Visual acuity test (using a Snellen chart);
  - Confrontation visual field test; and
  - Ocular motility exam.
- Remind subject to continue eDiary data entries.

Visit V7-d: 4 weeks post-retreatment safety follow-up (+ 7 days)

Note: This visit is only for subjects who received retreatment at Visit V7-a.

- Review and record changes in any concomitant medications/procedures. Confirm subject remains compliant with any applicable study restrictions.
- Review and record any AEs.
- Review subject eDiary (from the retreatment). The treating investigator will acknowledge review of the eDiary and determine if any entries should also be recorded as AEs on the AE eCRF.
  - *Note: If subject returns greater than 28 days after the retreatment (within the + 7 day window), eDiary information is not required beyond 28 days.*
- Administer lip function and sensation questionnaires to subject.
- Have treating investigator or qualified delegate conduct lip symmetry and movement assessments.
- The subject will complete an assessment to test their lip function and active lip sensation.
- Have treating investigator or qualified delegate perform vision function assessments **on both eyes**:
  - Visual acuity test (using a Snellen chart);
  - Confrontation visual field test; and
  - Ocular motility exam.

Visit V8: End of Study for BIL subjects (60 weeks post last injection or 12 weeks post retreatment) (± 14 days)

- Review and record changes in any concomitant medications/procedures.
- Review and record any AEs.
- Record subject's weight.
- Have treating investigator and/or study personnel take standardized photographs.
  - *Note: Make-up must be removed prior to photography.*
- Have blinded evaluator independently perform the MLFAS assessment.

- *Note: Every effort should be made to ensure that the same blinded evaluator perform the MLFAS assessment at all visits.*

- Have treating investigator complete iGAIS.

  Note: Standardized photographs, previously taken during the screening/baseline visit, will be available for the treating investigator to reference when completing the live GAIS assessment.

- Have subject complete the sGAIS.

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

- Administer **three** FACE-Q assessments to subject:
  - Satisfaction with Lips;
  - Satisfaction with Outcome; and
  - Psychological Function Scale.

  - *Note: Subjects should use the study-specific, standardized mirror when answering FACE-Q questionnaires.*

- Administer lip function and sensation questionnaires to subject.
- Have treating investigator or qualified delegate conduct lip symmetry and movement assessments.
- Administer lip hydration and appearance questionnaires to subject.
- Administer likelihood of retreatment survey to subject.
- The subject will complete an assessment to test their lip function and active lip sensation
- Have treating investigator or qualified delegate perform vision function assessments on **both** eyes:
  - Visual acuity test (using a Snellen chart);
  - Confrontation visual field test; and
  - Ocular motility exam.

11.1.2 Unscheduled Visits

To ensure subject safety, any subject requiring additional follow-up during the study for safety (i.e., that does not occur during a scheduled study visit) should be seen for an unscheduled visit, and the following safety assessments should be completed: review of AEs, concomitant medications/procedures, and subject eDiary entries; conduct of vision

function, lip function, and lip symmetry assessments, and collection of lip photographs, if applicable.

An unscheduled visit for reasons other than safety will be conducted at the discretion of the investigator and documented appropriately in the site source documents.

11.1.3 Modified Visit Schedule During a Pandemic

In the event of a pandemic disease outbreak (e.g., COVID-19 public health emergency), the sponsor's primary goal is to ensure the safety and well-being of participating subjects. In general, the following recommendations apply if a pandemic disease outbreak occurs:

- In general, limit scheduled visits to those necessary for subject safety, clinical care, or follow-up of AEs.
- Use phone or virtual study visits for routine, mandated safety follow-up visits as described in the study protocol.
- Determine if effectiveness data can be collected remotely.
- Exercise flexibility when necessary and possible to continue performing protocol required procedures (e.g., subject photography, if applicable).

11.1.4 Public Health Emergency Mitigation Rules for This Protocol Include:

- Prolong screening period to 28 days. In case subject quarantines, site closures, or travel limitations do not allow subject on-site randomization within this time, re-screening of subjects will be allowed after liberalization of public restrictions.
- Increase the visit time window to ± 28 days for visits V4-V7-a and V8 for on-site visits.
- If on-site visits are not possible due to subject quarantines, site closures, travel limitations, supply-chain for the investigational or comparator product, or other considerations, or if site personnel or trial subjects become infected, visits should be conducted via phone to collect subject safety data and effectiveness data remotely. The following applies to visits V2-a, V3-V7-a, and V8:
    - Remotely collected effectiveness data related to the primary endpoint (subject's mean change from baseline at Visit V3 in MLFAS score) could be conducted via video assessment by the blinded evaluator, assuming technical prerequisites are available at the site and subject-level data are protected under applicable laws.
    - Remotely collected effectiveness data for secondary and other endpoints would include:
        1. iGAIS assessment;

2. Electronically submitted subject photographs; and/or
3. sGAIS, lip hydration and appearance questionnaires, and FACE-Q assessments.

- Forms will be provided to subjects electronically or via mail and will be completed by subjects at home. Subjects will return the initialed and dated forms to the site via mail or at the next possible visit.

- Visual safety assessments cannot be conducted remotely. If subjects experience any changes in vision associated with vascular occlusion, they will be instructed to immediately contact the ophthalmology practice identified by the site prior to contacting the site investigator. If a subject is unable to contact the ophthalmology practice identified by the site, the subject should be instructed to either call 911 or visit a local emergency room immediately.

11.2 Study Assessments

11.2.1 Effectiveness Assessments

For the timing of assessments, please refer to the Schedule of Events (Section 16.1) or the Visit Schedule (Section 11.1).

11.2.1.1 Merz Lip Fullness Assessment Scale

The validated MLFAS (CCI [redacted]) was designed to assess the volume of the upper and the lower lips. Each grade of the MLFAS is distinct; Grade 0 is anchored to depict very thin lips with minimal volume, and Grade 4 is anchored to depict very full lips with significant volume. Assessments will be performed separately for the upper and lower lip by a blinded evaluator.

For each of the five severity grades presented on the scale, three reference subjects are displayed. For each subject, a frontal view is presented to indicate specific characteristics of the lip region. The upper and lower lip of each subject is assessed independently on the MLFAS within this study.

During screening and subsequent study visits, subjects will be evaluated live on the MLFAS by a trained evaluator (i.e., a qualified healthcare practitioner delegated by the treating investigator); this evaluator is blinded to the subject's treatment assignment and will perform the respective assessment independently from any study staff. Prior to study enrollment, at least one blinded evaluator at each site will be trained and qualified by the study sponsor to perform scale-grading assessments. Training will consist of an instructional session, followed by a qualification where blinded evaluator trainees will score two sets of photographs, representing a variety of different MLFAS grades, at least

two weeks apart. The purpose of this assessment is to obtain intra- and inter-evaluator reliability qualification analyses prior to starting the study at their respective site (i.e., weighted Kappa/ICC analyses). Any blinded evaluator who does not successfully achieve an intra- and inter-rater (each rater against the median) reliability point estimate value of ≥ 0.70 will be retrained and requalified up to two times. If evaluator retention (e.g., change in personnel) becomes an issue during the study, new blinded evaluators must be trained by the sponsor, and respective qualification analyses must be performed. Qualification and training of blinded evaluators will be documented. At each study-site, all efforts should be made to plan for and maintain the same blinded evaluator for all assessments throughout the study. To account for illness or unplanned absence of the blinded evaluator, it is recommended to have at least one back-up blinded evaluator trained and qualified per site. Blinded evaluators will be retrained on the MLFAS at regular intervals (approximately every 3 months at a minimum).

The treating investigator will also attend a MLFAS-instructional session to ensure understanding of the subject eligibility criteria of upper and lower lip volume deficit with a rating of 0 (very thin), 1 (thin), or 2 (medium) at study entry.

Additionally, three blinded IPRs will assess subject photographs for the baseline[5] and Visit V3 using the MLFAS. Note: For subjects randomized to treatment, if no touch-up is performed, the photographs assessed will be eight (8) weeks post-baseline injection. If a touch-up is performed, the photographs assessed will be eight (8) weeks post touch-up injection. These board-certified IPRs, plastic surgeons or dermatologists, who are not part of the study sites, will be qualified using the methodology described for blinded evaluators above. Further details regarding photographs are provided in Section 11.2.1.2.

11.2.1.2 Photographs

For all subjects standardized photographs of the lips will be taken at the screening visit (prior to treatment) and at multiple intervals throughout the study. Photographs collected at screening will be reviewed and accepted by the central photography vendor prior to subjects presenting for treatment (Day 1). The screening photograph will default to the baseline photograph and will be used for reference throughout the study. If a subject's screening photographs **are deemed unsatisfactory** by the central photography vendor, **a reshoot is needed and photographs will be retaken at Day 1** (prior to treatment) and will be used for reference throughout the study. Since baseline photographs are of critical importance as a reference measure throughout the study, it is essential that all study-specific photography procedures, as described in a separate user manual, are followed.

[5]Photographs taken at screening will be used as baseline values during analysis. If issues were detected with the screening photographs and a reshoot is deemed necessary by the central photography vendor prior to treatment; baseline photos will be used for the IPR.

Every effort should be made to have the same study personnel take photographs throughout the study; furthermore, the same photography conditions/environment should be maintained at every visit. Screening photographs and/or reference time point photographs will be used for comparison for the treating investigator and subject GAIS assessments conducted at multiple time points during the study (see Section 11.2.1.3 and Section 11.2.1.4 for reference to the GAIS assessments) as well as for the IPRs assessment (i.e., independent photographic assessment) comparing pre-treatment and Visit V3 images according to the MLFAS scale separately for the upper and the lower lip. Photography procedures and specifications, including subject positioning and camera and lighting set-up requirements, will be described in a separate user manual.

11.2.1.3 Treating Investigator Global Aesthetic Improvement Scale (iGAIS)

The treating investigator will use the 7-point iGAIS to assess global aesthetic improvement among treated subjects using pre-treatment photos for comparison (CCI [redacted]).

The treating investigator will use photographs collected before treatment and at referenced post-treatment time points to make comparisons to the baseline cosmetic condition.

Refer to the study endpoints (Section 7.2.1) and visit schedule (CCI [redacted]) for additional information on the iGAIS assessment and its associated reference time points.

11.2.1.4 Subject Global Aesthetic Improvement Scale (sGAIS)

Treated subjects will use the 7-point sGAIS to assess their global aesthetic improvement using pre-treatment photos for comparison (CCI [redacted]).

Subjects will use photographs collected before treatment and at referenced post-treatment time points to make comparisons to the baseline cosmetic condition.

Refer to the study endpoints (Section 7.2.1) and visit schedule (CCI [redacted]) for additional information on the sGAIS assessment and its associated reference time points.

11.2.1.5 FACE-Q Assessments

FACE-Q is a set of validated, standardized patient-reported outcome scales for subjects receiving facial cosmetic procedures.[12, 20, 21] In this study, subjects will evaluate treatment outcomes using three FACE-Q instruments:

1. FACE-Q Satisfaction with Lips Scale (CCI [redacted]);
2. FACE-Q Satisfaction with Outcome Scale (CCI [redacted]); and
3. FACE-Q Psychological Function Scale (CCI [redacted]).

The FACE-Q Satisfaction with Lips Scale and Psychological Function Scale will be completed at baseline and at various post-treatment visits. The FACE-Q Satisfaction with Outcome Scale will be completed only at various post-treatment visits. Refer to the study endpoints (Section 7.2.1) and visit schedule (CCI) for additional information on the FACE-Q assessments and their associated reference time points.

For all FACE-Q Satisfaction assessments, a sum score will be calculated; higher scores indicate a better outcome. Sum scores will then be Rasch-transformed (range: 0 to 100) as described in Section 13.4.1.3. When answering the FACE-Q questionnaires, subjects will utilize a standardized mirror, as provided to the investigational sites (i.e., same size, shape).

CCI

11.2.2 Safety Assessments

Standard safety assessments, including documentation of AEs and SAEs reported by the investigator throughout the study, will be evaluated.

Refer to the safety endpoints (Section 7.2.2), the Schedule of Events CCI), and the safety definitions (Section 12) for additional information on the safety assessments.

11.2.2.1 Adverse Events/Serious Adverse Events

All AEs/SAEs reported by study subjects, investigators, or other study personnel after the time of informed consent through EOS will be recorded, regardless of causality. The period of observation for an AE extends from signing of the ICF through the subject's last study visit. Additional information (e.g., definitions, reporting requirements) regarding AEs and SAEs is provided in Section 12.1and Section 12.2, respectively.

In this study, any AE of visual disturbance is considered an adverse event of interest, whether considered to be related to IMD/comparator or not (including, but not limited to, any loss of vision, blurry vision, double vision, pain in or around eye (other

than typical injection-induced pain), blind spot or shadow in the visual field, trouble moving eyes, etc.). Any events involving a stroke or stroke-like symptoms are also considered adverse events of interest. The investigator will be instructed to report any AE of interest within 24 hours to the sponsor on the Adverse Event of Interest Form. The incident will then be reported to FDA within 10 business days of receipt by the sponsor. These reports will be generated by the sponsor or designee and will include the depth of injection, injection volume, symptoms observed, time to onset and resolution, and any interventions implemented.

11.2.2.2 72-hour Follow-Up Phone Call

All subjects will receive a follow-up phone call 72 hours (+1 day) after the initial treatment at baseline, after the touch-up treatment, if applicable, and after the retreatment, if applicable.

During this phone call, study personnel will discuss and record any changes in concomitant medications/procedures and confirm the subject remains compliant with any applicable study restrictions. Study personnel will also discuss completion of the subject eDiary and remind the subject how to utilize the eDiary for daily entries. If any safety concerns arise that would necessitate an unscheduled visit to the site, this visit should be scheduled during the phone call.

