1 TITLE PAGE

Evaluation of Effectiveness and Safety of Belotero Balance® (+) Lidocaine for Volume Augmentation of the Infraorbital Hollow

Study Identifier:	M930121002 / NCT04594239
Version Date:	04-NOV-2021, Amendment 4 Version 5 27-JAN-2021, Amendment 3 Version 4 20-JUL-2020, Amendment 2 Version 3 14-JUL-2020, Amendment 1 Version 2 12-JUN-2020, Version 1
Investigational Medical Device:	Belotero Balance® (+) Lidocaine
Indication:	Correction of volume loss in the infraorbital hollow area
Study Design:	Prospective, multicenter, randomized, evaluator-blinded, comparative, pivotal study
Sponsor:	Merz North America, Inc. CCI [redacted]

Document References (For Internal Use Only)
CCI [redacted]

Changes to Previous Versions of this Report

Version and Date	Change
Version 5.0, 04-NOV-2021	An incorrect instruction in footnote 6 in the schedule of events for the control/delayed-treatment subjects was included in previous versions of this protocol. The footnote incorrectly stated that IOH photos should only be taken at Visit C1-a (8 weeks after screening), if the screening photos were deemed unsatisfactory. In fact, all subjects in the control/delayed-treatment group should have IOH photos taken at Screening and Visit C1-a, as outlined in other sections of the protocol. The issue was noted after all control/delayed-treatment subjects had completed the affected Visit C1-a and for the majority of control/delayed-treatment subjects, no photo had been taken at Visit C1-a. The following changes to the planned IPR assessments, and statistical analyses were therefore included in this protocol amendment: • Updated timepoints of photos used for IPR assessment in Section 7.2.1.3 Other Effectiveness Endpoints and Section 11.2.1.1 Merz Infraorbital Hollow Assessment Scale (MIHAS). For subjects in the control/delayed treatment group, photos from Screening, 8 weeks post-screening and 8 weeks post last injection will be included in the IPR assessment. • Adapted the analyses of IPR assessment data to the change in timepoints of photos used in the assessment. For subjects in the control/delayed-treatment group, summaries will be provided for 8 weeks after screening and 8 weeks post-last injection, using the screening photo as reference. • Reference to pre-treatment photos taken at the delayed treatment baseline were removed from the definition and analysis descriptions for the GAIS endpoints. In Section 11.1 Visit Schedule, the definition of the primary endpoint visit, which is 8 weeks post screening for the control/delayed treatment subjects, was corrected. Minor formatting errors and wording changes were implemented.
Version 4.0, 27-JAN-2021	• Updated safety email address and removal of fax number (Section 12.2.2) • Increased the maximum enrollment per site from 24 to 26 (Sections 8.1, 9.1, 13.1) • Updated internal functional contributors (Section 16.5)
Version 3.0, 20-JUL-2020	In order to address the agency's (FDA) concerns regarding changes in visual function assessments that may occur immediately after treatment,

	the protocol has been modified to ensure that subjects with detected abnormalities on visual-function assessments post-treatment will be referred to an ophthalmologist for evaluation. The following language has been added to Section 11.2.2.2.1 of the protocol. An abnormality is defined as any parameter that is clinically significant in nature or a drop-in vision by one line or more. If any such abnormality is detected on the visual-function assessments at a treatment visit (initial injection, touch-up, retreatment), the subject will be referred to an ophthalmologist for further evaluation. In addition, the abnormality will be documented as an AE.
Version 2.0,14-JUL-2020	• An abnormality in visual acuity using the Snellen chart was previously defined as a drop-in vision by two lines or more. The agency (FDA) indicated that the Snellen chart lacks uniformity and thus the definition of abnormal visual assessment as a drop by 2 lines or more is inherently flawed. To address this concern, the protocol was revised to include an evaluation for any subject who experiences a worsening of their visual acuity (i.e., drop-in vision by one line or more on the Snellen chart). • Previously, pre-treatment vision assessments were to be performed at the screening visit and not the first treatment visit prior to injection. In order to address the FDA's concerns regarding the need to ensure that subjects are appropriately screened for any vision changes during the course of the study, CCI has been revised to indicate that vision assessments will be performed at the screening visit, as well as, the treatment visit prior to injection.

2 SYNOPSIS

Title of Study	Evaluation of Effectiveness and Safety of Belotero Balance® (+) Lidocaine for Volume Augmentation of the Infraorbital Hollow
Study Identifier	M930121002
Investigators, Study Sites	This study will be conducted at up to 9 study centers in the United States.
Investigational Medical Device	Belotero Balance® (+) Lidocaine (BBL)
Indication	Correction of volume loss in the infraorbital hollow area
Objectives	*Effectiveness* Confirm the effectiveness of BBL injection for the correction of volume loss in the infraorbital hollow (IOH) area by demonstrating superiority to untreated control. *Safety* Confirm the safety of BBL injection for the correction of volume loss in the IOH area.
Effectiveness Evaluation	*Primary endpoint* • Proportion of responders at Week 8 on the Merz Infraorbital Hollow Assessment Scale (MIHAS), as assessed live by a blinded evaluator. *Note: Responder is defined as a subject with at least 1-point improvement from baseline on MIHAS of both IOHs.* *Note: For subjects randomized to treatment, if no touch-up is performed, the primary effectiveness MIHAS assessment will occur 8 weeks post baseline injection. If a touch-up is performed, the primary effectiveness MIHAS assessment will be completed 8 weeks post touch-up. For subjects randomized to control/delayed-treatment, the primary effectiveness assessment will occur 8 weeks from the screening visit.* *Secondary endpoints* *Note: For all secondary endpoints, Week 8 corresponds to the time from last injection (either baseline or touch-up injection) for subjects randomized to treatment only (TN and TC groups).* • Global Aesthetic Improvement Scale (GAIS) score at Week 8, as assessed by the treating investigator. • GAIS score at Week 8, as assessed by the subject. • FACE-Q™ Satisfaction with Eyes scores and changes from baseline to Week 8, as assessed by the subject. *Note: FACE-Q evaluates both eyes concurrently.*

Safety Evaluation	<u>*Secondary endpoints*</u> • Incidence of treatment-emergent adverse events (TEAEs) related to BBL. • Incidence of treatment-emergent serious adverse events (TESAEs) related to BBL.
Introduction, Study Design Overview, and Methodology	This is a prospective, multicenter, randomized, evaluator-blinded, comparative, pivotal study designed to evaluate the effectiveness and safety of BBL for the correction of volume loss in the IOH area. All eligible subjects will be randomized to 4 groups using a 2:2:1:1 ratio as follows: BBL with needle (TN), BBL with cannula (TC), control/delayed treatment BBL with needle (CDTN), and control/delayed treatment BBL with cannula (CDTC). Subjects randomized to treatment will receive a BBL injection in both IOHs and will be assessed at Week 4 for a touch-up in one or both IOHs. These subjects will also be eligible for a retreatment at 48 weeks post last injection (i.e., baseline injection or touch-up, if applicable) and then be followed for an additional 24 weeks, for a total study duration of 72 weeks if no touch-up is performed and 76 weeks if a touch-up is performed. Subjects randomized to the control/delayed-treatment group will remain untreated for 8 weeks. After all applicable effectiveness endpoint assessments have been completed, the control/delayed-treatment subjects will receive BBL injections and will be assessed 4 weeks after their initial injection for a touch-up in one or both IOHs. These subjects will be followed for 48 weeks post last injection (i.e., baseline injection or touch-up, if applicable) and will not be offered retreatment.
Number of Study Subjects	A total 150 subjects will be randomized.
Main Inclusion/ Exclusion Criteria	*Select inclusion criteria are as follows:* • Subject is a candidate for bilateral IOH treatment. • Subject has symmetrical right and left IOHs with the same MIHAS score of 2 or 3 (moderate or severe), as assessed live by a blinded evaluator. • Female or male ≥ 22 and ≤ 65 years old. *Select exclusion criteria are as follows:* • Prior lower-eyelid surgery, including orbital or midface surgery, or a permanent implant or graft in the midfacial region that could interfere with effectiveness assessments. • Previous treatment with fat injections or permanent and/or semi-permanent dermal fillers in the midfacial region. • Previous lower-eyelid and/or malar-region treatments with any dermal fillers (e.g., collagen, hyaluronic acid (HA), calcium hydroxyapatite, poly L-lactic acid (PLLA)) within the past 24 months.

	• Tendency to accumulate fluid in the lower eyelids, has developed festoons, or has large and/or herniating infraorbital fat pads.
Duration of Treatment	Subjects will have a screening period of up to 10 days and participate for a maximum duration of 76 weeks (± 14 days).

3 TABLE OF CONTENTS

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3.1 List of In-Text Tables

CCI

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3.2 List of In-Text Figures

CCI

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation/Term	Definition
ADE	Adverse device effect
AE	Adverse event
ASADE	Anticipated serious adverse device effect
ATC	Anatomical Therapeutic Chemical classification system of the World Health Organization
BDDE	1,4-butanediol diglycidyl ether
BBL	Belotero Balance® (+) Lidocaine
BMI	Body mass index
CAN	Pooled groups TC and DTC of subjects treated with cannula
CDTC	Untreated control until Week 8 / Delayed-treatment BBL with cannula (starting at Week 8)
CDTN	Untreated control until Week 8 / Delayed-treatment BBL with needle (starting at Week 8)
CFR	Code of Federal Regulations
CI	Confidence interval
CIP	Clinical Investigational Plan
COVID-19	Coronavirus disease 2019
CRO	Contract research organization
CSP	Clinical study protocol
CTL	Untreated control subjects until Week 8
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DTC	Randomized control subjects with delayed treatment BBL using a cannula (untreated control until Week 8)
DTN	Randomized control subjects with delayed treatment BBL using a needle (untreated control until Week 8)
DTRT	Delayed-treatment groups DTN and DTC pooled
eCRF	Electronic case report form
eDiary	Electronic Diary
EDC	Electronic data capture
FACE-Q™	Set of subject-reported questionnaire modules

Abbreviation/Term	Definition
FDA	Food and Drug Administration, US
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GCP	Good Clinical Practice
HA	Hyaluronic Acid
HIV	Human immunodeficiency virus
ICC	Intraclass correlation
ICF	Informed consent form
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent ethics committee
IFU	Instructions for use
IMD	Investigational medical device
IOH	Infraorbital Hollow
IPR	Independent panel review
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intent to treat population
ITT-OC	ITT observed cases
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MedDRA	Medical Dictionary for Regulatory Activities
MIHAS	Merz Infraorbital Hollow Assessment Scale
N	Number of non-missing observations
NED	Pooled groups TN and DTN of subjects treated with needle
NSAID	Non-steroidal anti-inflammatory drug
OC	Observed cases
PLLA	Poly L-lactic acid
PP	Per protocol population
PT	Preferred term
SADE	Serious adverse device effect
SAE	Serious adverse event

Abbreviation/Term	Definition
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SOC	System organ class
SOP	Standard operating procedure
SP	Safety population
TC	Randomized treatment group subjects treated with BBL using a cannula
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TN	Randomized treatment group subjects treated with BBL using a needle
TOTT	Pooled groups NED and CAN (or TRT and DTRT)
TRT	Pooled treatment groups TN and TC
UADE	Unanticipated adverse device effect
US(A)	United States of America
UV	Ultraviolet
VAS	Visual analogue scale

Definitions of Terms

Clinical Study Protocol

The use of the term "Clinical Study Protocol (CSP)" is synonymous with the term "Clinical Investigational Plan (CIP)".