In addition, subjects should be asked if they are experiencing any new or unusual symptoms related to a potential vascular occlusion (e.g., signs of a stroke, changes in vision, tissue necrosis) as noted in the ICF. If the subjects report any signs or symptoms of a stroke, they must call 911 immediately. If the subjects report any changes in vision associated with vascular occlusion, they must contact the ophthalmology practice identified by the site prior to contacting the site investigator. If any other such symptoms related to a potential vascular occlusion are reported by the subjects, they should be assessed, and referred for immediate medical treatment as deemed necessary per best medical practices. If any change to vision is reported during the 72-hour follow-up phone call, the subject may be referred immediately to the ophthalmology practice identified by the site or a local emergency room (if the ophthalmology practice cannot be reached or available) for further evaluation.

11.2.2.3 Subject eDiaries and Common Treatment Responses

CTRs are common clinical presentations and/or side effects that a study subject may experience following treatment. For all treated subjects (either with BIL or RS), a subject web-based eDiary will be initiated at the baseline visit.

All subjects will be asked to complete the eDiary daily for 28 days following initial treatment (starting on the day of treatment). eDiary entries will be reviewed by site staff on

an ongoing basis, during the 72-hour phone call (Section 11.2.2.2) and at the corresponding safety follow-up visit to ensure adequate and appropriate completion; entries will then be discussed with the subject during the visit, as necessary.

If the subject receives a touch-up treatment, either with BIL or RS, another 28-day eDiary will be completed. For subjects who receive optional retreatment with BIL, another 28-day eDiary will be completed. eDiary review will be performed continuously, at each issue, by site staff as described in the previous paragraph.

The investigator will acknowledge his/her review of each subject's eDiary and determine if any entries should also be documented and reported as AEs. Reports of any safety concerns by telephone should be escalated to an unscheduled site visit at the discretion of the investigator. All CTRs are expected to be mild and transient in nature. Any CTR that is longer or more severe than expected and/or is not resolving, as well as any unforeseen/unanticipated events reported by the subject, should be evaluated by the investigator as a possible AE or SAE and be reported accordingly.

For all eDiaries, subjects will be asked to record daily, for 28 days, the following data:

- Presence of any new or unusual symptoms related to a possible vascular occlusion including signs of stroke, changes in vision, tissue necrosis from a pre-defined list (i.e., sudden difficulty speaking, numbness or weakness in face, arms or legs, changes in alertness/consciousness, face drooping, severe headache (more intense or longer than usually experienced), dizziness, confusion, fever, loss of vision, blurry vision, double vision, pain in or around eye, blindness, blind spot, trouble moving eyes, changes in skin color comparing one side to another, sudden onset of severe pain on one or both sides, blistering/peeling skin, scabby/crusty skin);
- Presence or absence of any pre-defined CTRs that may occur i.e., injection site erythema (including redness), injection site swelling, injection site lip numbness, injection site pain (including tenderness, soreness, burning, stinging), injection site bruising, injection site itching, injection site induration (including firmness, hardness), injection site nodules (including lumps, bumps), injection site discoloration (not bruising or redness); and/or
- Any other sign or symptom that the subject experiences that is not already listed in the eDiary.

Subjects should start completing the eDiary the day of the treatment after injection. The treating investigator will acknowledge his/her review of each subject eDiary and determine if any entries should be captured as AEs. At the discretion of the investigator, he/she will determine if a CTR will be reported as an AE, such as if the duration of the event is longer or more severe than expected.

Note: When a subject reports in the eDiary that they have experienced any new or unusual symptom related to a possible vascular occlusion, the site personnel will receive an immediate notification and should contact the subject within one business day to assess whether additional medical attention is necessary.

Subjects must be informed that, at any time over the study interval, if they experience any signs or symptoms of a stroke, they must call 911 immediately. If they experience any changes in vision associated with vascular occlusion, they must contact the site identified ophthalmology practice prior to contacting the site investigator. In the event a subject is unable to contact the site identified ophthalmology practice, the subject should be instructed to either call 911 or visit a local emergency room immediately. If any other new or unusual symptoms occur related to a potential vascular occlusion (e.g., signs of a stroke, changes in vision, tissue necrosis), they must seek immediate medical attention and notify the study doctor immediately. The study doctor must refer the subject to a specialist if additional medical attention is deemed necessary. A list of symptoms related to potential vascular occlusion will be provided to all subjects in the ICF for the subject's reference.

If any change to vision is reported over the study interval (e.g., during a telephone follow-up, scheduled or unscheduled visit), the subject may be referred immediately to the site`s identified ophthalmology practice for further evaluation.

11.2.2.4 Visual Safety Assessments

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

Vision function assessments will include a visual acuity test (using a Snellen chart), a confrontation visual field test and an ocular motility exam. These assessments will be completed at screening, pre-treatment, post initial injection, pre- and post-treatment for the touch-up and retreatment injections (if applicable), safety follow-up visits and EOS visits. At all other follow up visits study subjects will be queried for the presence or absence of any visual symptoms. If the study subject reports a visual symptom then the visual assessments will be performed. The aforementioned vision function assessments can be performed by the trained treating investigator or a trained delegate. Every effort should be made that the subject's vision will be assessed wearing the same permitted spectacle correction and in the same exam room to help to control for differences in room lighting and other conditions.

Any abnormality identified during the visual safety assessments at screening and/or baseline before initial injection should be documented as medical history. During the screening period, if a subject is diagnosed with a clinically relevant visual pathology that may potentially interfere with study results or potentially enhance the safety concerns of a subject as a result of treatment, the subject will need to be evaluated for whether he/she

meets one or more exclusion criteria and should not be treated. In addition, the subject may be referred to the site identified ophthalmology practice for further evaluation.

Within 30 minutes following the injection of one or both lips (either baseline treatment, touch-up, or retreatment, if applicable), the visual safety assessments will be performed.

When the subject returns for the 2-week or 4-week safety follow-up visits, vision function assessments will be repeated and assessed for any changes that could indicate a safety signal or concern. An abnormality is defined as any parameter that is clinically significant in nature or a drop in vision by one line or more for the Visual Acuity Assessment. In addition, the abnormality will be reported as an AE.

Subjects will not be eligible for a touch-up injection or retreatment (if applicable), if:

- Abnormalities related to changes in vision are documented by the treating investigator to be related to study treatment;
- Any constriction on visual field testing is observed (treating investigator should refer the subject to an ophthalmologist or retinal specialist); or
- Any new symptomatic changes in ocular motility are determined by the treating investigator to be clinically relevant and/or related to study treatment.

If during the study a subject is diagnosed with a clinically relevant visual pathology that may potentially interfere with study results or might result in increased safety concerns, the subject may be referred to the ophthalmology practice identified by the site for further evaluation.

In this study, any AE of visual disturbance, is considered an adverse event of interest, whether considered to be related to IMD/comparator or not (including, but not limited to, any loss of vision, blurry vision, double vision, pain in or around eye (other than typical injection-induced pain), blind spot or shadow in the visual field, trouble moving eyes, etc.). ~~will be reported to the sponsor on the Visual Disturbance Event Form.~~ Any events involving a stroke or stroke-like symptoms are also considered adverse events of interest. The investigator will be instructed to report any AE of interest within 24 hours to the sponsor on the Adverse Event of Interest Form. The incident will then be reported to FDA within 10 business days of receipt by the sponsor. These reports will be generated by the sponsor or designee and will include the depth of injection, injection volume, symptoms observed, time to onset and resolution, and any interventions implemented.

11.2.2.5 Vision Function Assessments

11.2.2.5.1 Visual Acuity

Visual acuity will be determined using the Snellen chart. Each site will be equipped with a Snellen chart. The lane and distance from the chart will be confirmed by the monitor prior to beginning the screening activities at the site.

The site will follow standard directions for using the Snellen chart in determining visual acuity. The subject will be asked to cover one eye (if the subject wears glasses/contacts for distance vision they will be asked to keep them on/in). The trained treating investigator or a trained delegate will point to each line as the subject reads the letters aloud. The smallest line where the subject identified the majority of letters correctly will be recorded. Visual acuity is expressed as a fraction. The visual acuity will be recorded per eye.

11.2.2.5.2 Confrontation Visual Field Test

The confrontation visual field test will measure how sensitive the vision is in different parts of the visual axis. A confrontation visual field test can determine if the subject has blind spots in their vision and if so, where the blind spots are. The examination should be performed without the subject wearing glasses (Note: contacts are permitted). To measure the visual field, the trained treating investigator or a trained delegate will use the standard finger test.

The subject will be asked to look directly at an object in front while one of their eyes is covered. The investigator or delegate may hold up different numbers of fingers in areas of the subject's peripheral vision field and asked how many they see as they look at the target in front.

11.2.2.5.3 Ocular Motility Exam

The trained treating investigator or a trained delegate should determine if the subject's range of ocular movements is intact in each direction of gaze. The examination should be performed without the subject wearing glasses (Note: contacts are permitted). To begin, the subject should be asked to look at a distant object while their head is facing straight ahead. The subject's head should not be tilted up, down or to the side. Symmetry between the eyes should be noted in primary position. Then the subject should be asked to follow the trained treating investigator or a trained delegate finger without moving their head. The trained treating investigator or a trained delegate should use his/her index finger in either right or left hand for guiding directions of eye movements. The trained treating investigator or a trained delegate should move the index finger to the left, right, up and right, up and left, down and left, down and right, straight up and straight down. The subject should be asked to voice if they experience double vision in any position of gaze. The subject should

be instructed to voice if they have any double vision in any of the fields. The trained treating investigator or a trained delegate should look for and document any asymmetry in ocular motility or abnormal ocular motility.

11.2.2.6 Neurological Exam

Although there were no reports of neurological events of concern in a previously conducted pilot study (M930041001), treating investigators will conduct a neurological exam (FAST test; CCI) 30 minutes post-treatment at each treatment visit. The FAST test stands for Facial drooping, Arm weakness, Speech difficulties and Time to call emergency services. The FAST test is commonly used to help detect when a person may be experiencing a stroke.[22] The test was designed for assessment of a seated subject and therefore omits assessment of leg weakness.

The subject may either pass or fail the FAST test:

- If the subject **fails** the FAST test, the treating investigator will direct the subject to visit a local emergency room immediately for further evaluation.

Any facial asymmetry, arm weakness, and/or speech impediment identified at screening and/or before initial injection should be documented as medical history. Investigators will take into consideration any documented medical history that could potentially act as a confounding factor while performing the FAST test (e.g., speech impediment not to be confused with speech being slurred).

CCI

CCI [redacted]

11.2.3 Additional Data Collected

Data for other assessments will be collected as follows:

- Demographics and other baseline characteristics, including FST CCI [redacted]), height, and weight;
- Urine pregnancy tests (only if subject is of childbearing potential);
- Relevant medical history/concomitant diseases;
- Concomitant therapies;
- Injection technique, depth of injections, number of injection points, injection volume and needle (27G or 30G) used.

11.2.4 Appropriateness of Assessments

The MLFAS is a clinical instrument shown to be valid and highly reliable in clinical grading of lip fullness.

During validation [23], the MLFAS demonstrated excellent reliability when live subjects were scored by trained physicians. Evaluated subjects included both sexes, ranged in age from 18 to 82 years, and including diversity in race and FSTs. Both intra-rater and inter-rater agreements were almost always within one grade. Upper and lower lips were rated with comparable reliability by all raters, and the weighted kappa coefficients exceeded 0.7 in both individual pairwise and overall intra- and inter-rater reliabilities. These findings demonstrate the MLFAS scales are valid in terms of content and structure and establish a threshold for treatment benefit.

Furthermore, the MFLAS was used in a clinical study [24] conducted outside US to assess the primary effectiveness endpoint (responder rate for treated and for untreated lips at Week 4) live by the blinded rater, where a response was defined as ≥ 1-point improvement on both the upper and lower lips compared to baseline. Of the 71 subjects in the full analysis set in this study, 87.2% were MLFAS responders in the treated subjects and 4.2% were

responders in the control group. The difference between the two rates (Etermis 4 – control) was +83.1% and was statistically significant.

Based upon the results from scale validation and the clinical study, the MLFAS is fit-for-use in the clinical setting when assessing the fullness of the upper and lower lip region of male, female, and transgender subjects of various ages and FSTs.

The Lip Hydration and Appearance questionnaire has been selected as a tool to evaluate lip hydration satisfaction based on subject self-assessment. It will compare standardized items of a subject's pre-treatment satisfaction to post-treatment responses. Sites will be provided with standardized mirrors to allow subject assessment.

Lip function and lip sensation questionnaires, lip symmetry scoring, and lip movement tests have been added to ensure that the performed lip augmentation treatment does not alter lip function. Tests will assess a subject's lip function, lip sensation, and lip symmetry, as well as their ability to pronounce preselected words. Assessments (lip symmetry coring and lip movement tests) have been previously utilized in comparator pivotal studies (see Restylane® Silk Summary of Safety and Effectiveness Data [SSED; P040024/S072] and Restylane® Kysse [SSED, P140029/S021])

Visual assessments were selected to ensure that subjects with detected abnormalities on visual-function assessments post-treatment are referred to an ophthalmologist for evaluation.

The remaining effectiveness assessments (i.e., sGAIS, iGAIS, FACE-Q) and safety assessments are considered standard for clinical investigations of aesthetic medical devices, as they are widely used and recognized as relevant, reliable, and accurate.

12 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

12.1 Definition of an Adverse Event

An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical sign (including abnormal laboratory findings) in subjects, users, or other persons, whether or not related to the IMD or the comparator.

Note:

1. This definition includes events related to the IMD or the comparator.
2. This definition includes events related to the procedures involved.
3. For users or other persons, this definition is restricted to events related to the use of IMD or the comparator.

12.1.1 Details of an AE

The period of observation for an AE extends from when the ICF is signed until the subject's last study visit. Any untoward medical occurrence between the time the ICF is signed and the first treatment with the IMD or the comparator is an AE and has to be documented in the subject's file and on the AE eCRF. Any observed AE will be fully investigated, documented, and followed until the event is either resolved or adequately explained. In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered the AE rather than the procedure itself. New AEs reported to the investigator during the observational period, after the last treatment with the IMD or the comparator, must be documented, treated, and followed like all other AEs.

A pre-existing condition noted in the medical history should not be reported as an AE, unless the condition worsens, or the disease reoccurs during the reporting period. To determine whether a condition has worsened, it is compared to the subject's condition at screening.

Elective treatments planned before screening, and which are documented in the subject's source data, are usually not regarded as AEs. However, elective procedures should be postponed, if possible, until the subject completes participation in the trial.

12.1.2 Reporting and Handling of an AE

Data pertaining to AEs will be collected during each clinical study visit based on the subject's spontaneous description, through investigator inquiry, or upon discovery in the course of examinations completed during the visit. The investigator will assess and record

any AE in detail in the subject file and on the AE eCRF. The following information must be recorded:

- AE diagnosis or main symptom;
- Treatment area affected (yes/no). If treatment area was affected, specify the location in the reported term (yes/no);
- Date of onset;
- Intensity (maximum observed using the Severity Grading scale; Section 12.1.3);
- Causal relationship to IMD or the comparator (not related, related);
- Causal relationship to injection procedure (not related, related);
- Serious (yes or no), date serious since and reason for seriousness;
- Outcome (Section 12.1.5);
- AE leading to discontinuation of the clinical study (yes or no);
- Action taken with medical device;
- Other action taken; and
- Stop date.

All non-serious AEs should be collected for both BIL and RS. The investigator must record any non-serious AEs in detail in the subject file and on the AE eCRF. Additionally, non-serious and serious AEs that were caused by RS should be reported to Galderma by calling 1-855-425-8722 or by mail at:



In cases of an SAE (defined in Section 12.2), the investigator must also complete an SAE Report Form and report it to the sponsor within 24 hours, as described in Section 12.2.2.

12.1.3 Severity Grading for an AE

The clinical severity (i.e., intensity) of an AE will be classified as:

Mild: Signs and symptoms that can be easily tolerated. Symptoms can be ignored and disappear when the subject is distracted.

Moderate: Signs and symptoms that cause discomfort and interfere with normal functioning but are tolerable. They cannot be ignored and do not disappear when the subject is distracted.

Severe: Signs and symptoms that affect usual daily activity and incapacitate the subject, thereby interrupting daily activities.

The investigator is required to grade the severity (i.e., intensity) of each AE.

12.1.4 Causal Relationship of an AE with an Investigational Medical Device

An AE is considered to be "related" to IMD/comparator or the injection procedure if a causal relationship between the IMD/comparator or the injection procedure and an AE is at least reasonably possible (i.e., the relationship cannot be ruled out). In this case, the non-serious event is considered an adverse device effect (ADE; Section 12.3). If the event is serious, it is a SADE; Section 12.4).

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

12.1.5 Outcome Categories for an AE

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.

If there is more than one AE, only the AE leading to death will be attributed with a "fatal" outcome.

12.2 Definition of a Serious Adverse Event

An SAE is an AEs that:

- led to death;
- led to serious deterioration in the health of the subject, that either resulted in:
    - a life-threatening illness or injury;
    - a permanent impairment of a body structure or a body function, including chronic diseases;
    - inpatient or prolonged hospitalization; or
    - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
- led to fetal distress, fetal death, or a congenital abnormality or birth defect including physical or mental impairment.

Note: Planned hospitalization for a pre-existing condition, or a procedure required by the CSP, without serious deterioration in health, is not considered an SAE.

12.2.1 Details of an SAE

In cases of fatality, the cause of death is considered the AE, and the death is considered its outcome. In this case, the primary cause of death (i.e., the event leading to death) should be recorded and reported as an SAE. "Death" will be recorded as the outcome of this respective event; death will not be recorded as a separate event. Only if no cause of death can be reported (e.g., sudden death, unexplained death), the death *per se* might be reported as an SAE. In cases of death, an autopsy report should be submitted (if available). The date and cause of death should be recorded.

Planned hospitalization for a pre-existing condition is not considered an SAE. If a subject experiences an additional AE that prolongs a pre-planned hospitalization, this event is considered an SAE and should be reported as such. Hospitalizations for elective treatments planned before screening and which are documented in the subject's source data are not regarded as SAEs.

In addition, device deficiencies, as defined in Section 12.8, that might have led to an SAE if:

- suitable action had not been taken, or

- intervention had not been made, or
- if circumstances had been less fortunate should be categorized as an SAE and reported accordingly.

12.2.2 Reporting and Handling of an SAE

All SAEs that occur during the clinical study period, whether considered to be related to an IMD/comparator or not, must be reported via email, and an SAE Report Form should be submitted to the sponsor within 24 hours upon knowledge of the event. Further reporting details will be outlined in a separate document.

Although all information required for completion of an SAE Report Form may not be available within the specified time period, an initial report should be submitted if the following minimal information is available:

- An identifiable subject (unique subject number);
- A suspect product and how the treatment relates to the SAE;
- An identifiable reporting source (investigator/investigational site identification); and/or
- An event or outcome that can be identified as serious.

The investigator must report SAEs to Merz as defined in Section 12.2 and the site's IRB per their reporting guidelines.

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

The investigator must supply further supporting information, and a detailed SAE description is an integral part of this supporting information. Follow-up SAE reports should be sent without delay to the sponsor or designee as an SAE Report Form (marked as a "follow-up" report), and the eCRF has to be updated accordingly to avoid discrepancies. The SAE has to be followed until the SAE is resolved / recovered or a plausible explanation is available. The SAE will be followed only in the Global Product Safety database after final SAE reconciliation is completed.

An SAE occurring after the end of the observational period will need to be reported if the investigator considers the event to be related to IMD/comparator. These reports generally will not be entered into the study database. Following database close for the study, any ongoing SAEs will be followed until resolution or stabilization under the responsibility of the investigator per their standard of care.

The investigator should complete and send any SAE Report Forms (including any follow-up forms) to Merz North America Product Safety via the email provided below:

Merz North America, Inc. Product Safety
6501 Six Forks Road
Raleigh, NC 27615
USA
Product Safety Email: AxUS-adverse.events@merz.com

12.3 Definition of an Adverse Device Effect

An ADE is defined as an AEs related to the use of an IMD.

Note:

1. This definition includes AEs resulting from insufficient or inadequate IFU, deployment, implantation, installation, or operation or any malfunction of the IMD.
2. This definition includes any event resulting from use error or from intentional misuse of the IMD.

12.4 Definition of a Serious Adverse Device Effect

A SADE is defined as an ADE that has resulted in any of the consequences characteristic of an SAE (Section 12.2).

12.4.1 Definition of an Anticipated Serious Adverse Device Effect (ASADE)

An ASADE is a SADE which by its nature, incidence, severity, or outcome has been identified in the current version of the risk analysis report.

12.4.2 Definition of an Unanticipated Adverse Device Effect

A UADE is defined as follows:

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

12.5 Reporting of Pregnancy

Any pregnancy that starts during the clinical study must be reported, using the Pregnancy Form, by the investigator to the sponsor within 24 hours of learning of its occurrence. Pregnancies and pregnancy follow-up should be reported on a Pregnancy 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 to the IMD. In addition, each pregnancy has to be reported on the AE eCRF (i.e., as a non-serious AE due to device exposure before or during pregnancy). Pregnancy forms (including any follow-up forms) should be submitted to the contacts referenced in Section 12.2.2. If a subject becomes pregnant during the study, the subject must not receive further treatments (i.e., additional treatments or optional retreatment); however, the subject will remain in the study.

12.6 Adverse Events of Interest (AEI)

Adverse events of interest are serious or non-serious AEs that have special importance for this product or program. The alert terms, as noted below, are events that Merz wishes to monitor more closely throughout the study. Only events with onset on or after date of first administration of study treatment will be monitored.

Any AE of visual disturbance including, but not limited to, any loss of vision, blurry vision, double vision, pain in or around the eye, blind spot, trouble moving eyes, etc. will be reported as an AE of interest. Any events involving a stroke or stroke-like symptoms will also be reported as an AE of interest.

The investigator will be instructed to report any AE of interest within 24 hours to the sponsor using the Adverse Event of Interest Form. The incident will then be reported to the FDA within 10 business days of receipt by the sponsor. These reports will be generated by

the sponsor or designee and will include the depth of injection, injection volume, symptoms observed, time to onset and resolution, and any interventions implemented.

12.7 Definition of Common Treatment Responses (CTRs)

CTRs are common clinical presentations and/or side effects that a subject may experience following treatment. In the current study, subjects will self-report CTRs, as defined *a priori* in the protocol, in a 28-day eDiary after each treatment. The treating investigator will review the eDiary and determine if any entries are beyond what is typically expected following injection. A CTR that is more severe than what is generally expected and/or is not resolving should be evaluated by the investigator as a possible AE or SAE and reported accordingly.

A CTR that has not resolved and is still ongoing upon completion of the eDiary shall be recorded as an AE by the investigator. Subjects can also report any unforeseen/ unanticipated events (i.e., as free text) in the eDiary. Any event recorded by the subject that is not pre-defined shall be recorded as an AE by the investigator except if the additional event is already covered by a pre-defined CTR and does not describe a new event.

12.8 Definition of Device Deficiency

A device deficiency is defined as an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance.

Note: Device deficiencies include malfunctions, use errors, and inadequate labeling.

12.9 Definition of Technical Complaint

A technical complaint, also referred to as a product complaint, is an apparent or suspected deficiency of a product in which the product does not meet its specification (e.g., leaking tube, incorrect consistency, cracked vial). Note: The term “technical complaint” is synonymous with the term “device deficiency”. The term device deficiency is used in this study.

12.9.1 Reporting and Handling of Device Deficiencies

All device deficiencies shall be documented and reported by the investigator throughout the clinical investigation and appropriately managed by the sponsor.

For reporting of device deficiencies:

- For device deficiencies related to a specific subject's treatment, a Device Deficiency eCRF must be completed and submitted by the investigative site, irrespective of the seriousness of the case.
- For device deficiencies related to a specific subject's treatment, a Device Deficiency eCRF must be completed and submitted by the investigative site, irrespective of whether the complaint led to an AE. The investigator will attempt to evaluate if the deficiency or complaint might have led to an AE if suitable action had not been taken, intervention had not been made, or circumstances had been less fortunate.
- If a device deficiency is associated with an SAE, the investigator must also complete and submit an SAE Report Form (Section 12.2.2) in addition to the Device Deficiency eCRF. SAE Report Forms should be sent to Merz Product Safety for processing (Section 12.2.2).
- If a device deficiency is not related to a specific subject (e.g., damaged packaging occurring prior to the subject's visit), the investigator should complete a paper device deficiency form , instead of the eCRF, and send within 24 hours to both their clinical study representative as well as to the Merz Technical Complaint Department for processing using the following email address: complaints2@merz.com.

The investigator should retain the device in question for future inspection and investigation by the sponsor, if necessary. The Merz Technical Complaint Department will decide if the device in question needs to be returned and to whom it should be sent for investigation.

13 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 close.

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

In the event of a pandemic disease outbreak (e.g., COVID-19 public health emergency), if on-site visits are not possible due to site closures, travel limitations, or other considerations (e.g., if site personnel or trial subjects become infected with SARS-CoV-2), the following mitigations should be considered and assessed in an updated SAP:

- Changes to planned and additional analyses due to the public health emergency should be described. Drop-out patterns and sources of bias such as missing values and virtual instead of live assessments (if applicable) should be thoroughly assessed.
- Systematic identification of protocol deviations due to the pandemic should be included.

13.1 Estimation of Sample Size

To provide a sufficient exposure in terms of safety, it is intended to treat n = 165 subjects with BIL. In 165 subjects, an AEs with a true incidence of 1.5% will be observed at least once with a probability of 91.7%. It has been decided to randomize with a ratio of 3:1 (i.e., 55 subjects to RS) and 220 subjects in total.

The planned study is pivotal. Therefore, at least 90% power for effectiveness is anticipated. It is intended to demonstrate non-inferiority with a margin of δ = -0.5 points and a one-sided type I error rate of 2.5%. Further, up to 10% of the randomized subjects might need to be excluded from the per-protocol set (PPS) due to major protocol deviations. CCI

CCI

CCI For this calculation the Statistical Analysis Software (SAS) procedure PROC POWER (SAS 9.4) was used.

Further it is intended to show that the response rate of the BIL group is statistically significantly larger than 50%. Sample-size estimation for this test is performed with a one-sided exact binomial test at an error level of 2.5%. The binomial test is applied to the

treatment Group BIL only. CCI [redacted] CCI [redacted]

For this calculation the NQuery version 8.5 was used.

A hierarchical-testing procedure will be applied for co-primary and primary effectiveness endpoint to keep the overall one-sided type I error rate of $\alpha = 0.025$, and no adjustment for multiplicity is necessary.

In summary, the sample size of n=220 randomized subject with a randomization ratio of 3:1 leading to at least 198 in the PPS analysis, provides sound balance between power for effectiveness and ability for detection level of safety risks.

In general, discontinued subjects will not be replaced. In case of more than 10% missing primary effectiveness data due to e.g., a public health emergency (e.g., COVID-19) or other incident leading to missing values completely at random, additional subjects can be randomized (for details see Section 13.5.1).

13.2 Randomization

The investigation is planned as a multicenter investigation. Subjects will be assigned to treatment groups according to a balanced randomization. Balanced randomization in blocks of appropriate size and block-wise distribution of the IMD/comparator to investigational sites will ensure an approximately equal number of enrolled subjects in every treatment group per investigational site. The block size will not be disclosed to the blinded evaluators until data base close.

For this study, randomization will be block-stratified by investigational site. Subjects will be randomized centrally via interactive EDC system at a 3:1 ratio to one of two groups:

- Belotero Intense Lidocaine (n = 165) or
- Restylane Silk (n = 55).

13.3 Populations for Analysis

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

– **Safety Evaluation Set (SES)**

  The SES is the subset of all subjects who were exposed to the IMD or Comparator Device at least once. Subjects in the SES analyses will be analyzed as treated.