Early study termination

Study halted prematurely and did not resume; subjects were no longer examined or treated.

Effectiveness

The use of the term "effectiveness" is synonymous with the term "clinical performance".

Investigational medical device

The terms "investigational medical device" is synonymous with the term "investigational device".

Rater

The term "rater" is synonymous with the term "evaluator".

Study

The term "study" is synonymous with the term "investigation".

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 the standards for Good Clinical Practice described in EN ISO 14155, the Code of Federal Regulations, and any applicable regional or national laws and regulations. The study will adhere to all applicable subject privacy requirements.

All required approvals, favorable opinions, or additional requirements of the appropriate Independent Ethics Committee (IEC), 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 protocol. The investigator will ensure that all personnel involved in the conduct of this study are qualified to perform the assigned study responsibilities. Investigators will adhere to all applicable study reporting requirements.

In the event of a pandemic disease outbreak (e.g., new 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 IEC/IRB. In addition, changes in protocol conduct necessary to ensure subject safety, such as conducting telephone or virtual visits for safety monitoring rather than on-site visits, can be implemented immediately with subsequent review by the IEC/IRB and notification to regulatory authorities.

5.2 Informed Consent

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. The original and any amended signed and dated informed consent form (ICF) must be retained at the study site, and a copy must be given to the subject.

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

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

During the study, the subject will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study. If an adverse event (AE) should occur, the subject should inform the investigator,

who then will make a judgment whether continuing in the study serves the subject's best interests. The subject, however, is free to withdraw consent at any time and for any reason, whether expressed or not.

Each ICF will include contact information (with a phone number) for the investigator and an ophthalmology practice; the subject should use this information to communicate any medical concerns 24 hours a day.

In the event of a pandemic disease outbreak (e.g., new COVID-19 public health emergency), if re-consenting of the subjects is deemed necessary due to significant changes made to the protocol 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 obtaining re-consent. For example, subjects will be contacted via phone or video calls to provide verbal consent supplemented with written (e.g., e-mail) confirmation.
- The IEC/IRB approved, updated subject information sheet and consent form will be provided by e-mail, mail, or courier to obtain a re-consent.
- All instances of consent that is obtained through alternative ways will be documented.

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

5.3 Confidentiality of Subject Information

Subject pseudo-anonymity is to be maintained during the study. Subjects will be identified by a unique subject number on all study documentation. Non-pseudonymized documents must be maintained in strict confidence by the investigator to the extent permitted by applicable laws and regulations, unless their disclosure is necessary to allow auditing by regulatory authorities, the sponsor, or the sponsor's designee.

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

6 INTRODUCTION

6.1 Background and Rationale

There is increasing interest among patients to seek minimally invasive alternatives to aesthetic surgical procedures to improve the appearance of the face. Because of the aging process, a noticeable concave deformity may develop in the under-eye area; this hollowing of the infraorbital region results in a fatigued and aged appearance on the face. While many anatomical and physiological factors must be considered as contributing to infraorbital hollowing, subjects with an inherent level of volume loss may benefit from dermal-filler augmentation. However, treating the infraorbital hollow (IOH) may present challenges, and only a few fillers are suitable for this area.

To address the aforementioned issues, the objectives of this study will be to demonstrate the effectiveness and safety of Belotero Balance® (+) Lidocaine (BBL) injection for the treatment of volume loss in the infraorbital hollow area in a scientifically robust and adequately powered pivotal study.

6.2 Potential Benefits and Risks

The potential benefit of BBL is the correction of volume loss in the IOH area. In a pilot study conducted using Belotero Balance (M930121001; A Pilot Study to Assess the Effectiveness and Safety of Belotero Balance Injection for Volume Augmentation of the Infraorbital Hollow), the majority of treated subjects achieved at least 1-point improvement on the Merz Infraorbital Hollow Assessment Scale (MIHAS) at Week 8 (81.6% of treated subjects; $p < 0.0001$). The findings also demonstrated aesthetically pleasing outcomes with strong agreement between the blinded MIHAS evaluators and Global Aesthetic Improvement Scale (GAIS) assessments completed by both the treating investigator and the subject. FACE-Q™ assessments assessing satisfaction with eyes and lower eyelids improved over time after injection with Belotero Balance. Additionally, treated subjects reported looking younger after treatment when compared to untreated subjects.

The following are AEs that have been reported during post-approval use of Belotero Balance[1] : allergic reactions including Quincke's edema, anaphylaxis, rash, hives, necrosis, inflammation, granuloma, indurations, papule/nodule, hematoma, Tyndall effect, bumps/lumps, pustule, scabbing/scarring, swelling/edema, erythema/redness, pain, bruising, discoloration, infection, migration/displacement, asymmetry, numbness, itching/pruritus, vascular occlusion, and visual disturbance.

[1] Belotero Balance (BB) and Belotero Balance (+) Lidocaine (BBL) are the same formulation with the exception that lidocaine hydrochloride is added to the BBL formulation. Belotero Balance has been commercially available in the US since 2011 for the treatment of mid-to-deep dynamic and static wrinkles and folds, such as nasolabial folds. The events listed in this section were reported during post-approval use.

Potential risks associated with the use of BBL are similar to those of other commercially available, deep soft-tissue fillers. Previously reported injection-site responses to Belotero Balance consisted mainly of short-term inflammatory symptoms including: swelling, induration, bruising, redness, erythema, pain, nodule formation, discoloration, pruritus, and rash. These observations began soon after treatment and resolved within 14 days or less.

Although rare, serious adverse events (SAEs) associated with the intravascular injection of soft-tissue fillers in the face have been reported and include: temporary or permanent vision impairment; blindness; cerebral ischemia or cerebral hemorrhage leading to stroke; skin necrosis; abscesses; granulomas; eyelid muscle degeneration; eyelid ptosis; and damage to the underlying facial structures. Implantation of fat cells or any soft-tissue filler into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction.

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

An additional risk associated with the use of BBL includes disappointment due to lack of or less than expected performance and/or undesirable aesthetic effect.

The use of a cannula may increase the duration of local/site irritation or erythema by 1 to 2 days when compared to the use of a needle.

A pilot study conducted using Belotero Balance in the IOH area (M930121001) demonstrated an acceptable AE profile, with no treatment-related SAEs or unanticipated adverse device effects (UADEs) reported. Many common treatment responses (CTRs) resolved within 1 to 14 days post injection and prior to a follow-up visit. No AEs were categorized as unexpected or atypical with use of Belotero Balance in the IOHs. No events associated with retinal-artery occlusion or visual disturbance, or the late onset of such events related to Belotero Balance in the IOH region were reported.

Currently, no dermal fillers are approved for volume correction around the eyes. Alternative interventions may include various surgical and non-invasive procedures, potential topical therapies, or no treatment at all.

Additional information on product- and injection-related contraindications, warnings, and precautions can be found in Sections 10.1 and 10.5.1.2, CCI [redacted]

7 STUDY OBJECTIVES AND ENDPOINTS

7.1 Objectives

Effectiveness

Confirm the effectiveness of BBL injection for the correction of volume loss in the IOH area by demonstrating superiority to untreated control.

Safety

Confirm the safety of BBL injection for the correction of volume loss in the IOH area.

7.2 Endpoints

7.2.1 Effectiveness Endpoints

7.2.1.1 Primary Effectiveness Endpoint

Proportion of responders at Week 8 on the MIHAS, as assessed live by a blinded evaluator.

Note: Responder is defined as a subject with at least 1-point improvement from baseline on MIHAS of both IOHs.

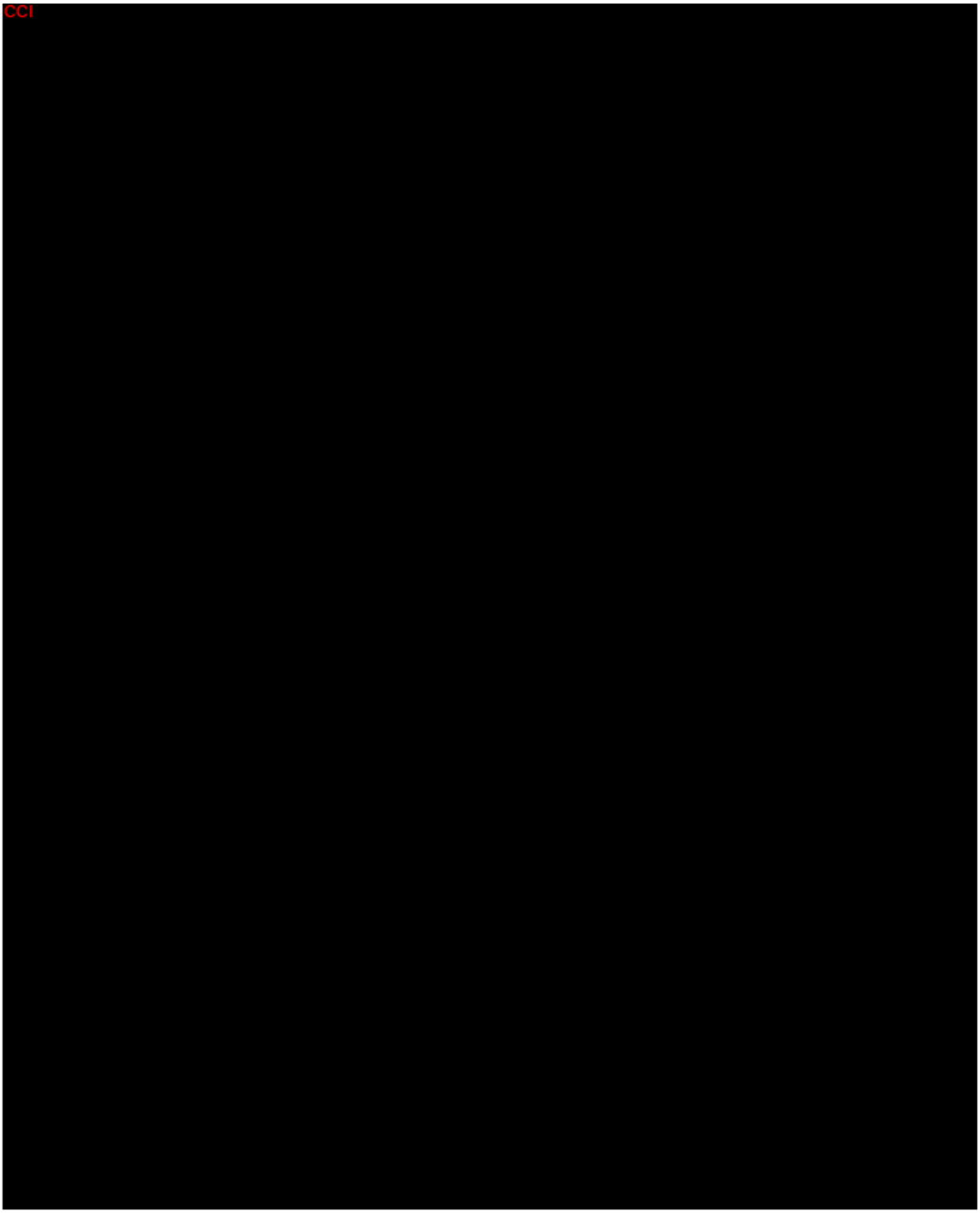
Note: For subjects randomized to treatment, if no touch-up is performed, the primary effectiveness MIHAS assessment will occur 8 weeks post baseline injection. If a touch-up is performed, the primary effectiveness MIHAS assessment will be completed 8 weeks post touch-up. For subjects randomized to control/delayed-treatment, the primary effectiveness assessment will occur 8 weeks from the screening visit.