– **Intent to treat (ITT)**

The ITT is the set of all randomized subjects. Subjects in the ITT analyses will be analyzed as randomized.

– **Per protocol set (PPS)**

The PPS is the subset of subjects in the ITT without major deviations. Following protocol deviation will be classified as major:

- No exposure
- Deviation from randomized treatment
- Missing primary effectiveness endpoint
- Unblinding of blinded evaluator before or at Visit V3
- Visit window deviation at Visit V3 of more than 14 days
- Treatment with Hyaluronidase between Screening and Visit V3
- Cosmetic plastic surgery in the lower third part of the face or oral surgery procedures between Screening and Visit V3
- Facial treatments with permanent and/or semi-permanent dermal fillers in the lower face between Screening and Visit V3

The PPS will be the primary population used for the effectiveness analyses because this is a non-inferiority study.

13.4 Analysis of Study Data

Effectiveness, safety, and other endpoints are provided in Sections 7.2.1 to 7.2.3.

13.4.1 Effectiveness Analyses

The primary effectiveness analysis and the analyses of the co-primary and secondary effectiveness endpoints will be based primarily on the PPS and additionally, for sensitivity purposes, on the ITT. All the remaining effectiveness endpoints will be analyzed based on the PPS.

Continuous endpoints (values and changes from baseline) will be summarized by n, the number of missing values, mean, standard deviation, median, quartiles, minimum, and maximum. For qualitative endpoints, absolute and percent frequencies (N, %) will be displayed. Confidence limits and p-values will be given, where appropriate.

13.4.1.1 Primary Effectiveness Endpoint

The primary and the co-primary effectiveness endpoint are defined in Section 7.2.1.1. If only one lip was treated, then only this lip will be used for calculation of the primary and co-primary effectiveness endpoint.

Two hypothesis tests will be performed (see Table 2). These tests will be evaluated in a sequential order on the PPS. To control for multiplicity, a hierarchical-testing procedure will be performed at a one-sided α level of 2.5%.

The first hypothesis is to demonstrate that the response rate of the BIL group is statistically significantly larger than 50%. This 50% threshold is commonly used in aesthetic medical device studies to measure a meaningful response. This hypothesis will be tested for the co-primary effectiveness endpoint of the BIL group using the lower limit of the exact 95% CIs (two-sided), based on binomial distribution. The lower limit of the 95% Wilson CI must exceed the margin of 50% responder rate to reject Hypothesis 1 (H_{10}).

With the second hypothesis, it is intended to show non-inferiority of BIL compared to an approved HA dermal filler for the subject's mean change from baseline to Visit V3 of treated lips on the MLFAS as assessed by the blinded evaluator at a non-inferiority margin of δ = -0.5 points. This margin is justified because it was used in comparator pivotal studies (see Juvéderm® Volbella [SSED; P110033/S018] and Restylane® Kysse [SSED, P140029/S021]). Non-inferiority is to be demonstrated in this study at type I error one-sided α level of 2.5%.

A baseline adjusted analysis of covariance (ANCOVA) with fixed effects treatment, site, and Fitzpatrick skin type groups (I – III & IV – VI) will be used to derive a two-sided 95% confidence interval (CI) for the LS means difference difference of BIL – control (RS) on the PPS. Subject's mean MLFAS at baseline of treated lips as assessed by a blinded evaluator will be covariate in the ANCOVA model. The model is specified as follows

$$y_i = \sum_{j=1}^{4} x_{ij}\,\beta_j + \varepsilon_i\,, i = 1, \ldots., n$$

where y_i is the observation of the dependent variable (Section 7.2.1.1) in subject *i*, x_{11}, , …, x_{14}, x_{21}, ….x_{24}, …., x_{n1}, …, x_{n4} are regression type variables modeling baseline covariate and dummy variables modeling treatment, site and Fitzpatrick skin type class, respectively, β_1, …, β_4 are unknown fixed-effects parameters to be estimated and ε_1, …, ε_n are unknown independent and identically distributed normal (Gaussian) error variables with mean 0 and variance σ^2.LS means per treatment group will be estimated from this ANCOVA model. Hypothesis 2 (H_{20}) will be rejected and non-inferiority will be concluded if the lower bound of the two-sided 95% CI lies above -0.5 points.

Missing values due to reasons likely related to treatment outcome

- adverse events related to treatment
- lack of effectiveness

will be imputed using worst case imputation: Post-baseline values of the MLFAS will be imputed with subject's baseline MLFAS value of the corresponding lip, i.e. change from baseline on the MLFAS will be 0 for these subjects with missing values due to adverse events related to treatment or lack of effectiveness. Within the time frame of eight weeks until Visit V3 it is not expected that the lips decrease lip volume compared to baseline through the aging process of the lips. That is why the baseline value can be seen as the worst-case imputation for the primary effectiveness endpoint.

Data missing due to other reasons (if any) will be imputed by multiple imputations (MI) using the SAS procedure PROC MI with 1000 iterations and seed 930041001. The variables (VAR) statement will consider the variables treatment group, site, Fitzpatrick skin type group (I – III & IV – VI), sex, touch-up at Visit V2-a, age at screening as well as subject's mean MLFAS values of treated lips at screening; Visit V2-a (Week 4) and Visit V3 (Week 8) of treated lips. Due to the lack of information about the missing data pattern in MLFAS values over time, the fully conditional specification (FCS) option will be chosen for the model. Replaced will be all missing MLFAS values for the post-baseline Visits V2-a and V3.

The multiple ANCOVA results will be combined with SAS PROC MIANALYZE. The robustness of the results will be assessed by the following sensitivity analyses:

– Analogous analysis in the ITT in case amount of missing values in ITT exceeds 10% in any randomization group

– Observed cases in ITT

– Observed cases for the PPS subset.

Table 2: Confirmatory Analysis of Primary and Co-primary Effectiveness Endpoint

Primary and co-primary analysis						
1:	H_{10}:	$\Pi_{BIL} \leq 50\%$	vs.	H_{11}:	$\Pi_{BIL} > 50\%$	within Group BIL
Rejection of H_{10}			yes ↓	no →		end
2:	H_{20}:	$\mu_{BIL} - \mu_{control} \leq -0.5$	vs.	H_{21}:	$\mu_{BIL} - \mu_{control} > -0.5$	Group BIL compared to control group
Rejection of H_{20}			yes ↓	no →		end
Effectiveness of BIL confirmed						

Π_{BIL}: BIL group response rate; μ_{BIL}: BIL group average mean change from baseline; $\mu_{control}$: Control group mean change from baseline.

Further metric descriptive statistics for absolute values and changes from baseline will be provided per treatment group. Moreover, descriptive statistics will also be provided for subgroups by sex, race, ethnicity, Fitzpatrick Skin Type (I-III vs. IV-VI), and age group.

Responder rates of BIL and control group at Visit V3 will be summarized as frequency tables with absolute and percent frequencies (n, %), exact 95% Cis based on binomial distribution (as described above) and by a two-sided 95% Newcombe CI based on Wilson scores for the risk difference BIL – RS (control). If only one lip was treated, then only the MLFAS values for this lip will be used for calculation of responder rates.

Subjects with missing MLFAS values of treated lips at Screening or V3 will be excluded as major PDs from PPS set. Therefore, the main analysis of the co-primary effectiveness endpoint is based on the observed cases for the PPS. The robustness of the results of the co-primary effectiveness endpoint will be assessed by a sensitivity analysis on ITT in which subjects with missing values will be evaluated as non-responders.

Co-primary endpoints will be descriptively summarized by investigational site.

13.4.1.2 Secondary Effectiveness Endpoints

Secondary effectiveness endpoints are defined in Section 7.2.1.2. Secondary effectiveness endpoints will be analyzed primarily on the PPS using observed cases and additionally, for sensitivity purposes, on the ITT using observed cases.

iGAIS and sGAIS at Visit V3 will be displayed using descriptive summary statistics for continuous endpoints and as frequency tables with absolute and percent frequencies (N, %).

Rasch-transformed scores ranging from 0 to 100 of FACE-Q Satisfaction with lips at Visit V3 will be summarized using descriptive statistics for absolute value and change from baseline. Higher scores reflect a better outcome. If missing data is less than 50% of the scale's items, the mean of the completed items will be inserted.

CCI



CCI



13.4.2 Safety Analyses

All safety analyses will be performed on the SES in total and by treatment group. AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version in effect at the time the database is closed. Only TEAEs will be analyzed, which are defined as AEs with onset or worsening on or after date of first administration of BIL or comparator. In this regard, an AE with onset prior to treatment that worsens at or after first administration of study treatment must be documented as a new TEAE with onset at the time of worsening.

13.4.2.1 Secondary Safety Endpoint

The secondary safety endpoint is defined in Section 7.2.2.1. The main analysis for the secondary safety endpoint will be the overall TEAE rate of related serious TEAEs and of related TEAEs with delayed onset. Furthermore, incidences will be calculated for subjects with related serious TEAEs, number of related serious TEAEs, subjects with treatment-related late onset TEAEs, number of treatment-related late onset TEAEs on the system organ class level, and on the preferred term level.

CCI



CCI



Device deficiencies will be listed only.

13.4.3 Other Subject Data

Subject dispositions, demographic data and baseline characteristics, data of injection technique, depths of injections, number of injection points, and volume will be presented using standard descriptive statistics; no homogeneity tests will be performed. Demographic data will be summarized for all randomized subjects, the SES, the ITT, and the PPS. Data of injection technique, depths of injections, number of injection points, and volume will be summarized descriptively only for the SES.

Frequencies of previous and concomitant treatments will be given based on different Anatomical Therapeutic Chemical (ATC) Classification system of the World Health Organization code levels for the SES. Indications for concomitant therapies will not be coded and will only be listed. Medical history and concomitant diseases will be described based on MedDRA system organ class and preferred term levels for the SES.

13.5 Special Statistical/ Analytical Issues

13.5.1 Subject Discontinuation and Missing Data

Missing values due to reasons likely related to treatment outcome (adverse events related to treatment or lack of effectiveness) will be imputed using worst case imputation. Missing values in the primary effectiveness analysis due to other reasons will be imputed by multiple imputation. Further details and sensitivity analyses are described in Section 13.4.1.1.

In general, if not otherwise stated, secondary and other effectiveness endpoints will be analyzed using observed cases; i.e., without replacement of missing value. Only if missing data of FACE-Q scales is less than 50% of the scale's items, the mean of the completed items will be inserted.

Missing data in the eDiary will affect the analysis of the duration of the CTRs. Therefore, the duration of CTRs will be computed using the following algorithm:

- Each subject is expected to have eDiary entries from Visit V1-a/Day 1 (day of the initial treatment) up to and including Day 28 or the day of their discontinuation, whichever comes first. Each subject with a touch-up treatment at V2-a is expected to have eDiary entries from Visit V2-a (day of the touch-up) up to and including 28 days following touch-up treatment or the day of their discontinuation, whichever comes first. Each subject with a retreatment at V7-a expected to have eDiary entries from Visit V7-a (day of there-treatment) up to and including 28 days following retreatment or the day of their discontinuation, whichever comes first. If any subject does not have an eDiary entry for any of the required days, then for the purposes of CTR analysis it will be assumed that on the missing days they had all those CTRs (if any) that they had on the day before or on the day after the missing day, with the same severity.
- For any CTR with an uninterrupted single episode event, the duration will be computed as the number of days from the beginning of event to last date of event (i.e., last day of episode − first day of episode + 1).
- For any CTR with multiple episodes, the CTR will be regarded as a continuous event if consecutive episodes are not more than one (1) day apart. Duration will be computed as the number of days from the beginning of first episode to last date of last episode that fulfill the condition described above (i.e., are not more than 1 day apart).
- For any CTR with multiple episodes, the CTR will not be regarded as a continuous event if consecutive episodes are at least two (2) days apart. In such instances, the duration of the episode with the longest duration will be used for duration of that particular CTR.
- For any CTR with multiple continuous and non-continuous events, the algorithm as aforementioned will be adopted, in which case the maximum of all CTR durations will be selected as the CTR duration to be used for summary purposes.

In general, discontinued subjects will not be replaced. In case of more than 10% missing primary effectiveness data due to a public health emergency (e.g., COVID-19), additional subjects can be randomized. General circumstances potentially related to a public health emergency which are independent of study treatment will result in missing values at completely random (e.g., site closed for study subjects, site decided to perform virtual visit due to unfavorable epidemiological situation, subject refused to come to site due to unfavorable epidemiological situation, curfew, or restricted travel). Only for these missing values completely at random due to circumstances of a public health emergency, additional subjects can be randomized. For missing values which are potentially also related to study treatment, or which are not related to a public health emergency, no additional subjects will be randomized. With this approach of randomization of additional subjects only in case of missing values completely at random, the type one error is not affected. The decision about recruitment of additional subjects will be made by Merz study team before database close.

13.5.2 Other Planned or Subgroup Analyses

For co-primary effectiveness endpoint and for incidences of TEAEs and CTRs subgroups by sex, race, ethnicity, FST (I-III vs. IV-VI), and age group will be provided.

Pooling of investigational sites will be performed according to the algorithm described below. If convergence problems are observed in the ANCOVA model described above, the following steps will be performed:

1. The site with the lowest number of randomized subjects will be pooled with the site with second lowest number of subjects. If two or more sites with the same number of subjects are suited for pooling, the site with the lowest number of subjects in the control group will be pooled. If two or more sites with the same number of subjects and same number of subjects in the control group are suited for pooling, then the site to be pooled will be chosen randomly among all suited sites.

2. ANCOVA model will be re-run with pooled site as factor.

3. If convergence problems are resolved, no further pooling of investigative sites will be performed. Otherwise, steps 1) and 2) above will be repeated until convergence problems resolve.

14 ADMINISTRATIVE PROCEDURES

14.1 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:

- Data authenticity, accuracy, and completeness;
- Protection of subject rights and safety; and
- 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 5.3 and Section 5.4). Further details of monitoring activities will be set forth in the monitoring manual.

In the event of a pandemic disease outbreak (e.g., COVID-19 public health emergency), and by this, if on-site visits are not possible due to site closures, travel limitations, or other considerations (e.g., if site personnel or trial subjects become infected with SARS-CoV-2), the following mitigations should be considered and assessed in an updated monitoring plan:

- On-site monitoring visits might be cancelled and/or the period between monitoring visits extended. When planned on-site monitoring visits are not possible, the reason should be clearly documented and made available for review during audits and/or inspections.
- Phone and/or video visits will be implemented when feasible, considering site closures, reduced staff, and any other circumstances.
- Remote monitoring or central monitoring could substitute on-site monitoring, when technically feasible.
- Protocol deviations will be tracked and documented if deviations occurred due to the public health emergency.
- Current local regulations, including data privacy regulations, will be considered when accessing source data remotely.

14.2 Data Quality Assurance

Inspections by regulatory authority representatives and IRBs are possible at any time, even after the EOS. The investigator is to notify the sponsor immediately of any such inspection. The investigator and institution will permit study-related monitoring, audits, reviews by

the IRB and/or regulatory authorities and will allow direct access to source data and source documents for such monitoring, audits, and reviews.

14.2.1 Standardization Procedures

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

This study will be monitored regularly by a qualified monitor from the CRO according to GCP guidelines and the respective standard operating procedures (SOPs; see Section 14.1).

14.2.2 Data Management

Data required according to this protocol are to be recorded in the web-based eCRFs provided by a CRO. All users who will enter data into the eCRF must successfully complete training before system access is granted. Participant training will be documented. Access to the eCRF will be password controlled and will conform with 21 CFR Part 11.

Data-plausibility checks will be performed according to a data validation plan. Inconsistencies in the data will be queried to the investigators via the EDC system; answers to queries or changes to the data will also be documented in this system directly by an authorized member of the investigator's study personnel. The audit trail in the EDC system will document all changes. Edit checks generate automatic queries during data entry when a field is not populated, according to specifications defined in the data validation plan. Manual queries to be answered by study personnel can be raised during source data verification and/or during medical, safety, and/or data management review. If any data changes are required after database close, these changes will be documented according to the respective SOP.

Photographs will be archived by the central photography vendor in a system separate from the database (Section 14.3). Web-based eDiary data and photo ratings by IPRs will be transferred electronically to the data management CRO. Checks will be performed to ensure plausibility and completeness of these data. The data management activities and photographs processing will be delegated to the CROs listed in CCI [redacted].

Further details of the data management process will be described in the data management plan.

14.2.3 Data Review and Clarification Procedures

By electronically signing the eCRF with an automated time stamp, the investigator will confirm that all investigations have been completed and conducted in compliance with the study protocol and that reliable and complete data have been entered into the eCRF.

All data required by this study protocol are to be recorded in the eCRF as soon as possible. However, direct entries are not allowed; data must be transcribed from the source documentation (e.g., subject file, scales) to the eCRF.

All data required by this study protocol, except photography ratings and web-based eDiary entries, are to be entered into a sponsor-validated database of eCRFs.

If corrections are necessary, an authorized member of the investigator's site staff will enter the correct data into the web-based eCRF. The audit trail in the EDC system documents all changes.

The data management CRO's and sponsor's data management function will be responsible for data processing, in accordance with the CRO's and sponsor's data management procedures. Database close will occur only after quality assurance procedures have been completed.

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

In the event of a pandemic disease outbreak (e.g., COVID-19 public health emergency), and by this, if data entry and cleaning is limited or not possible due to site closures, travel limitations, or other considerations (e.g., if site personnel become infected with SARS-CoV-2), the following mitigations should be considered for data cleaning processes:

- Data entry and response to data clarifications will proceed depending on availability of investigational site personnel and investigators.
- Depending on the content of the response to data clarifications, the need for source data review will be assessed by the sponsor.
- If applicable, a risk-based assessment for closing long opened data clarifications will be applied considering their impact on trial conclusion and data validity.
- The need for data clarifications and/or eCRF pages to be signed by staff that is not yet on the delegation log will be assessed. The delegation log is to be updated, if applicable.

14.2.4 Auditing

To ensure compliance with applicable standards and regulations, the sponsor, 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.

14.3 Record Retention

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 documentation (e.g., subject files);
- Subject identification code list (i.e., provided by template to the investigator, along with the Investigator Site File, at the beginning of the investigation), which identifies the subject by number, name, and date of birth;
- A copy of the study protocol and any amendments;
- A CD/DVD/USB flash drive with eCRF data and any associated subject related source data (or, where applicable, authorized copies of source data);
- Signed ICFs;
- Copies of site investigators' and co-workers' curricula vitae;
- Copies of all direct correspondence with the IRB and with the regulatory authority(ies);
- Copies of all relevant correspondence between the investigator and the monitor, and between the investigator and the sponsor;
- Copies of any photographs;
- Copies of IMD receipt forms and device inventory forms; and
- Copies of safety information reported during the investigation and submitted by the sponsor.

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 investigator or the institution must inform the sponsor in due time if the investigator leaves the institution during the retention period. This rule also applies when the institution closes within the retention period.

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.

14.4 Publication Policy

The results of this study and any discoveries related to this study, regardless of whether they have technical or medical character, are the property of the sponsor.

The CSP, 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 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 SOP.

The sponsor will ensure that a description of this clinical study is registered, and study results are disclosed on http://www.ClinicalTrials.gov, as required by US law. Study registration may include a list of investigational sites, as applicable.

14.5 Financial Disclosure

The US FDA Financial Disclosure by Clinical Investigators (21 CFR 54) regulations require sponsors to obtain certain financial information from investigators participating in covered clinical studies. By participating in the study, the investigator agrees to provide the required financial information and to promptly update the sponsor with any relevant

changes to this financial information throughout the course of the study and for up to one year after its completion if necessary.

14.6 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 US FDA 21 CFR Part 812 Subpart E—Responsibilities of Investigator and ISO 14155:2020—Good Clinical Practices.

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 IRB approval, 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 or assigned CRO, 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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16 APPENDICES

16.1 Schedule of Events

Activity	Screening	Treatment Phase							Maintenance Phase				Retreatment Phase				
		Initial Treatment			Touch-up (TU)								Re-Tx for BIL[13]				EOS / ET for BIL
													EOS/ET for RS				
		V1-a	V1-b	V1-c	V2–a[7]	V2-b[7]	V2-c[7]	V2-d[7]	V3[9]	V4[9]	V5[9]	V6[9]	V7-a[8,9,12]	V7-b[8]	V7-c[8]	V7-d[8]	V8[10]
	Screening (Day -10 to Day -3)	Baseline (Day 1)	72 hr post-Tx call	+2 wk post-Tx safety FUP	4 wk post-Tx (opt. TU)	72 hr post-Tx call (only if TU)	+2 wk safety FUP (only if TU)	+4 wk safety FUP (only if TU)	8 wk post last injection	16 wk post last injection	24 wk post last injection	36 wk post last injection	48 wk post last injection (opt. Re-Tx for BIL)	72 hr post-Tx call (only if Re-Tx)	+2 wk safety FUP (only if Re-Tx)	+4 wk safety FUP (only if Re-Tx)	60 wk post last injection or 12 wk post Re-Tx
			+1d	±3 d	+5 d	+1d	±3 d	+7 d	±7 d	±14 d	±14 d	±14 d	±14 d	+1d	±3 d	+7 d	±14 d
Informed consent	X																
Inclusion/Exclusion	X	X															
UPT[1]	X	X			X[11]								T[11], C				T
Demographics/FST[2]	X																
Height and weight[3]	X								X				T, C				T
Medical history	X																
Previous and Concomitant Rx/Px	X	X	X	X	X	X	X	X	X	X	X	X	T, C	T	T	T	T
Lip Photographs	X	X[14]			X				X		X		T, C				T
MLFAS[5]	X				X				X	X	X	X	T, C				T

Activity	Screening	Treatment Phase							Maintenance Phase				Retreatment Phase				
		Initial Treatment			Touch-up (TU)								Re-Tx for BIL[13]				EOS / ET for BIL
													EOS/ET for RS				
		V1-a	V1-b	V1-c	V2–a[7]	V2-b[7]	V2-c[7]	V2-d[7]	V3[9]	V4[9]	V5[9]	V6[9]	V7-a[8,9,12]	V7-b[8]	V7-c[8]	V7-d[8]	V8[10]
	Screening (Day -10 to Day -3)	Baseline (Day 1)	72 hr post-Tx call	+2 wk post-Tx safety FUP	4 wk post-Tx (opt. TU)	72 hr post-Tx call (only if TU)	+2 wk safety FUP (only if TU)	+4 wk safety FUP (only if TU)	8 wk post last injection	16 wk post last injection	24 wk post last injection	36 wk post last injection	48 wk post last injection (opt. Re-Tx for BIL)	72 hr post-Tx call (only if Re-Tx)	+2 wk safety FUP (only if Re-Tx)	+4 wk safety FUP (only if Re-Tx)	60 wk post last injection or 12 wk post Re-Tx
			+1d	±3 d	+5 d	+1d	±3 d	+7 d	±7 d	±14 d	±14 d	±14 d	±14 d	+1d	±3 d	+7 d	±14 d
iGAIS									X	X	X	X	T, C				T
sGAIS									X	X	X	X	T, C				T
FACE-Q – Satisfaction with Lips	X								X	X	X	X	T, C				T
FACE-Q – Psychological Function	X								X	X	X	X	T, C				T
FACE-Q – Satisfaction of Outcome										X	X	X	T, C				T
Lip Function and Sensation Questionnaire				X	X		X	X	X	X	X	X	T, C		T	T	T
Active lip function assessment	X			X	X		X	X	X	X	X	X	T, C		T	T	T
Active lip sensation assessment	X			X	X		X	X	X	X	X	X	T, C		T	T	T

Activity	Screening	Treatment Phase							Maintenance Phase				Retreatment Phase				
		Initial Treatment			Touch-up (TU)								Re-Tx for BIL[13]				EOS / ET for BIL
													EOS/ET for RS				
		V1-a	V1-b	V1-c	V2–a[7]	V2-b[7]	V2-c[7]	V2-d[7]	V3[9]	V4[9]	V5[9]	V6[9]	V7-a[8,9,12]	V7-b[8]	V7-c[8]	V7-d[8]	V8[10]
	Screening (Day -10 to Day -3)	Baseline (Day 1)	72 hr post-Tx call	+2 wk post-Tx safety FUP	4 wk post-Tx (opt. TU)	72 hr post-Tx call (only if TU)	+2 wk safety FUP (only if TU)	+4 wk safety FUP (only if TU)	8 wk post last injection	16 wk post last injection	24 wk post last injection	36 wk post last injection	48 wk post last injection (opt. Re-Tx for BIL)	72 hr post-Tx call (only if Re-Tx)	+2 wk safety FUP (only if Re-Tx)	+4 wk safety FUP (only if Re-Tx)	60 wk post last injection or 12 wk post Re-Tx
			+1d	±3 d	+5 d	+1d	±3 d	+7 d	±7 d	±14 d	±14 d	±14 d	±14 d	+1d	±3 d	+7 d	±14 d
Lip Symmetry and Movement Questionnaire	X			X	X		X	X	X	X	X	X	T, C		T	T	T
Lip Hydration & Appearance Questionnaire	X				X				X	X	X	X	T, C				T
3 Vision Function Assessments	X	X[13]		X	X[13]		X	X	X	X			T[13], C		T	T	T
Neurological Exam		X			X[11]								T[11]				
Randomization[4]		X															
Treatment		X											T[11]				
Touch-up					X[11]												
Likelihood of Re-Tx Survey																	T
Post-Tx phone call			X[6]			X[6]								T[6]			

Activity	Screening	Treatment Phase							Maintenance Phase				Retreatment Phase				
		Initial Treatment			Touch-up (TU)								Re-Tx for BIL[13]				EOS / ET for BIL
													EOS/ET for RS				
	Screening (Day -10 to Day -3)	V1-a	V1-b	V1-c	V2–a[7]	V2-b[7]	V2-c[7]	V2-d[7]	V3[9]	V4[9]	V5[9]	V6[9]	V7-a[8,9,12]	V7-b[8]	V7-c[8]	V7-d[8]	V8[10]
		Baseline (Day 1)	72 hr post-Tx call	+2 wk post-Tx safety FUP	4 wk post-Tx (opt. TU)	72 hr post-Tx call (only if TU)	+2 wk safety FUP (only if TU)	+4 wk safety FUP (only if TU)	8 wk post last injection	16 wk post last injection	24 wk post last injection	36 wk post last injection	48 wk post last injection (opt. Re-Tx for BIL)	72 hr post-Tx call (only if Re-Tx)	+2 wk safety FUP (only if Re-Tx)	+4 wk safety FUP (only if Re-Tx)	60 wk post last injection or 12 wk post Re-Tx
			+1d	±3 d	+5 d	+1d	±3 d	+7 d	±7 d	±14 d	±14 d	±14 d	±14 d	+1d	±3 d	+7 d	±14 d
Safety/AE assessment	X	X	X	X	X	X	X	X	X	X	X	X	T, C	T	T	T	T
Subject eDiary completion		X	X	X	X[11]	X	X[11]	X[11]					T[11]	T	T[11]	T[11]	
Subject eDiary reviewed			X	X	X	X	X[11]	X[11]						T	T[11]	T[11]	

[T=treatment group (BIL); C= control comparator group (RS)]

Key: Tx = Treatment, FUP = follow -up; Re-Tx = Retreatment; EOS = End of Study; ET = Early termination; UPT = urine pregnancy test; Rx = medications; Px = procedures; MCLAS = Merz Lip Fullness Assessment Scale; wk = week; iGAIS = Treating Investigator Global Aesthetic Improvement Scale (GAIS) assessment; sGAIS = Subject GAIS assessment; BIL=Belotero Intense Lidocaine; RS= Restylane Silk

[1] Only if female subject is of childbearing potential; negative result is required prior to randomization and initial treatment and any subsequent treatment (touch-up and/or retreatment).