7.2.1.2 Secondary Effectiveness Endpoints

Note: For all secondary endpoints, Week 8 corresponds to the time from last injection (either baseline or touch-up injection) for subjects randomized to treatment only (TN and TC groups).

- GAIS score at Week 8, as assessed by the treating investigator.
- GAIS score at Week 8, as assessed by the subject.
- FACE-Q™ Satisfaction with Eyes scores and changes from baseline to Week 8, as assessed by the subject.

  Note: FACE-Q evaluates both eyes concurrently.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7.2.2 Safety Endpoints

7.2.2.1 Secondary Safety Endpoints

- Incidence of treatment-emergent adverse events (TEAEs) related to BBL.
- Incidence of treatment-emergent serious adverse events (TESAEs) related to BBL.

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8 CLINICAL INVESTIGATION PLAN

8.1 Overview of Study Design

This is a prospective, multicenter, randomized, comparative, evaluator-blinded pivotal study designed to evaluate the safety and effectiveness of BBL for the correction of volume loss in the IOH. Study subjects will have a screening period of up to 10 days and participate for a maximum duration of 76 weeks (± 14 days).

A total of 150 subjects will be randomized at up to 9 investigational sites in the United States (US). At each study site, the number of subjects randomized should not exceed 26. A minimum of 20% of enrolled subjects will be Fitzpatrick Skin Type IV, V, or VI CCI [redacted] CCI Subjects from the Fitzpatrick Skin Type IV, V, or VI group will be distributed as follows: at least 16 subjects of Type IV; 7 subjects of Type V; and 7 subjects of Type VI. At least 10% of the subjects enrolled will be male.

Subjects eligible for study enrollment will have symmetrical right and left IOHs with the same MIHAS score of 2 or 3 (moderate or severe), as assessed live by a blinded evaluator. All blinded evaluators will be qualified healthcare practitioners, delegated by the treating investigator and trained by the sponsor. At screening, eligible subjects will be randomized to 4 groups using a 2:2:1:1 ratio as follows: BBL with needle (TN), BBL with cannula (TC), control/delayed-treatment BBL with needle (CDTN), and control/delayed-treatment BBL with cannula (CDTC). The needle or cannula assignment for a subject cannot be interchanged during the study; that is, needle and cannula cannot be used in the same subject.

Subjects randomized to treatment will receive a BBL injection in both IOHs at Day 1. Treated subjects who do not achieve optimal aesthetic correction or at least 1-point improvement on the MIHAS, as assessed by the blinded evaluator 4 weeks post treatment compared to baseline, may have a touch-up injection in one or both IOH(s). If a touch-up is necessary, it will only be administered if there are no medical contraindications or existing AEs of concern, as determined by the treating investigator. The treating investigator will be responsible for reviewing whether the threshold for optimal aesthetic correction or at least 1-point MIHAS improvement is met, as assessed by the blinded evaluator, since the blinded evaluator will not have access to the subject's study records.

Subjects who achieve at least 1-point improvement on the MIHAS 4 weeks post treatment when compared to baseline may have a touch-up injection in one or both IOH(s) to achieve optimal correction, at the discretion of the treating investigator and the subject.

Subjects randomized to treatment at Day 1 will have the option for retreatment, upon agreement between the subject and the treating investigator, at 48 weeks post last injection

(i.e., baseline injection or touch-up, if applicable) and will then be followed for an additional 24 weeks, for a total study duration of up to 76 weeks (72 weeks if no touch-up is performed).

Subjects randomized to the control/delayed-treatment group will remain untreated until Week 8. After all applicable effectiveness endpoint assessments have been completed at their Week 8 visit, control subjects will receive BBL IOH injections (i.e., delayed treatment) and will be followed for 48 weeks. Subjects who do not achieve optimal aesthetic correction or at least 1-point improvement on the MIHAS as assessed by the blinded evaluator 4 weeks post treatment compared to the delayed-treatment baseline (Week 8), may have a touch-up injection in one or both IOH(s). If a touch-up is necessary, it will only be administered if there are no medical contraindications or existing AEs of concern, as determined by the treating investigator. The treating investigator will be responsible for reviewing whether the threshold for optimal aesthetic correction or at least 1-point MIHAS improvement is met, as assessed by the blinded evaluator, since the blinded evaluator will not have access to the subject's study records.

Subjects who achieve at least 1-point improvement on the MIHAS 4 weeks post treatment when compared to the delayed-treatment baseline (Week 8) may have a touch-up injection in one or both IOH(s) to achieve optimal correction, at the discretion of the treating investigator and the subject.

Control/delayed-treatment subjects will not be offered retreatment.

Any time a subject is treated (i.e., initial injection, touch-up, and/or retreatment), he/she will have a 72-hour post-treatment phone call to evaluate safety. If a subject reports a safety concern during any phone call, an unscheduled visit may be necessary.

Effectiveness assessments include blinded evaluator MIHAS, treating investigator and subject GAIS, subject-reported FACE-Q Satisfaction with Eyes, FACE-Q Appraisal of Lower Eyelids, FACE-Q Patient-Perceived Age VAS, a Patient-Perceived Pain VAS, and a likelihood of future treatment assessment. These assessments will be performed throughout the study. Additionally, three blinded, board-certified IPR experts who are not part of the study sites will assess subject IOHs using the MIHAS and subject photographs.

Standard safety parameters will be monitored throughout the study. Additionally, visual assessments (i.e., visual acuity, confrontation visual field test, ocular motility, and an undilated central retinal exam using non-mydriatic retinal cameras and read by a central reader) will be conducted. A subject eDiary will be used to record predefined CTRs for 28 days after the initial injection, touch-up injections (if applicable), and retreatment (if applicable).

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

As detailed in Section 8.1, this is a prospective, multicenter, randomized, comparative, evaluator-blinded, pivotal study designed to evaluate the effectiveness and safety of BBL for the correction of volume loss in the IOH area.

Since no approved, marketed products are currently available in the US for treatment of the IOH region, an untreated-control group will be utilized for this study. To maximize the number of subjects exposed for generation of adequate safety data, control subjects will receive delayed treatment with BBL upon completion of all Week 8 effectiveness assessments.

As subject satisfaction is the primary goal of aesthetic medicine, subjects may undergo a touch-up treatment after initial injection to achieve optimal correction. Subjects randomized to treatment will also be eligible for retreatment at 48 weeks post last injection (i.e., baseline injection or touch-up, if applicable) for further aesthetic IOH enhancement. Optional retreatment will help improve compliance with the study protocol (i.e., minimize early discontinuation) and ensure subjects will complete the study with aesthetic IOH improvement. Retreating subjects at 48 weeks post last injection will also provide additional safety data associated with repeat treatment.

Injection volumes to be administered in this study (see Section 10.5.1.2.6) represent a safe standard for IOH treatment and are consistent with volumes utilized in a Belotero Balance pilot study of IOH treatment (M930121001).

8.3 Definitions

8.3.1.1 Subject Enrollment and Randomization

Subjects are considered to be enrolled when they sign informed consent and meet all eligibility criteria. Eligible subjects will be randomized at the screening visit.

Screen failures are defined in Section 9.2.4.

8.3.1.2 End of Study

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

9 STUDY POPULATION AND RESTRICTIONS

9.1 Number of Subjects and Sites

A total of 150 subjects will be randomized at up to 9 investigational sites in the US. At each study site, the number of subjects randomized should not exceed 26. A minimum of 20% of the enrolled subjects will be Fitzpatrick Skin Type IV, V, or VI. Subjects from the Fitzpatrick Skin Type IV, V, or VI group will be distributed as follows: at least 16 subjects of Type IV; 7 subjects of Type V; and 7 subjects of Type VI. At least 10% of the subjects enrolled will be male.

Any randomized subject who does not complete the study will not be replaced.

Additional information regarding subject enrollment is provided within the sample size justification in Section 13.2.

9.2 Selection of Subject Population

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

9.2.1 Inclusion Criteria

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

1. Is a candidate for bilateral IOH treatment.
2. Has symmetrical right and left IOHs with the same MIHAS score of 2 or 3 (moderate or severe), as assessed live by the blinded evaluator.
3. Is ≥ 22 and ≤ 65 years old.

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9.2.2 Exclusion Criteria

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

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4. Had prior lower-eyelid surgery, including orbital or midface surgery, or has a permanent implant or graft in the midfacial region that could interfere with effectiveness assessments. Note: Rhinoplasty is permitted if the procedure was ≥ 12 months prior to study enrollment.
5. Has ever been treated with fat injections or permanent and/or semi-permanent dermal fillers in the midfacial region.
6. Has received lower-eyelid and/or malar-region treatments with any dermal fillers (e.g., collagen, hyaluronic acid (HA), calcium hydroxyapatite, or poly L-lactic acid (PLLA)) within the past 24 months.

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16. Has a tendency to accumulate fluid in the lower eyelids, has developed festoons, or has large and/or herniating infraorbital fat pads.

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9.2.3 Subject Restrictions during the Study

By providing informed consent, subjects are also prohibited from the following actions and treatments after injection:

- Touching/pressing the treatment area for 12 hours after treatment.
- Applying makeup to the treatment area for 12 hours after treatment.
- Exercising strenuously for 24 hours after treatment.
- Consuming alcoholic beverages for 24 hours after treatment.
- Exposing the treated area to extensive sun or heat exposure for 24 hours after treatment.

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- Receiving any other procedures (i.e., dermal fillers, fat injections, facial ablative or fractional laser, microderm abrasion, superficial or deep chemical peels, platelet-rich plasma, non-invasive skin-tightening [e.g., Ultherapy, Thermage], mesotherapy, or any surgical procedures) on ANY part of the face during study participation.
- Receiving neurotoxin treatment in ANY part of the face.
- Initiation of any new topical over-the-counter or prescription facial skin product or oral medication that affects the facial appearance.
- Using prescription topical steroids on the face.
- Receiving anti-coagulation, anti-platelet, or thrombolytic medications (e.g., warfarin), anti-inflammatory drugs (e.g., oral/injectable corticosteroids or NSAIDs [e.g., aspirin, ibuprofen]), or other substances known to increase coagulation time (e.g., vitamins or herbal supplements, [e.g., Vitamin E, fish oil, garlic, gingko, St. John's Wort]) from 10 days before injection to 3 days after injection.
- Receiving immunosuppressive medications or systemic steroids (except intranasal/inhaled or intra-articular steroids).
- Gaining or losing ≥ 2 BMI units.
- Prolonged exposure of the face to UV radiation (sun, tanning bed).
- Oral surgery (e.g., orthodontia, extraction, implants).

9.2.4 Screen Failures

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

9.2.5 Subject Withdrawal

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

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

- The site will attempt to contact the subject at least twice and reschedule the missed visit as soon as possible. Every effort to regain contact with the subject will be made

(e.g., telephone contact on different dates/times, registered mail). All contact attempts will be documented.