[2] See CCI for definition of Fitzpatrick skin types (FST).

[3] Height will be collected at the screening visit only.

[4] Randomization includes randomization to treatment or control.

[5] Every effort must be made to ensure that the same qualified blinded evaluator performs the MLFAS assessment at all visits. At screening the blinded evaluator and the treating investigator must complete the MLFAS independently to determine eligibility. In addition, they must have the same MLFAS ratings at screening. The screening MLFAS will be considered the pre-treatment (baseline) score. At all other visits, only the blinded evaluator should complete the MLFAS assessment.

[6] A post-treatment telephone call will be made 72 hours (+ 1 day**)** following each treatment (initial, touch-up, retreatment). If touch-up and/or retreatment are not done, these telephone calls are not needed.

[7] All subjects will present for Visit V2-a and may receive a touch-up, as applicable; if no touch-up is performed, Visits V2-b, V2-c and V2-d are not needed.

[8] Treatment group subjects will present for Visit V7-a and may receive retreatment, as applicable; if no retreatment is performed, Visits V7-b, V7-c and V7-d are not needed.

[9] Visits V3-V7, during the maintenance phase, are to be scheduled based off the last injection, which is considered to be either the initial injection or the touch-up injection, if applicable. For example, if subject did not have a touch-up, Visit V3 is 8 weeks after Visit V1-a. If subject did receive a touch-up, Visit V3 is 8 weeks after Visit V2-a.

[10] Visit 8 is 12 weeks after Visit V7-a if subject had a retreatment; if no retreatment this visit is 60 weeks post initial injection or touch-up injection (if subject received a touch-up).

[11] These assessments are completed only if subject is receiving a touch-up injection and/or retreatment.

[12] Subjects randomized to the comparator group will not be retreated; Visit V7-a (48 weeks post last injection) is the EOS visit for all comparator subjects.

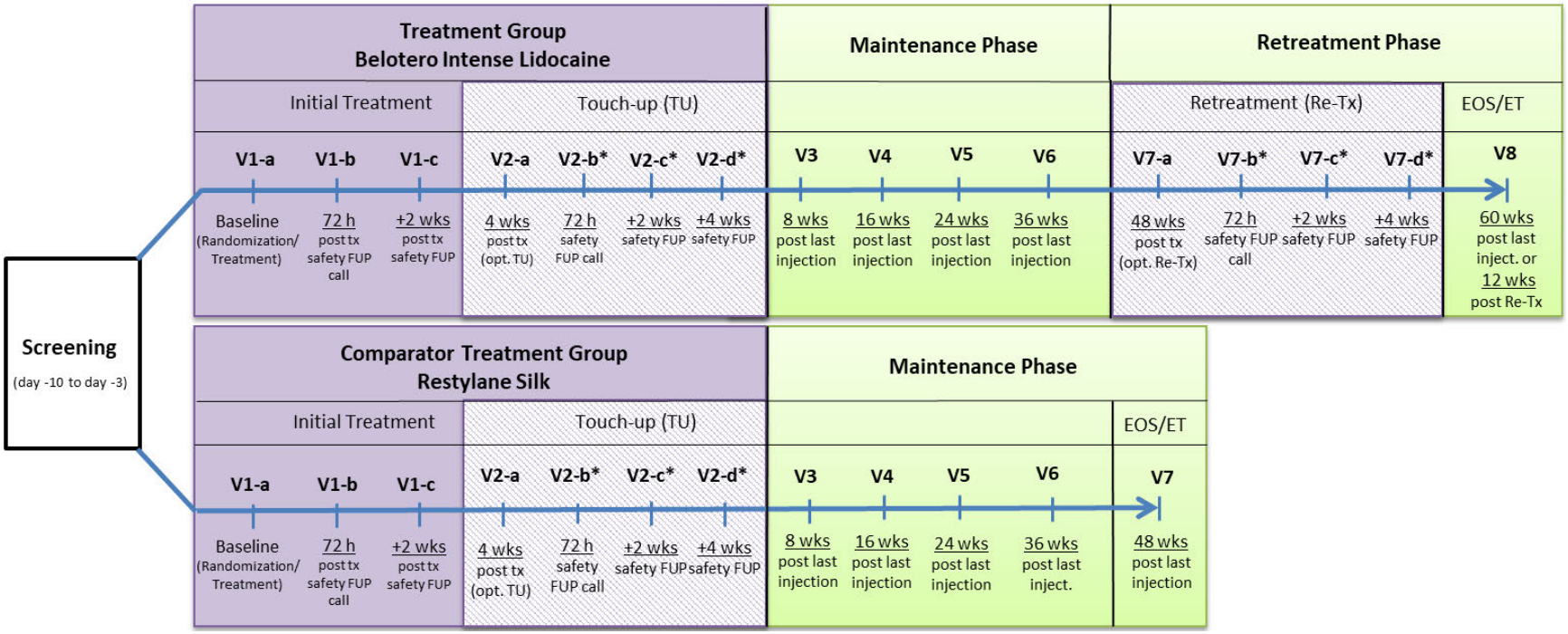
[13] Pre- and post-injection vision function assessments will be taken at these visits (e.g., initial, touch-up, retreatment).

[14] Standardized lip photographs may need to be retaken at the baseline visit pre-treatment if issues were detected with the screening photographs and a reshoot is deemed necessary by the central photography vendor prior to treatment.

Note: Unscheduled visit for safety concerns should include assessment of AEs; concomitant medications/ procedures, review of eDiary, vision function assessments, lip function, lip symmetry and lip photographs, if applicable.

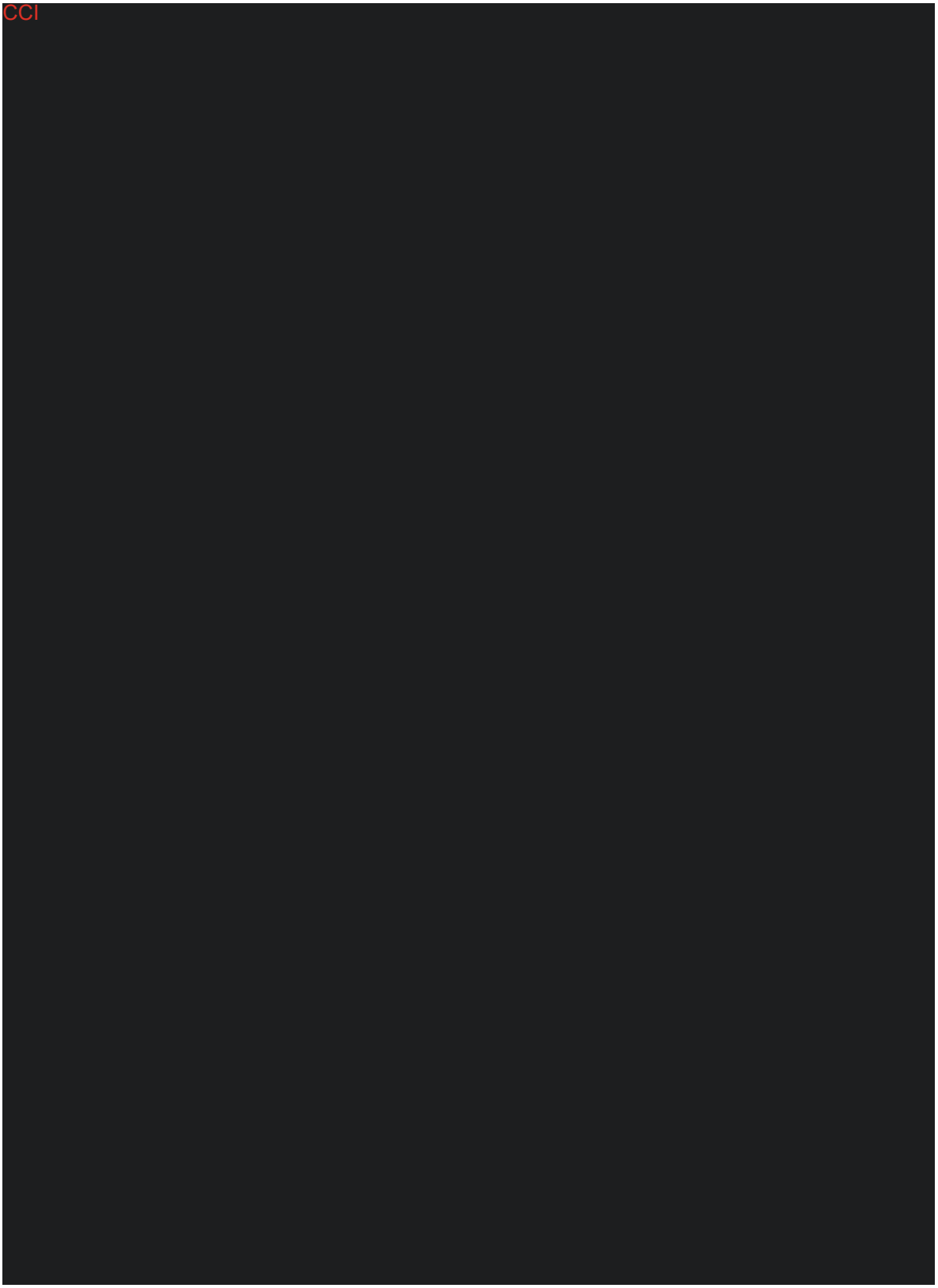
Note: All effectiveness assessments and lip photographs must be completed prior to administering any form of treatment (e.g., initial, touch-up, retreatment).

16.2 Investigation Flow Chart

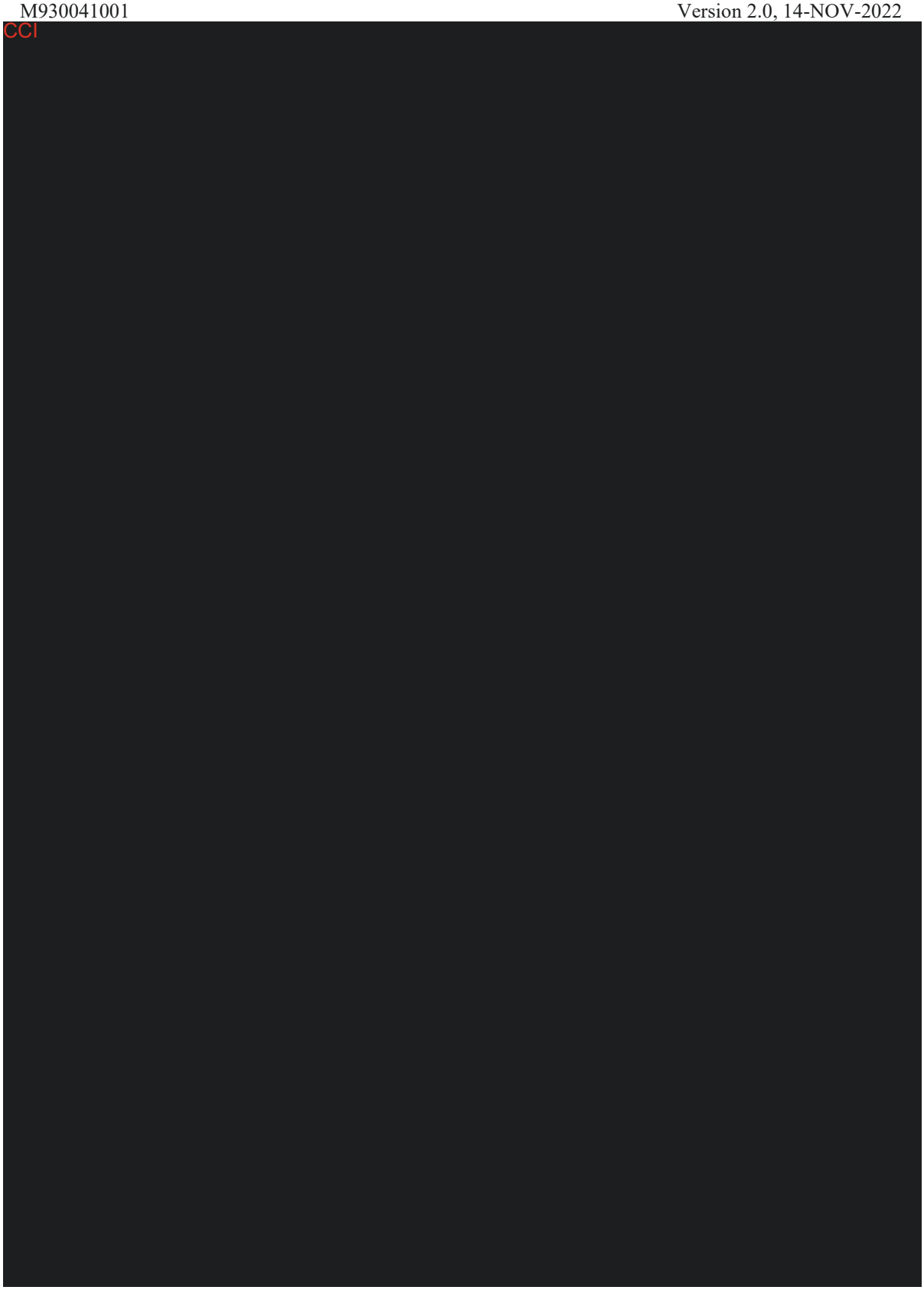


* = Visits only applicable if a touch-up or a re-treatment has been performed; wks = weeks, EOS/ET = end of study / early termination