- If attempts to contact the subject are not successful, the subject will be considered lost to follow-up and withdrawn from the study.

The reason for early withdrawal 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 last study visit.

In cases of withdrawn consent, data collected until the date consent was withdrawn will be analyzed as recorded.

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, the investigator will record the reason for treatment discontinuation in the study records. The investigator should request that a subject discontinuing treatment continue to participate in the study and complete all remaining visits and assessments. If a subject declines to continue study participation, the investigator will make every effort to perform the appropriate assessments for the End of Study/Early Termination visit CCI [redacted] CCI [redacted]

9.2.6.2 Subject Discontinuation

Each subject will be followed to the end of study, or until the sponsor decides to terminate the study, whichever comes first. The only reasons a subject will not be followed for all scheduled visits include withdrawal of consent (see Section 9.2.5), continuous non-compliance with protocol requirements, or loss to follow-up (e.g., moving away from study site; unresponsive to attempts to contact the subject).

The investigator can discontinue any subject, at any time, if medically necessary. The reason for the subject's discontinuation should be documented in the eCRF. The investigator should make every attempt to complete the recommended follow-up assessments specified for the last study visit.

If a non-serious AE is unresolved at the time of the subject's final study visit, an effort will be made to follow 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/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 study discontinuation, the sponsor will follow all applicable local regulations and guidelines with regard to a subject's follow-up care. The investigator will ensure that appropriate consideration is given to a subject's post-study care.

9.2.7 Premature Suspension or Termination of the Study

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

In the case of a reported vascular embolic event leading to skin necrosis, vision loss, or stroke, 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. If the evaluation reveals the outcome was unanticipated, the entire study will be immediately suspended, and no subjects will be enrolled or treated until the event can be properly characterized and an appropriate treatment strategy to avoid this unanticipated event can be devised.

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

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

In the event of a public health emergency, the sponsor will inform all investigators, the IEC/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).

In the event of premature study suspension or termination for safety reasons, the sponsor will inform all investigators and relevant regulatory authorities promptly of the study

suspension/termination and reason for the action. The investigator will conduct site-closure activities in accordance with all applicable sponsor and local/international guidelines and regulations.

9.2.8 Study Site Discontinuation

Study participation by individual sites may be discontinued by the sponsor for any of the reasons listed in Section 9.2.7. Additional reasons for the premature discontinuation of study sites include, but are not limited to:

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

In the event of a pandemic disease outbreak (e.g., new COVID-19 public health emergency), it might not be feasible for a study site to continue study participation. In this scenario, consideration should be made as to whether the trial site closure would affect the safety and well-being of participating subjects. Additionally, consideration should be made around impact and maintenance of data validity.

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

10 STUDY DEVICE AND TREATMENT OF SUBJECTS

10.1 Description of Study Device

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10.2 Instructions for Use and Administration

BBL should be used in the IOH treatment region according to the information and instructions presented in Section 10.5. Additional information on product usage is provided in the BBL Instructions for Use (IFU) CCI

10.3 Methods of Assigning Subjects to Treatment Groups

Subjects who complete all screening assessments, meet all eligibility criteria, and are accepted for enrollment into the study will be assigned a randomization number. Treatment-group assignments will be made based on the randomization scheme (see Section 13.1).

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10.5 Study Treatment

All protocol-specific criteria for the administration of study treatment must be met and documented prior to administration of any study treatment. All device administrations will be performed on-site by the treating investigator. All treating investigators will be board-certified physicians who are trained and qualified in administering aesthetic treatments in the facial region, or more specifically, the IOHs.

Subjects will not be dispensed any investigational material. Any site or subject that is noncompliant with study-treatment procedures specified in the protocol may be discontinued from the study (see Sections 9.2.8 and 9.2.6.2, respectively).

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NOTE: In the event of a public health emergency, treatments may be halted or postponed.

10.5.1 Planned Treatment Regimen

10.5.1.1 IOH Treatment Region

BBL is to be deposited in the supraperiosteal plane. Injection volume will be recorded. CCI illustrates the IOH treatment region. The infraorbital treatment area is at the junction of the lower eyelid and midface where a volume deficit has formed. The area is bordered by the nasal sidewall medially, the temporal region of the bony orbit laterally, the bulk of the lower eyelid superiorly, and the superior aspect of the midface inferiorly.

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10.5.1.2 Treatment Administration Procedure

Each IOH of each subject will be treated until the treating investigator feels an optimal result is achieved, defined as "optimal aesthetic correction" for the implant in that subject; however, treatment is not to exceed the maximum allowable injection volume as specified in Section 10.5.1.2.6. Treating investigators will be trained on the MIHAS and instructed that when treating subjects, the minimal result to be achieved per IOH is optimal aesthetic correction or at least 1-point improvement on the MIHAS compared to baseline. The treating investigator will be responsible for reviewing whether the threshold for optimal aesthetic correction or at least 1-point MIHAS improvement of both IOHs, as assessed by the blinded evaluator 4 weeks post treatment, is met since the blinded evaluator will not have access to the subject's study records. If a touch-up is necessary, it will only be administered if there are no medical contraindications or existing AEs of concern, as determined by the treating investigator.

Subjects who achieve at least 1-point improvement from baseline on the MIHAS of both IOHs 4 weeks post treatment may have a touch-up injection on one or both IOH(s) to achieve optimal correction, at the discretion of the treating investigator and the subject.

Additionally, IOH treatments will be administered at a minimum of 30 minutes apart. Visual-function assessments must be performed 30 minutes after treatment of each IOH (see Section 11.2.2.2.1). The contralateral IOH should not be treated until the visual-function assessments are performed on the treated side, and no clinically significant changes are noted. Additionally, retinal photographs of both eyes will be taken 30 minutes after the last treatment is complete. If injecting only one IOH during the touch-up and/or retreatment visits, only the IOH side being injected will require visual-function assessments at 30 minutes after treatment.

The sections below provide additional administration instructions.

10.5.1.2.1 Assembly of Cannula and Needle

Assembly of Cannula

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

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

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4. Pull off the cannula guard to expose cannula CCI

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

Assembly of Needle

Prepare the syringes of BBL injectable implant and the injection needle(s) as described below:

1. To attach the 27G ½" needle to the syringe, open the needle packaging to expose the needle hub. Use only the 27G ½" needle provided with the clinical trial product. Remove the Luer-syringe cap from the distal end of the syringe prior to attaching the needle CCI

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2. 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 CCI

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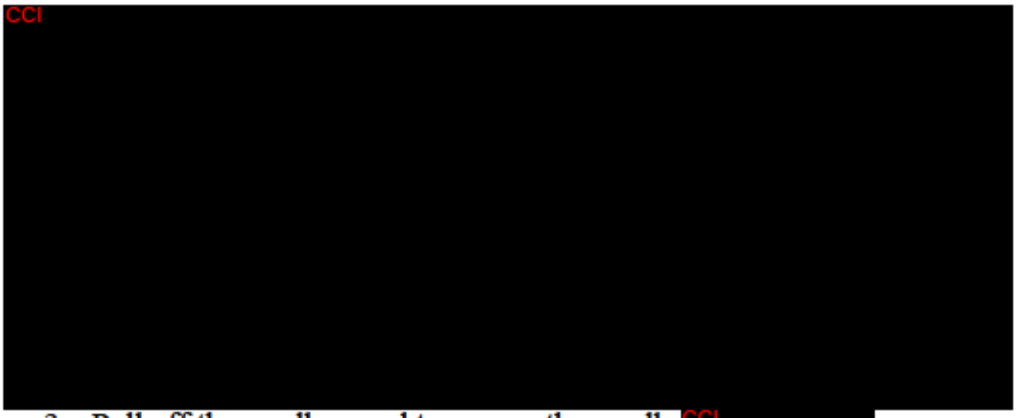

3. Pull off the needle guard to expose the needle CCI

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4. Prime the needle with BBL injectable implant.

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

10.5.1.2.2 Preparation of the Injection Region

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

10.5.1.2.3 Depth of Injection and Injection Technique

10.5.1.2.3.1 Cannula Technique

1. The cannula injection technique of BBL with regard to the angle and orientation of the bevel, the depth of injection, and the quantity administered may vary. Fewer injection points may be needed when a cannula is used rather than a needle. Insertion sites will typically be at the malar and zygomatic regions. For cannula insertion, a skin puncture should first be made at the desired insertion point using the provided introductory needle. The needle will be of slightly larger gauge than the cannula. After the introductory needle is withdrawn, the cannula is inserted through the skin puncture. Prior to each injection, the treating investigator will aspirate by pulling back gently on the plunger to confirm the cannula is not positioned intravascularly. Subsequently, a tunneling, fanning, or combination injection technique will be used to achieve optimal results. Care must be used to avoid intravascular injection regardless of technique used.
2. In general, when the introductory needle and then cannula are inserted, both will be parallel to the skin at an approximate angle of 30° or less. BBL will be placed at the junction of the lower eyelid and midface, along the inferior orbital rim in the supraperiosteal plane. The injection should be performed with a constant, low-to-moderate pressure on the plunger, while slowly and gradually withdrawing the cannula. Slight elevation of the skin should be observed without significant blanching of the skin. To avoid visible lumps and/or discoloration, avoid injection of BBL superficially when removing the cannula. When the injection is complete, the site may be gently massaged, if necessary.

3. The number of IOH injection locations and volumes (not to exceed the maximum allowable volumes, see Section 10.5.1.2.6) are at the discretion of the treating investigator until optimal results are achieved. Do not overcorrect.

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

Each subject must also be informed that, at any time over the study interval, if he/she experiences signs or symptoms of an intravascular event, similar to those noted above, or symptoms listed on the first page of the eDiary or within the ICF, he/she must seek immediate medical attention and notify the study physician immediately. The physician must refer the subject to a specialist if additional medical attention is deemed necessary.

10.5.1.2.3.2 Needle Technique

1. The needle injection technique of BBL with regard to the angle and orientation of the bevel, the depth of injection, and the quantity administered may vary, as in the cannula technique.
2. Needle injections will be performed at the junction of the lower eyelid and midface, along the inferior orbital rim in the supraperiosteal plane.
3. Prior to each injection, the treating investigator will aspirate by pulling back gently on the plunger to confirm the needle is not positioned intravascularly. The injection should be performed with a constant low-to-moderate pressure on the plunger, while slowly and gradually withdrawing the needle.
4. Linear threading (fanning) and serial puncture techniques, or a combination thereof, will be used to achieve the desired result. Minimizing the number of injection points may limit the degree of swelling and bruising.
5. Slight elevation of the skin should be observed without significant blanching of the skin. To avoid visible lumps and/or discoloration, avoid injection of BBL superficially when removing the needle.
6. When the injection is complete, the site may be gently massaged, if necessary.

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

Each subject must also be informed that, at any time over the study interval, if he/she experiences signs or symptoms of an intravascular event, similar to those noted above, or symptoms listed on the first page of the eDiary or within the ICF, he/she must seek immediate medical attention and notify the study physician immediately. The physician must refer the subject to a specialist if additional medical attention is deemed necessary.