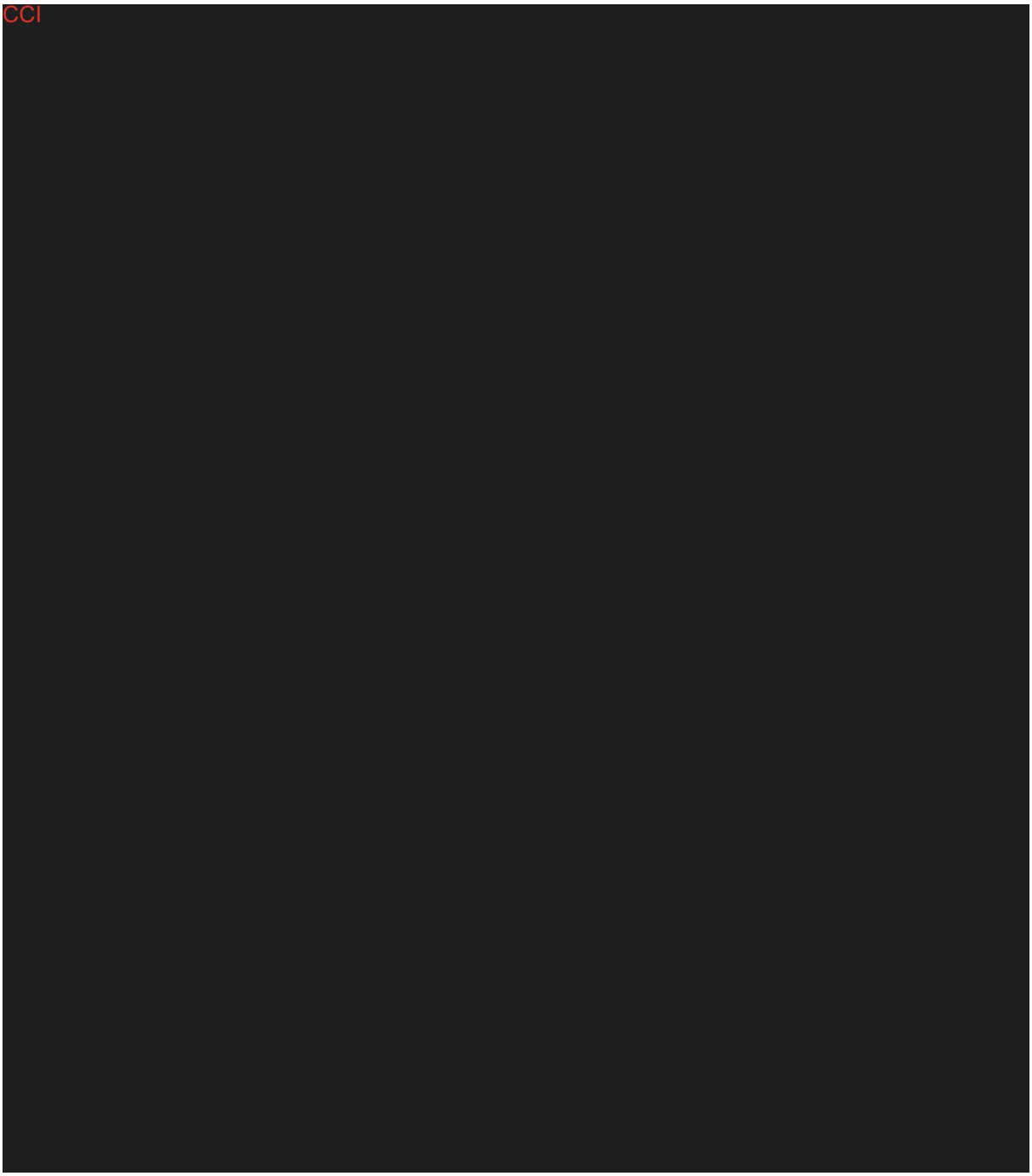
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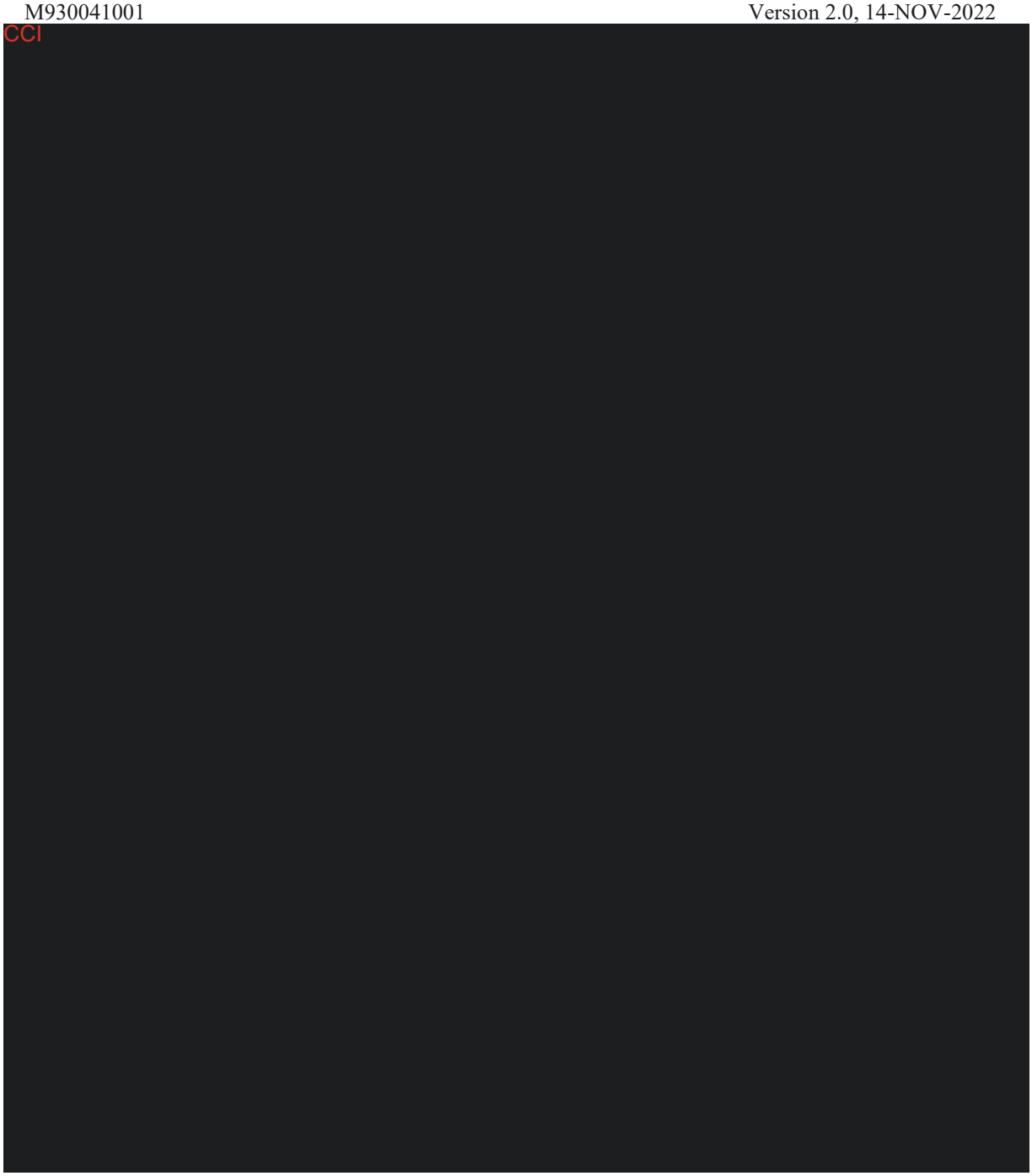
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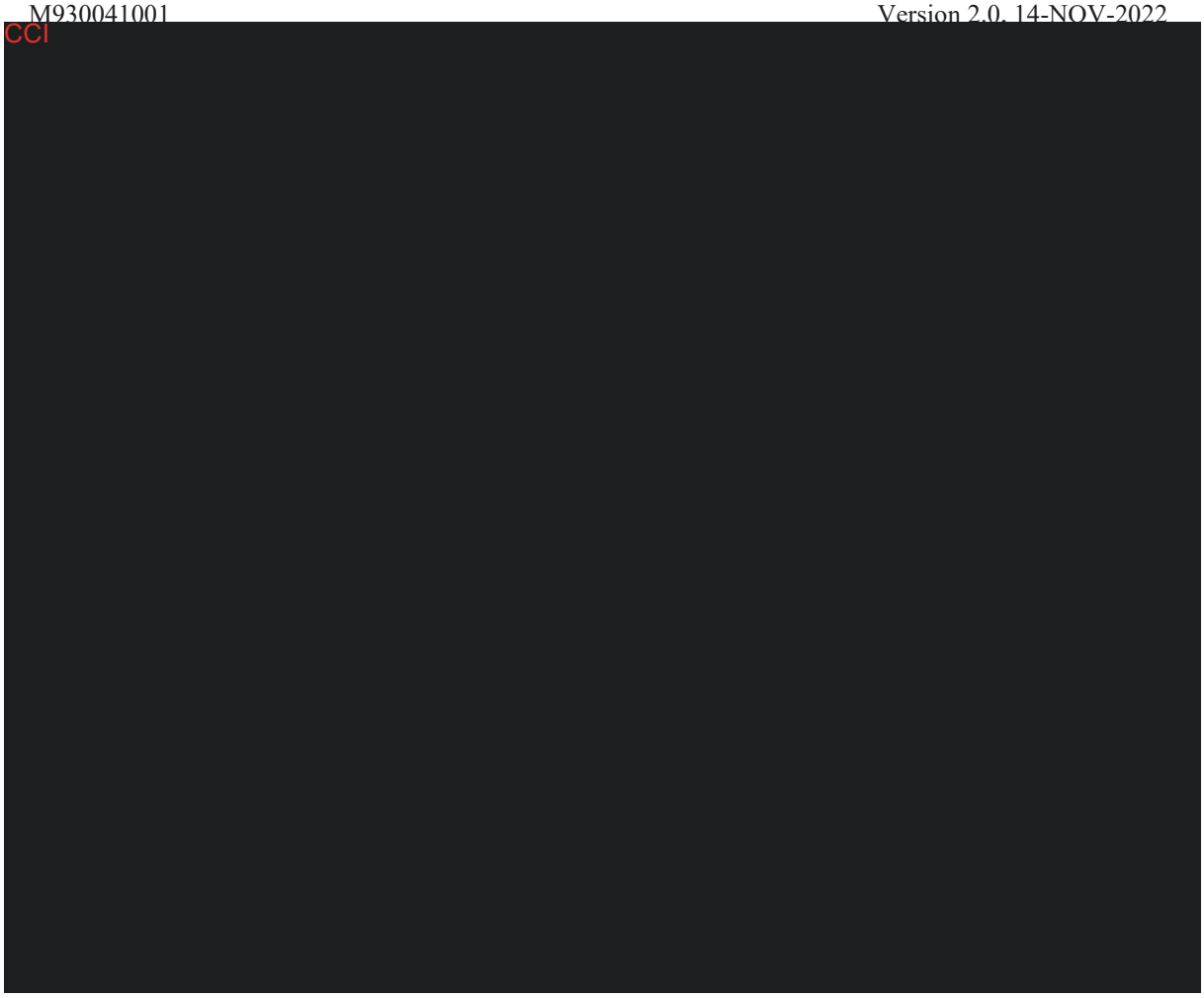
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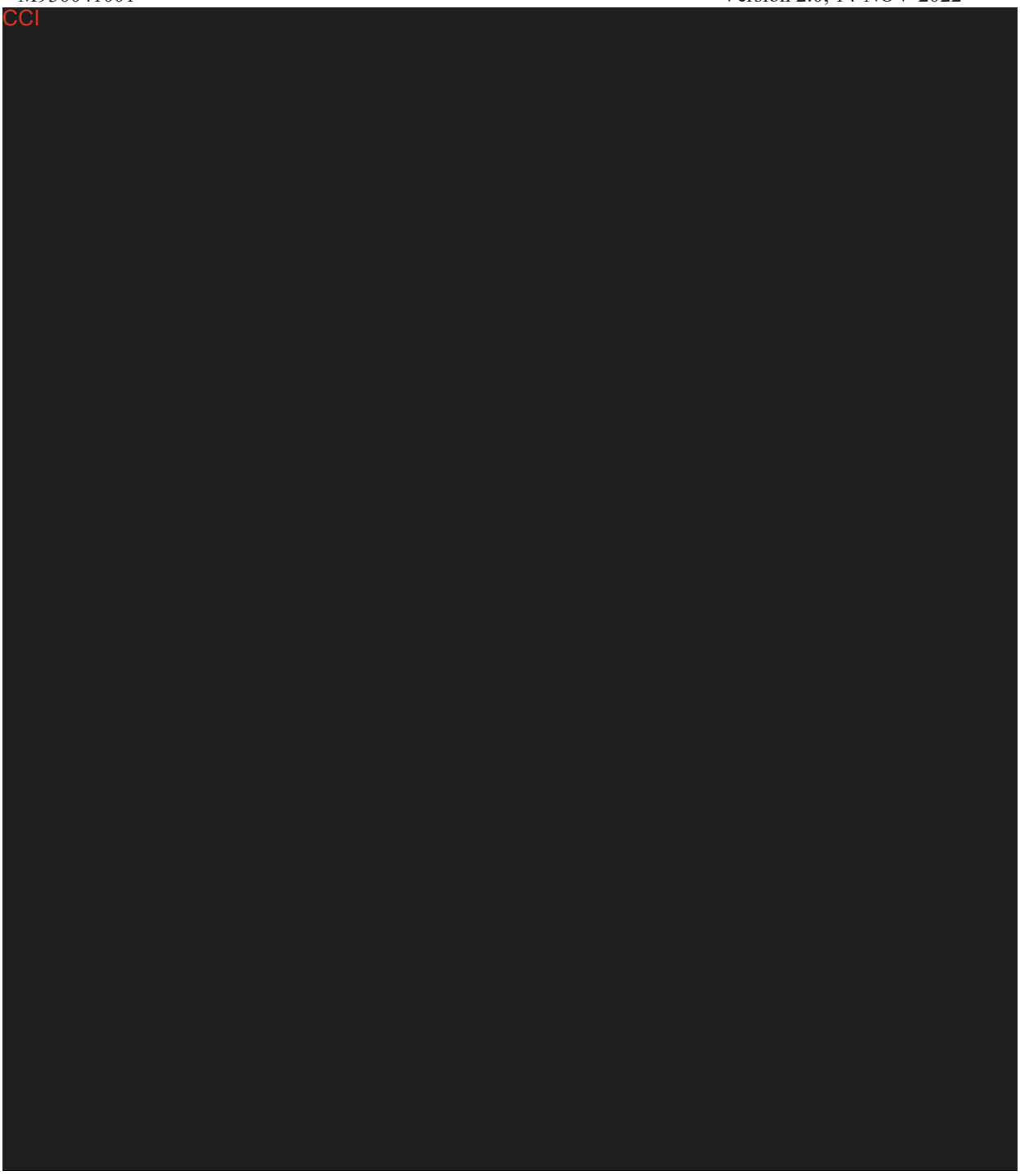
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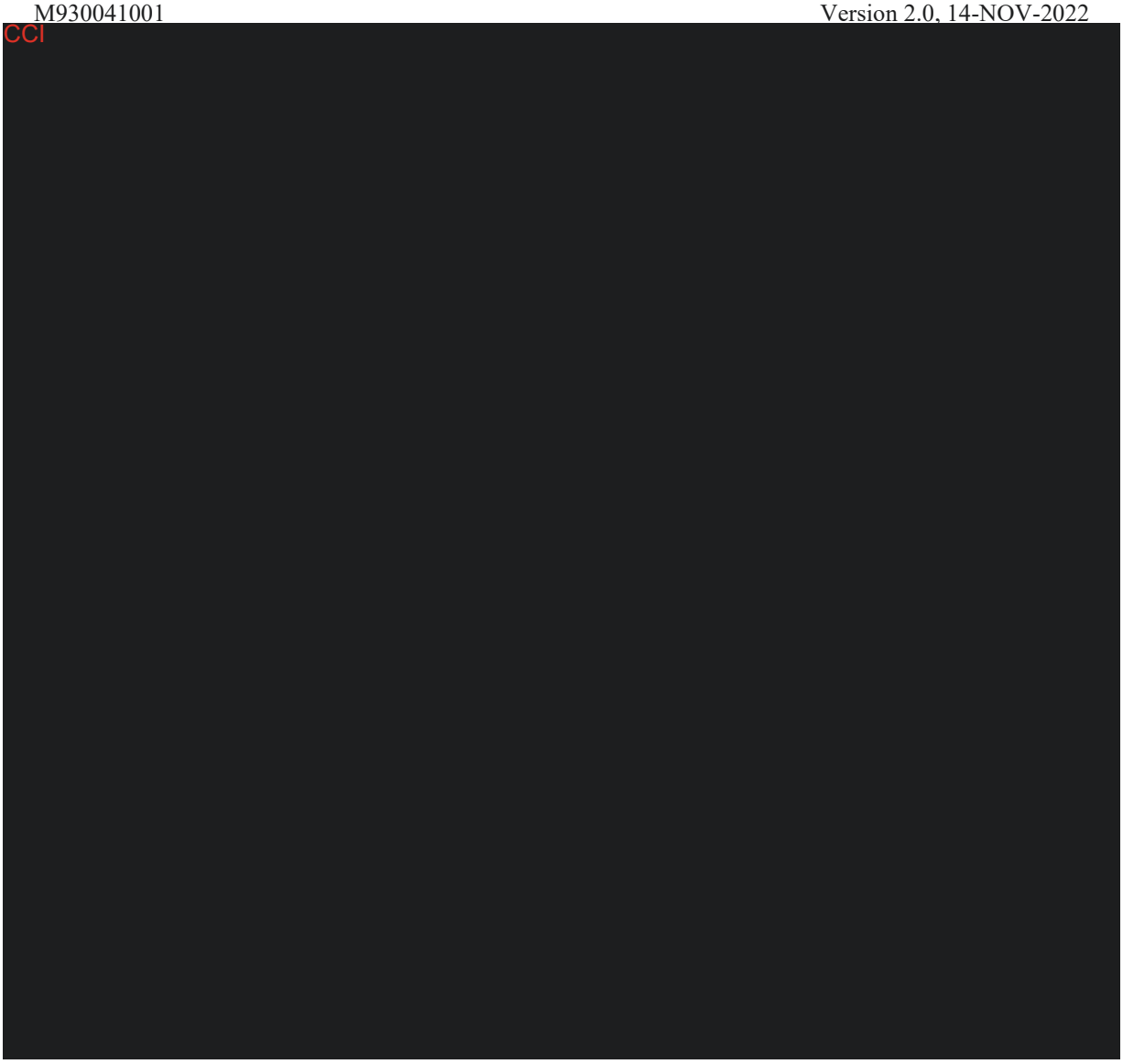
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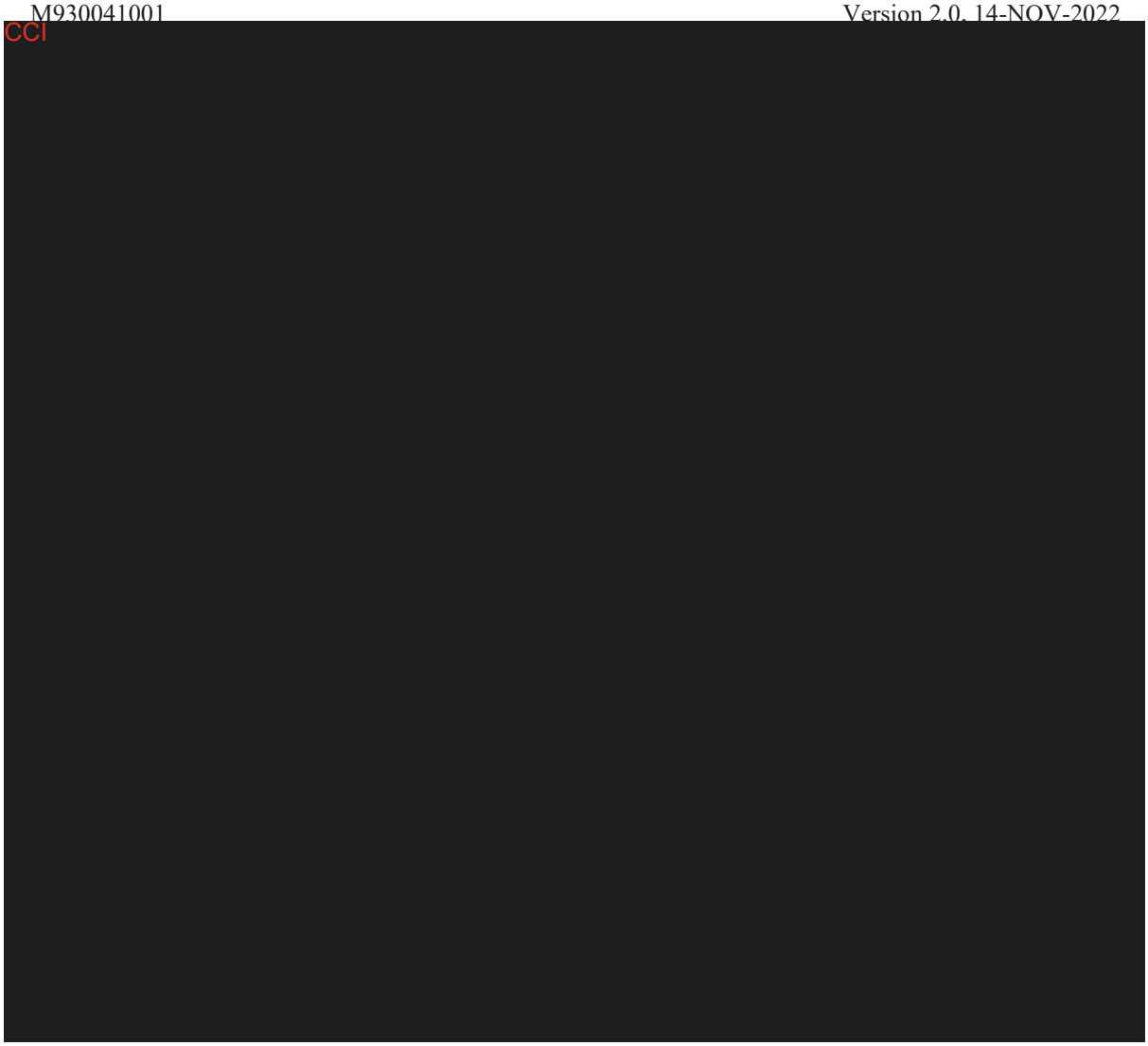
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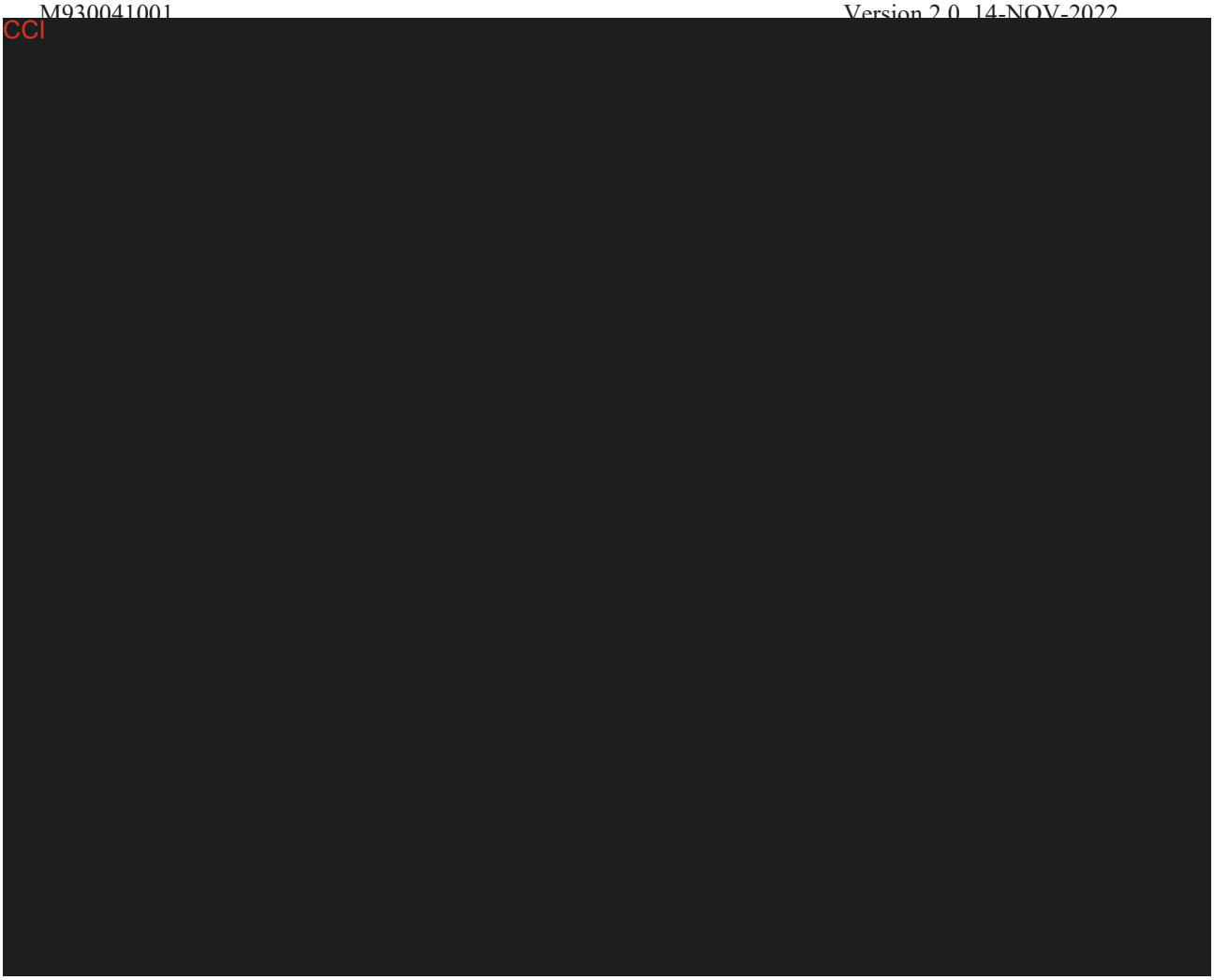
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16.12 Internal Functional Contributors