10.5.1.2.4 Additional injection information

- If blanching occurs, the injection should be stopped and the area massaged until it returns to a normal color. Blanching may be a sign of a vascular occlusion. If normal skin coloring does not return, do not continue with the injection. Treat in accordance with the American Society for Dermatologic Surgery guidelines, which include possible hyaluronidase injection.[1]
- Correct to the desired volume effect. Do not overcorrect. The degree and duration of the correction depend on the character of the defect treated, the tissue stress at the implant site, the depth of the implant in the tissue, and the injection technique. Markedly indurated defects may be difficult to correct.
- Follow national, local, or institutional guidelines for use and disposal of medical sharp devices. To help avoid needle or cannula breakage, do not attempt to straighten a bent needle or cannula. Discard it and complete the procedure with a replacement needle from the clinical supply. Do not recap used needles and cannulas. Recapping by hand is a hazardous practice and should be avoided. Discard unshielded needles and cannulas in approved sharps containers.

10.5.1.2.5 Post-Treatment Care/Pain Management

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

10.5.1.2.6 Maximum Injection Volume per IOH

Total maximum volume for initial injection or delayed-treatment injection is 1.0 mL per IOH; total maximum volume for touch-up injection is 0.5 mL per IOH. Subjects may receive no more than 1.0 mL per IOH at retreatment. CCI Total volume administered **per IOH** for the study should not exceed 2.5 mL for the treatment groups (TN and TC) or 1.5 mL for the control/delayed-treatment groups (CDTN and CDTC).

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10.6 Previous and Concomitant Non-drug Therapies

Previous therapies received prior to enrollment and concomitant therapies should be documented in the eCRF.

Restrictions regarding prior or concomitant non-drug therapies are discussed in detail in Sections 9.2.2 (Exclusion Criteria) and 9.2.3 (Restrictions during the Study).

10.7 Study Supplies and Packaging of Treatment Supplies

BBL and study accessories (needle, cannula pack) will be provided by the sponsor. The sponsor will package study materials according to applicable regulatory requirements. The sponsor will provide all pertinent labeling information as well as a description of the specific device-packaging conditions.

BBL is to be used exclusively for treatment of subjects enrolled in this study and will be labeled as follows: "CAUTION - Investigational Device. Limited by Federal (or United States) Law to Investigational Use." Device labels will also note the manufacturer name and address, as well as the quantity within the package. The IFU for the investigational product will be provided CCI The clinical trial supply should be stored in a controlled area with limited access and stored separately from any commercial supplies.

The following components are supplied for the injection procedure:

- BBL box containing one sterile 1-mL prefilled glass syringe of BBL with two 27G ½" or 30G ½" needles.
  - More than one BBL box may be used depending on injection volume.
  - Use only the 27G ½" needles provided.
  - If subject is randomized to cannula, these needles should not be used.
- A peel-off subject label, indicating product, to be placed in the source documents.
- A separate bulk supply of 27G 40 millimeter (mm) blunt-tipped cannula, with a 25G introductory needle, will be provided for the cannula-injection procedure.

In the event of a pandemic disease outbreak (e.g., new COVID-19 public health emergency), considerations may be made to supply study sites with sufficient study supplies to avoid interruptions to the supply chain for the investigational product during the outbreak.

10.8 Receipt, Storage, Dispensing, and Return/Disposal

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

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

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

Any used syringes of investigational device and needles or cannulas should be discarded per the appropriate handling and disposal procedures at the site. Any unopened product, needles, cannulas, and/or outer packaging of used kits should be retained so the monitor can perform device-accountability procedures.

At the end of the study and after verification of study device accountability, it is the investigator's responsibility to return all unused study supplies, as directed by the sponsor. Appropriate records of return must be maintained for accountability purposes.

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

10.9 Device Accountability Procedures

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

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

- The date of receipt and quantity of units received.
- Identification of each IMD (batch number/serial number or unique code).
- The expiration date (if applicable).
- The names of all persons who received, used, or disposed of each device.
- The date(s) of use.
- Unique subject identification number.
- Date and quantity of units returned.
- The date of return of unused, expired, or malfunctioning IMDs (if applicable).

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

10.10 Treatment Compliance

Treatment is administered by the treating investigator and thus assessment of compliance is unnecessary. Potential deviations from the defined study-treatment administration will be reported as protocol deviations.

10.11 Duration of Study

The planned duration of participation for individual subjects from baseline to the end of the study is 76 weeks (± 14 days). In addition, subjects will also undergo a screening period up to 10 days and at least 3 days prior to the baseline 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 to 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.

11 STUDY PROCEDURES

11.1 Visit Schedule

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To determine subject eligibility for study participation, a screening evaluation must be completed from − 10 to − 3 days before baseline. Eligible subjects will be randomized at the screening visit.

After screening evaluation, each subject randomized to treatment will have between 10 and 14 visits, depending on whether he/she receives a touch-up and/or retreatment injection.

Subjects randomized to control will remain untreated until Week 8, when the primary effectiveness endpoint is evaluated. Upon completion of all effectiveness assessments, control subjects will be treated with BBL (i.e., will receive delayed treatment). After screening evaluation, each subject in the control/delayed-treatment group will have between 8 and 10 visits, depending on whether he/she receives a touch-up injection.

The primary endpoint visit will occur at Week 8 (+ 7 days) post last injection (i.e., initial injection or touch-up, if applicable) for the treatment group and at Week 8 (+7 days) after screening for the control/delayed-treatment group.

For subjects in the treatment group, the final visit will occur 72 weeks (± 14 days) post last injection (initial or touch-up, if applicable) or 24 weeks post retreatment (if applicable).

For subjects in the control/delayed-treatment, the final visit will occur 48 weeks (± 14 days) post last injection (initial or touch-up, if applicable).

11.2 Study Assessments and Definitions

11.2.1 Effectiveness Assessments

Refer to the respective endpoints (see Section 7.2.1) CCI [redacted] CCI [redacted] for additional information including the timing of effectiveness assessments.

11.2.1.1 Merz Infraorbital Hollow Assessment Scale (MIHAS)

The MIHAS was designed to assess the infraorbital hollow that results from volume loss. Each grade of the MIHAS is distinct; Grade 0 is anchored to depict none to minimal signs of hollowing, and Grade 4 is anchored to depict extreme signs of hollowing CCI [redacted]

In the current study, the MIHAS will be used to detect clinically relevant, aesthetic changes as a result of volume correction in the IOH area.

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 IOH region. The left and right IOH of each subject is assessed independently on the MIHAS within this study.

During the baseline and subsequent study visits, subjects will be evaluated live on the MIHAS 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 MIHAS 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 (pair-wise against other raters) 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. Evaluators will be re-trained on the MIHAS at regular intervals (approximately every 3 months at a minimum).

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

Additionally, three blinded IPRs will assess subject photographs using the MIHAS.

Note: For subjects randomized to treatment, the photographs assessed will be from Screening or Day 1 (Visit V1a) **and** 8 weeks post last injection (Visit V3). For subjects randomized to the control/delayed-treatment group, the photographs assessed will be from Screening, Day 1 (8 weeks from the screening visit, Visit C1a) and 8 weeks post last injection (Visit C3).

These board-certified IPRs, 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 subjects randomized to treatment, standardized photographs 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 treatment-group subjects presenting for treatment (Day 1). If a subject's screening photographs are deemed unsatisfactory by the central photography vendor, photographs will be retaken at Day 1 (prior to treatment). If no reshoot is needed,

the screening photograph will default to the baseline photograph 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.

For subjects randomized to control/delayed-treatment, in addition to the screening/baseline photographs, standardized photographs will be taken at the delayed treatment baseline before treatment is administered and at multiple intervals throughout the study.

Every effort should be made to have the same study personnel take photographs throughout the study; furthermore, the same photography conditions/environment must 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 Sections 11.2.1.3 and 11.2.1.4 for reference to the GAIS assessments) as well as for the IPRs assessment (see Section 11.2.1.1). 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 (GAIS)

The treating investigator will use the 7-point GAIS [redacted] to assess global aesthetic improvement of the IOHs by making comparisons between photographs taken at various post-treatment time points and pre-treatment photographs (see Section 11.2.1.2). The respective post-treatment photograph will be displayed side-by-side with the baseline photograph for the treating investigator to assess aesthetic improvement. For subjects receiving retreatment, the post-retreatment photograph will be compared to both the baseline photograph and the 48-week photograph (taken prior to retreatment). All treating-investigator GAIS ratings should be based on the current cosmetic result for both IOHs. Investigators will rate both IOHs concurrently and will be asked the following question: "Please rate the overall impression of post-treatment aesthetic change specific to the IOHs on photographs taken during the visit compared with the reference photograph. Select one rating that best applies."

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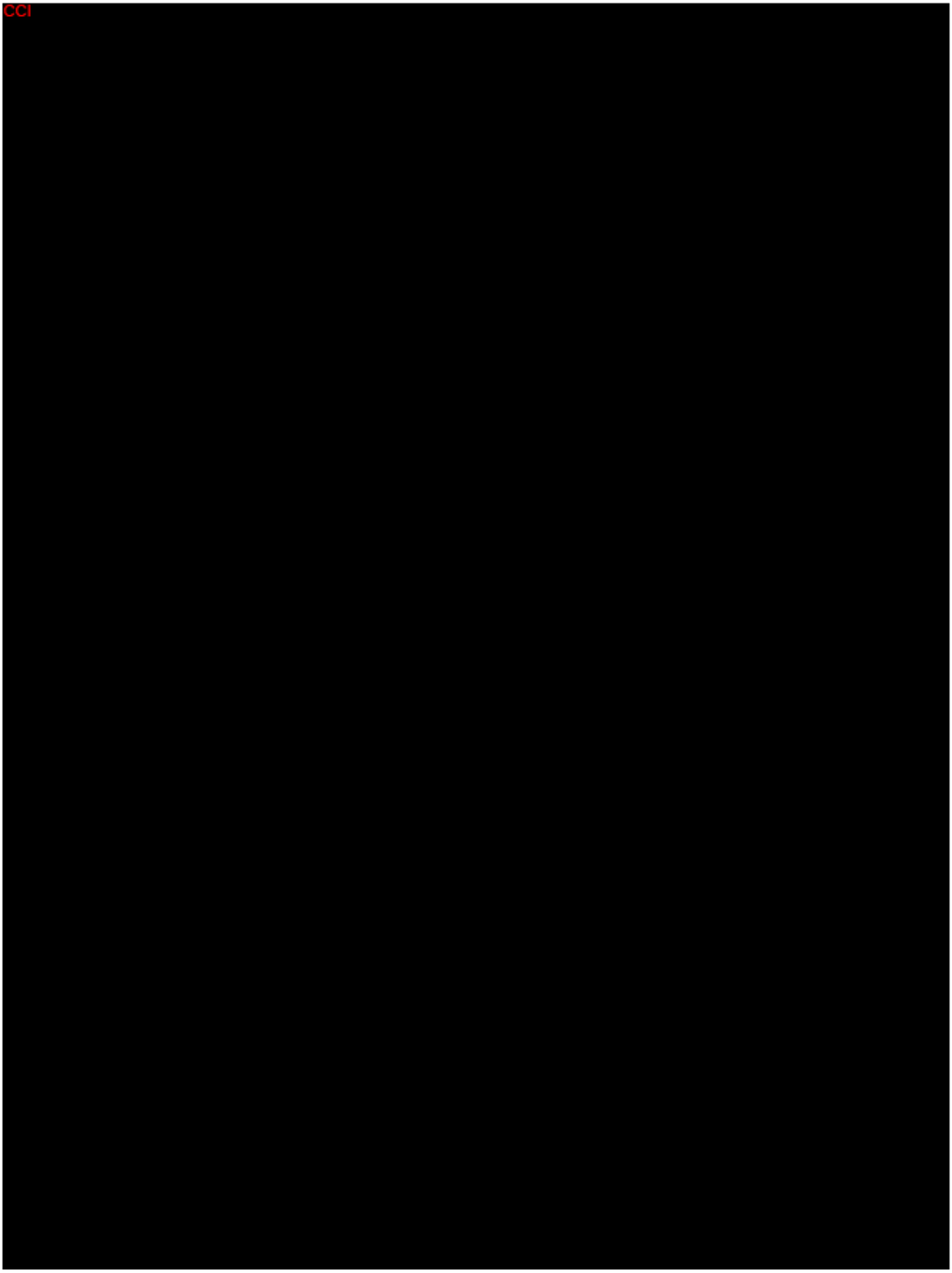

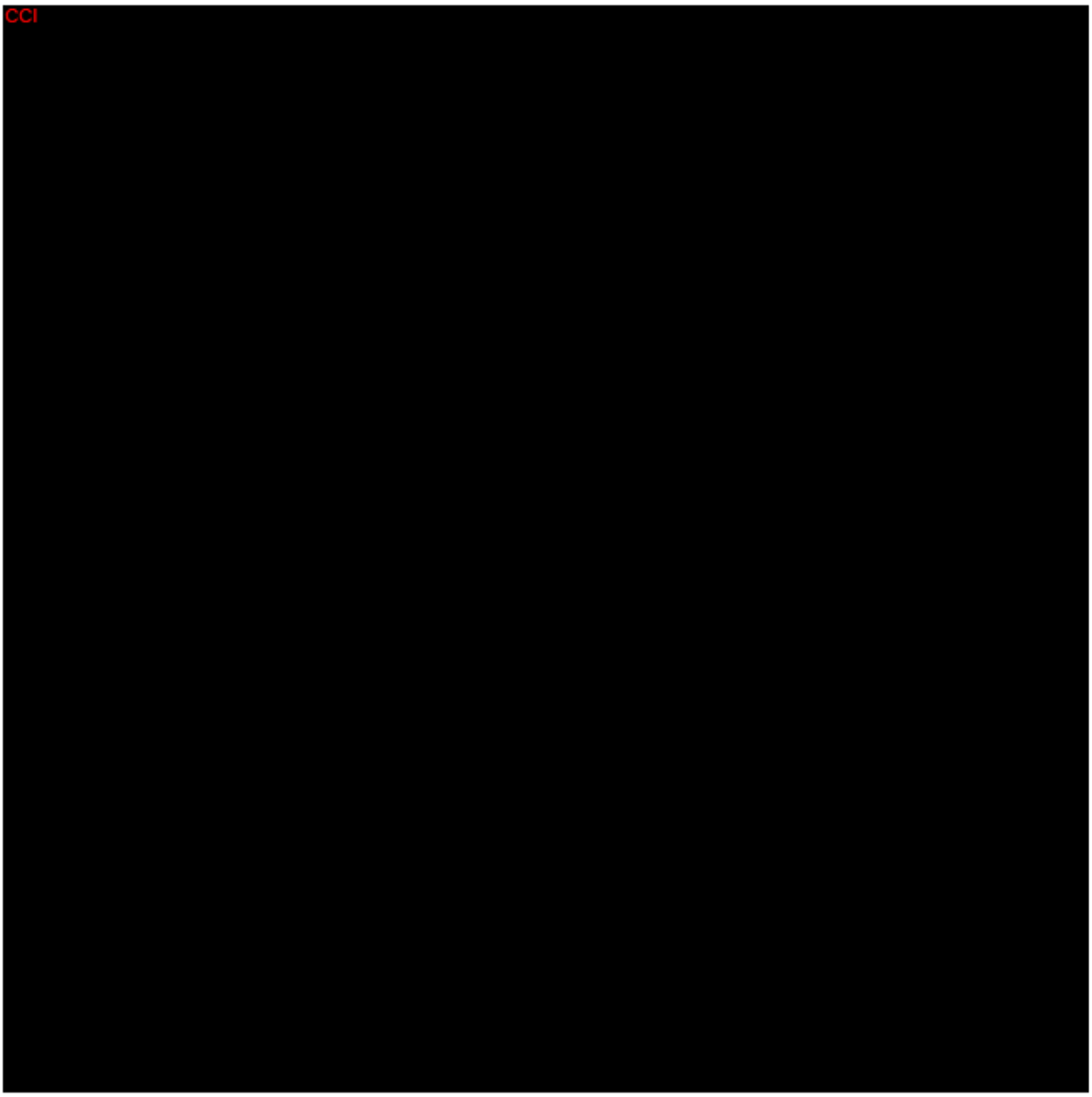
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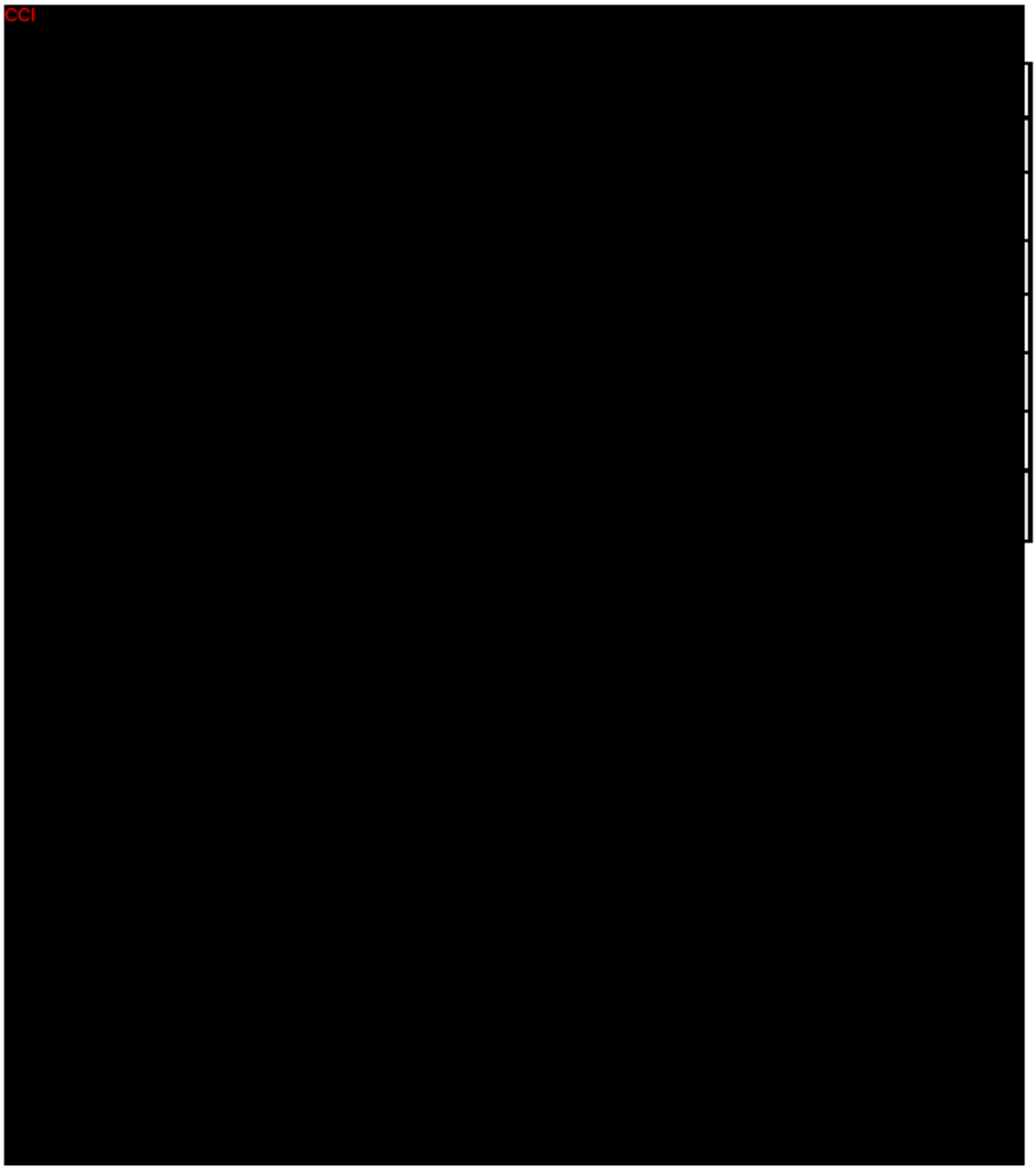

11.2.1.6 Pain Visual Analogue Scale (Pain VAS)

Pain will be assessed using a VAS.[2-4] This VAS includes 21-numbered circles at 0.5 cm increments, spanning 10 cm total, and is anchored by word descriptors CCI The overall level of pain will be evaluated 5 minutes post treatment taking into consideration both IOHs.

Subjects will be presented with the pain VAS and asked to circle the one (1) number that best describes their pain level post treatment.

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11.2.1.7 Likelihood of Retreatment Survey

At the end of study/early termination visit, all treated subjects will be asked: "How likely would you be to have future Belotero Balance with Lidocaine treatments in the infraorbital hollow (area under the eyes)? Please tick one box below"

CCI

If the subject responds "somewhat unlikely", "unlikely", "extremely unlikely", he/she will be asked for additional explanation as to why he/she is not likely to have future Belotero Balance with Lidocaine treatments in the IOH area.

11.2.2 Safety Assessments

Standard safety assessments, including documentation of AEs and SAEs reported by the investigator throughout the study, will be evaluated. Subjects will be followed for up until their end of study visit.

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

For safety definitions and additional information, please see Section 12.

11.2.2.1 Secondary Safety Assessments

11.2.2.1.1 Adverse Events (AEs)

All AEs reported by investigators or other study staff after the time of informed consent through the last study follow-up visit will be recorded. Events will be recorded regardless of causality. The period of observation for an AE extends from when the ICF is signed until the subject's last study visit. Additional information is provided in Section 12.1. Adverse events will be assessed at all on-site study visits and during follow-up telephone calls.

Any medical occurrence from the time the ICF is signed is an AE and must be documented in the subject's file and on the AE eCRF. Any AE observed will be fully investigated, documented, and followed until the event is either resolved or adequately explained, until the end of study/early termination visit.

In this study, any AE of visual disturbance will be reported (see Section 11.2.2.2.1). The investigator needs to report any AE of visual disturbance within 24 hours to the sponsor using the Report of Visual Disturbances Form (see Section 12.7).

11.2.2.1.2 Serious Adverse Events (SAEs)

All SAEs reported by investigators or other study staff after the time of informed consent through the last study follow-up visit will be recorded. Events will be recorded regardless of causality. Any SAE observed will be fully investigated, documented, and followed until the SAE is resolved or a plausible explanation is available. Serious AEs occurring after the end of the observational period need to be reported if the investigator considers the event to be related to the IMD. Additional information is provided in Section 12.2. Serious AEs will be assessed throughout the study, including on-site study visits and during follow-up telephone calls.