Name	Role	Contact Information
Merz North America, Inc.	Sponsor	6501 Six Forks Road Raleigh, North Carolina 27615 US
PPD	Scientific Expert	PPD
	Biostatistician	
	Clinical Study Manager	
	Product Safety Officer	
	Regulatory Affairs Manager	
	Clinical Scientist	

16.13 External Responsibilities

The administrative structure for external responsibilities includes, but is not limited to, the following participants:

CCI

16.14 Sponsor's Signature Page

This study will be conducted in compliance with the CSP and in accordance with the principles outlined in the Declaration of Helsinki and in compliance with the International Council on Harmonization's Good Clinical Practice (ICH-GCP), International Organization for Standardization (ISO) 14155, the Code of Federal Regulations, and any applicable regional or national laws and regulations.

The following individuals are responsible for the content of the CSP:

PPD	Signature	Date (dd-MMM-yyyy)
	Signature	Date (dd-MMM-yyyy)

16.15 Statement of Compliance and Investigator Signature

I have thoroughly read and reviewed the CSP 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 CSP, 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), ISO 14155, 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 CSP before the study formally starts.
- Wait until I have received approval from the appropriate IRB before screening any subject for 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, IRB review, and regulatory inspections and provide direct access to all study-related records, source documents, subject files, and case report forms for the sponsor, monitor, auditor, IRB, or regulatory authority upon request.
- Use all study materials only as specified in the CSP.
- Report to the responsible product safety officer, within 24 hours, any SAE and SADE, whether considered related or not related to the investigational device, and any device deficiency that could have led to a SADE.
- 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 IRB or regulatory authority.
- The content of the CSP is confidential and proprietary to Merz.
- Any deviation from the CSP may lead to early termination of the investigational site.

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