11.2.2.2 Other Safety Assessments

11.2.2.2.1 Visual-Function Assessments

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

Visual-function assessments will include a visual-acuity test (using a Snellen chart), a confrontation-visual field test, and an ocular-motility examination. 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), pre- and post-treatment for the delayed-treatment injections, and at all follow-up visits CCI The aforementioned visual safety assessments can be performed by the treating investigator or a trained delegate. 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.

In addition, undilated retinal photographs will be taken at the screening visit (pre-treatment), after initial treatment, after touch-up injection, if applicable, and at the optional retreatment visit before and after injection CCI Photographs will be captured using non-mydriatic retinal cameras and will be read by a central ophthalmic imaging center (central reader).

Any abnormality identified during the visual-function assessments at screening and/or before initial injection should be documented as medical history. Following the screening visit, if the central reader detects 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.

Visual-function assessments will be performed 30 minutes after treatment of each IOH. The contralateral IOH should not be treated until the visual-function assessments are performed on the treated side, and no clinically significant changes are noted. Additionally, retinal photographs of both eyes will be taken 30 minutes after completion of treatment of both IOHs.

An abnormality is defined as any parameter that is clinically significant in nature or a drop-in vision by one line or more. If any such abnormality is detected on the visual-function assessments at a treatment visit (initial injection, touch-up, retreatment), the subject will be referred to an ophthalmologist for further evaluation. In addition, the abnormality will be documented as an AE.

When the subject returns for the 2-week safety follow-up visit and all subsequent non-treatment visits, the visual-function assessments will be repeated, and the subject will be assessed for any changes that could indicate a safety concern. An abnormality is defined as any parameter that is clinically significant in nature or a drop-in vision by one line or more. If any such abnormality is detected on the visual-function assessments, retinal photographs will be taken and reviewed by the central reader. 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 in visual-function assessments vision change 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.

In this study, any AE of visual disturbance (including, but not limited to, any loss of vision, blurry vision, double vision, pain in or around eye [other than typical injection-induced pain], blind spot or shadow in the visual field, trouble moving eyes, etc.) will be reported. The investigator will be instructed to report any AE of visual disturbance within 24 hours to the sponsor using the Report of Visual Disturbances Form (see Section 12.7). 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.

CCI summarizes the schedule for visual assessments.

CCI

11.2.2.2.1.1 Visual Acuity

Visual acuity will be determined using the Snellen chart. Each site will be equipped with a Snellen chart. The lane and distance (10 feet) 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 he/she will be asked to keep them on/in). The examiner 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.

11.2.2.2.1.2 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 his/her vision, and if so, where the blinded spots are. The examination should be performed without the subject wearing glasses (note: contacts are permitted). To measure the visual field, the examiner will use the standard finger test according to the American Academy of Ophthalmology.

The subject will be asked to look directly at an object in front while covering one eye. The investigator or delegate will hold up different numbers of fingers in areas of the subject's peripheral-vision field and ask how many fingers he/she sees while looking at the target in front.

11.2.2.2.1.3 Ocular-Motility Exam

The examiner should determine if the subject's range of ocular movement 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 his/her 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. The subject should then be asked to follow the examiner's finger without the subject moving his/her head. The examiner should use his/her index finger on either the right or left hand for guiding the direction of eye movement. The investigator 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 he/she experiences double vision in any position of gaze and/or in any of the fields. The examiner should look for and document any asymmetry in ocular motility or abnormal ocular motility.

11.2.2.2.1.4 Undilated Central Retinal Exam Using a Non-mydriatic Retinal Camera

In this procedure, the treating investigator or delegate will take pictures of the undilated central retina and blood vessels using a non-mydriatic retinal camera system. Note: pictures must be taken without the subject wearing glasses or contacts. Subsequently, images will be uploaded and remotely evaluated by a specialist at a central ophthalmic imaging center. The investigational site will receive an assessment report from the central ophthalmic imaging center within 24 hours. If any retinal findings are noted, the site will contact the subject and the site-identified ophthalmology practice to arrange an immediate evaluation.

11.2.2.2.1.5 Directions for Intravascular Injection or Embolic Event

Each site will identify a local ophthalmology practice that is equipped and qualified to address any visual changes and a potential retinal artery occlusion that may occur as a result of injection (i.e., clinically significant changes in vision, such as blindness, blurriness, double vision, pain in or around the eye [other than typical injection-induced pain], blind spots, or restriction of eye motility).

In the event of intravascular injection or embolic event, the treating physician will provide prompt medical attention and follow the proper protocol in accordance with the American Society for Dermatologic Surgery guidelines.[1] If the injection is in progress, best practices should be used to stop the injection. The treating physician should consider the following: an immediate referral to the site-identified ophthalmology practice, injection of hyaluronidase (if applicable) in the anatomic area of treatment and/or retrobulbar, and consideration of active reduction of intraocular pressure. The investigator should treat in accordance with the American Society for Dermatologic Surgery guidelines.[1]

11.2.2.2.2 72-hour Post Treatment Phone Call

All subjects will receive a post-treatment phone call 72 hours (+ 1 day) after the initial treatment, after the touch-up treatment, if applicable, and/or after optional retreatment.

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

In addition, each subject will be asked if he/she experiences any new or unusual symptoms related to a potential vascular occlusion (e.g., signs of a stroke, changes in vision, tissue necrosis) as noted in the Study Information Guide for Subjects. If any other such symptoms related to a potential vascular occlusion are reported by the subject, he/she should be assessed, and referred for immediate medical treatment as deemed necessary per best medical practices. If any change in vision is reported during the 72-hour follow-up phone call, the subject may be referred immediately to the site-identified ophthalmology practice or a local emergency room (if the ophthalmology practice cannot be reached or is not available) for further evaluation.

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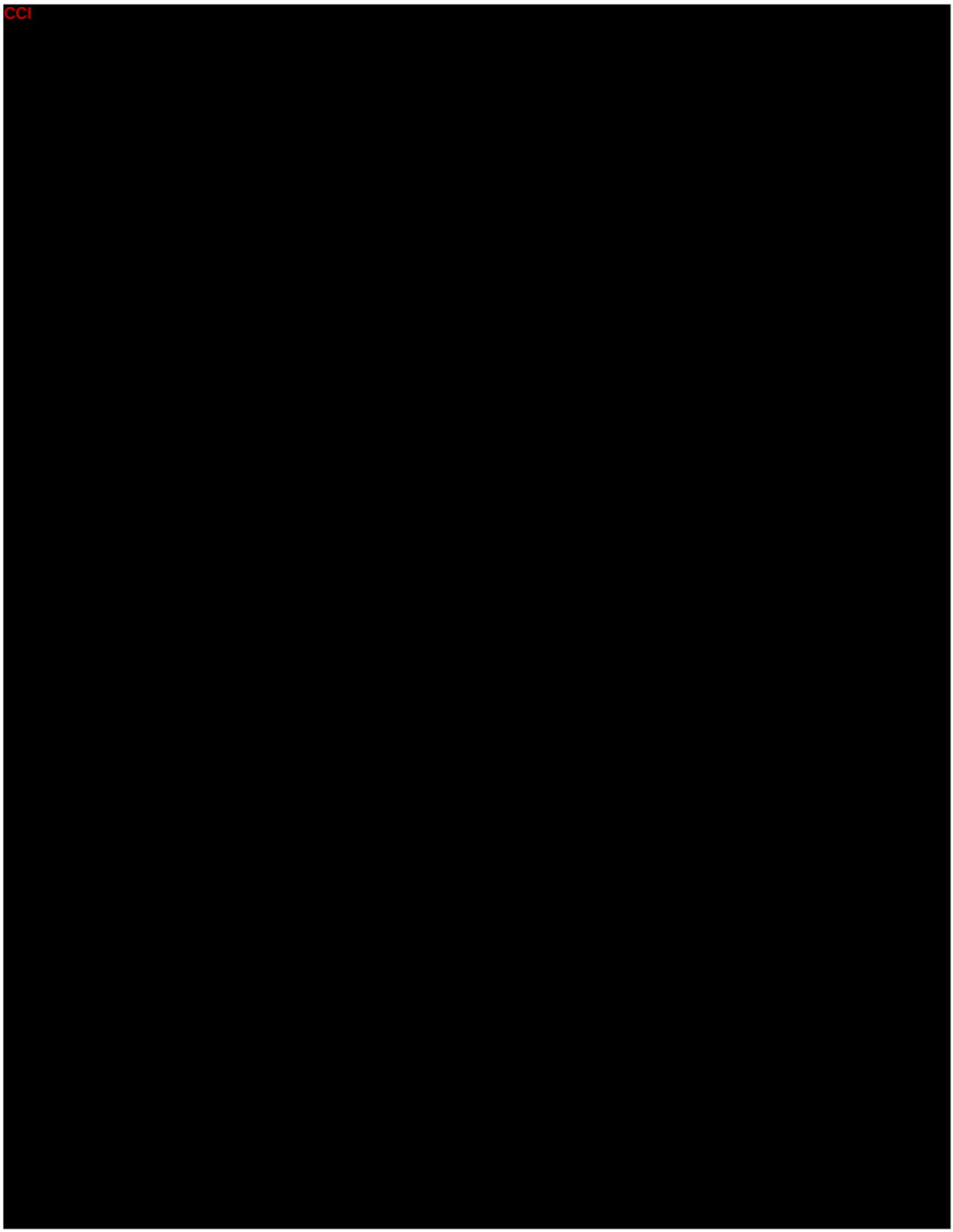

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11.2.3 Other Assessments

Data for other assessments will be collected as follows:

- Demographics and other baseline characteristics;
- Urine pregnancy tests (only if female subject is of childbearing potential);
- Injection volume at all injection visits (i.e., initial injection, delayed-treatment injection, touch-up, if applicable, and optional retreatment, if applicable);
- Injection technique, location, number of injection points, and injection plane;
- Medical history/concomitant diseases; and
- Previous and concomitant medications and non-drug treatments.

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11.3 Modifications to Study Procedures During a Pandemic

In the event of a pandemic disease outbreak, the study conduct may be affected. On-site visits may not be possible due to quarantines, site closures, travel limitations, interruptions to the supply chain for the investigational product, or other considerations. If site personnel or trial subjects become infected with SARS-CoV-2 (the virus that causes the illness known as COVID-19), visits should be conducted via phone or virtually to collect subject safety and effectiveness data (if possible) remotely.

The primary goal is to ensure the safety and well-being of subjects while efforts are made to ensure data integrity. Visit windows may be adjusted as follows:

- Prolong screening period to − 28 to − 3 days. In the event that quarantines, site closures, travel limitations will not allow subject on-site randomization within this time period, re-screening of subjects will be allowed based on easing of local and/or national restrictions.
- Expand the ± 7 day visit windows to ± 14 days.
- Expand the ± 14 day visit windows to ± 28 days.

Effectiveness assessments (i.e., GAIS assessments and FACE-Q) may be performed remotely, if feasible.

Forms for effectiveness assessments 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 back to the study site via mail or at the next possible visit.

Visual safety assessments cannot be conducted at post-treatment follow-up visits remotely. If subjects experience any changes in vision, they will be instructed to immediately contact the site-identified ophthalmology practice prior to contacting the site investigator. If 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.

12 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

12.1 Definition of an Adverse Event (AE)

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 investigational medical device (IMD).

Note:

1. This definition includes events related to the IMD.
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 IMD.

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 that happens between the time ICF is signed and the first treatment with the IMD 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, must be documented, treated, and followed like all other AEs.

Treatment-emergent adverse events (TEAEs) are defined as AEs with onset at or after the first administration of study treatment.

Pre-existing conditions 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 not regarded as AEs. However, elective procedures should be postponed, if possible, until the subject completes their participation in the study.

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 discovered in the course of examinations completed during the visit. The investigator will assess and record any AE

in detail in the subject file, and for all randomized subjects, on the AE eCRF. The following information must be recorded:

- AE diagnosis or main symptom;
- Location of AE: systemic or restricted to treatment area. If a local reaction, the corresponding area should be reported;
- Date of onset;
- Intensity (maximum observed; see Section 12.1.3);
- Causal relationship (not related, related; see Section 12.1.4);
- Serious (yes or no);
- Outcome (see Section 12.1.5);
- AE leading to discontinuation of the clinical study (yes or no);
- Action taken with medical device; and
- Stop date.

In cases of a serious adverse event (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 his/her 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 or the treatment procedure if a causal relationship between the IMD or the treatment procedure the 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" (Section 12.3). If the event is serious, it is a "serious adverse device effect" (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 (SAE)

An SAE is an adverse event that:

1. led to death;
2. led to serious deterioration in the health of the subject, that either resulted in:
   - a life-threatening illness or injury, or
   - a permanent impairment of a body structure or a body function, or
   - 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.
3. led to fetal distress, fetal death, or a congenital abnormality or birth defect.

Note: Planned hospitalization for a pre-existing condition, or a procedure required by the clinical study protocol, without serious deterioration in health, is not considered a serious adverse event.

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 12.5, that might have led to an SAE if:

1. suitable action had not been taken, or
2. intervention had not been made, or
3. 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 or not, must be reported via telephone, or e-mail and an SAE Report Form should be submitted to the sponsor within 24 hours of 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 is related to the SAE;
- An identifiable reporting source (investigator/study site identification); and/or
- An event or outcome that can be identified as serious.

The investigator must report SAEs to the sponsor as defined in Section 12.2 and the site's IEC/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, IECs/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-up only in the Global Product Safety database after final SAE reconciliation is completed.

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

The investigator should complete and send any SAE Report Forms or Pregnancy 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 (ADE)

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

Note:

1. This definition includes AEs resulting from insufficient or inadequate instructions for use, 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 (SADE)

A SADE is defined as an adverse device effect 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 serious adverse device effect 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 (UADE)

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 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.

12.6 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 product consistency, cracked vial).

Note: The term “technical complaint” is synonymous with the term “device deficiency”. The term device deficiency is used in this study.

12.6.1 Reporting and Handling of Device Deficiencies

All device deficiencies shall be documented and reported by the investigator throughout the clinical investigation and appropriately reported to 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. All device deficiencies shall be documented and reported by the investigator throughout the clinical investigation and appropriately reported to the sponsor. The investigator will attempt to evaluate if the device deficiency 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 (see Section 12.2.2) in addition to the Device Deficiency eCRF. SAE Report Forms should be sent to Merz Product Safety for processing (see 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 (e.g., Device Technical Complaint Form), instead of the eCRF, and send to the sponsor 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 or needle or cannula in question for future inspection and investigation by the sponsor, if necessary. The Merz Technical Complaint Department will decide if the device or needle or cannula in question need to be returned and to whom they should be sent for investigation.

12.7 Visual Safety Evaluation

Any adverse event of visual disturbance including, but not limited to, any loss of vision, blurry vision, double vision, pain in or around eye (i.e., other than typical injection-induced pain), blind spot or shadow in the visual field, trouble moving eyes, etc. will be reported. The investigator will be instructed to report any AE of visual disturbance within 24 hours to the sponsor using the Report of Visual Disturbances 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.

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12.9 Reporting of Pregnancy

Any pregnancy that starts during the clinical study must be reported, using the Pregnancy Report 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 Report Form. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous discontinuation; details of the birth; the presence or absence of any congenital abnormalities, birth defects, maternal or newborn complications, and their relation 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 (touch-up or retreatment); however, the subject will remain in the study.

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 finalized prior to database close.

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

Adequate descriptive statistics will be provided for each endpoint. Metric variables will be summarized by number of observations, mean, standard deviation, minimum, median, and maximum. Categorical variables will be summarized by frequencies and percentages per category where the denominator will be chosen according to the adequate analysis population. Ordered categorical data will be summarized by metric and categorical statistics, where appropriate. All variables will be analyzed as absolute data and as change from baseline, as applicable. Descriptive confidence limits (95%, two-sided) and descriptive p-values will be given, where appropriate.

All data captured in the eCRF will be listed.

In the event of a pandemic disease outbreak (e.g., new 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:

- Describe changes to planned and additional analyses due to the public health emergency. Thoroughly assess drop-out patterns and sources of bias such as missing values and virtual instead of live assessments (if applicable).
- Include systematic identification of protocol deviations due to the pandemic.
- Consider the need for involvement of an independent Data Monitoring Committee particularly if trial sample size changes are anticipated.

13.1 Randomization

Subjects who complete all screening assessments and meet all eligibility criteria will be randomized to the following four groups:

- Group TN: Treatment with BBL with needle at baseline;
- Group TC: Treatment with BBL with cannula at baseline;

- Group CDTN: Untreated control until Week 8 / Delayed-treatment BBL with needle (starting at Week 8);
- Group CDTC: Untreated control until Week 8 / Delayed-treatment BBL with cannula (starting at Week 8).

Randomization will be block-stratified by investigational site, and groups will be assigned via an electronic system linked to the eCRF. At each study site, the number of subjects randomized should not exceed 26 to ensure a reasonable distribution of subjects across all investigational sites.

13.2 Estimation of Sample Size

The primary effectiveness analysis considers the proportion of subjects with at least 1-point improvement on the MIHAS for both IOHs, as assessed by the blinded evaluator at Week 8 compared to baseline (see Section 7.2.1.1). For this analysis, subjects from TN and TC groups (Section 13.1) will be pooled into the Treatment Group (TRT), and subjects from CDTN and CDTC groups (data before any treatment) will be pooled into the Control Group (CTL).

A two-step hierarchical-testing procedure [CCI] Section 13.4.1.1) is foreseen for the primary analysis:

1. Treatment Group (TRT) shows a response rate of more than 50%, and
2. Treatment Group (TRT) is superior to the Control Group (CTL).

This hierarchical-testing procedure will keep the overall one-sided error rate of $\alpha = 0.025$, and no adjustment for multiplicity is necessary.

Sample size estimation is based on methods implemented for the binomial and Fisher's exact test. In this context it should be noted that the use of two-sided 95% Wilson confidence intervals (CI) and Newcombe CIs, instead of binomial and Fisher's exact tests later on, will deliver more efficient results (smaller CIs). The CI based methods have the advantage that they can be used for multiple imputation of missing data. Hence, sample size calculations are based on slightly more conservative test procedures, so that the determined power will also suffice for tests based on CIs.

Sample-size estimation for test Step 1 is performed with a one-sided binomial test at an error level of 2.5% to evaluate whether the response rate is significantly larger than 50%. It is aimed to ensure a power of 90%. The binomial test is conducted to the pooled data (TRT) from both treatment groups (TN and TC). Due to the allocation ratio of 2:2:1:1, the two treatment groups (TN and TC) will be approximately equally represented. Calculations for test Step 2 are performed with a one-sided Fisher's exact test for unequal n's, at an error

level of 2.5%, to detect a statistically significant difference between a response rate in Group TRT of 70% compared to 30% in Group CTL. A power of at least 90% is assumed.

Based on data from a pilot study in the same indication (M930121001) showing responder rates of above 80% for observed data and above 70% with missing data treated as no change from baseline (no response), a true responder rate of 70% for this pooled sample is assumed. Under these assumptions, a total of 80 subjects are needed to reach a power of at least 94% in test Step 1.

For test Step 2 and maintaining the assumption to have 70% response rate in the treatment group and 30% in the control group, a sample size of 80 subjects in Group TRT and 40 subjects in Group CTL will reach a power of at least 98% to demonstrate statistically different response rates between the groups [redacted]

To account for up to 20% drop-outs, 150 subjects will be randomized in this study (i.e., 50 subjects into each treatment group [TN and TC] and 25 subjects to each control group [CDTN and CDTC]). The conservative approach of this hierarchical-test procedure will have an overall power of above 92%.

If 150 subjects are treated, the sample size is sufficient to observe, with a probability of 80%, at least one AE with actual event probability of 1.1%.

Sample size calculations [redacted] were performed using nQuery software (Version 8, Statistical Solutions Ltd., 2017) [redacted] illustrates the two hierarchical-test steps for the primary effectiveness analysis.

13.3 Populations for Analysis

In addition to randomization groups (TN, TC, CDTN and CDTC; see Section 13.1), the following analysis groups will be defined for randomized subjects as follows:

- TRT: All subjects from TN and TC groups;
- CTL: All subjects from CDTN and CDTC groups with data until first treatment;

- DTN: Subset of subjects within CDTN with data collected from first treatment on;
- DTC: Subset of subjects within CDTC with data collected from first treatment on;
- DTRT: Delayed-treatment groups DTN and DTC will be pooled from CDTN and CDTC groups (Note: these subjects and their data until the first treatment will be part of the untreated CTL group);
- NED: Subjects that receive treatment with needle-injection technique will be pooled from TN and DTN groups;
- CAN: Subjects that receive treatment with cannula-injection technique will be pooled from TC and DTC groups; and
- TOTT: Subjects that receive treatment at any time during the study (TRT and DTRT) will be pooled from NED and CAN groups.

The following analysis sets will be defined for statistical analysis:

- The intent-to-treat$_{(1)}$ (ITT$_{(1)}$) population will include all randomized subjects of the untreated-control group (CTL) and all randomized and treated subjects of the treatment group (TRT).
- The intent-to-treat$_{(2)}$ (ITT$_{(2)}$) population will include all randomized and treated subjects of the treatment group (TRT) as well as all randomized and treated subjects of the delayed-treatment groups (DTRT).
- The Per Protocol (PP) population is a subset of subjects in the ITT$_{(1)}$ population without major protocol deviations. Final determination of what constitutes a major protocol deviation leading to exclusion from PP population will be made in a data review meeting prior to database close.
- The Safety population (SP) will consist of all subjects treated.

Subjects in analyses based on ITT and PP will be analyzed as randomized and subjects analyzed in the SP will be analyzed as treated.

13.4 Analysis of Study Data

Effectiveness and safety endpoints are provided in Sections 7.2.1 and 7.2.2.

13.4.1 Effectiveness Analyses

CCI illustrates the timepoints and the analysis groups to be used for the effectiveness analyses.

13.4.1.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint (Section 7.2.1.1) will be summarized as counts and percentages for the pooled treatment group (TRT) and the pooled control group (CTL).

Four hypothesis tests will be performed, based on the primary effectiveness endpoint. These tests will be evaluated in a sequential order on the $ITT_{(1)}$ population. To control for multiplicity, a hierarchical-testing procedure will be performed. Each test will hereby be performed at a one-sided α level of 0.025. The first two tests for the primary endpoint of treatment versus control will be confirmatory tests as outlined in CCI; if both null hypotheses are rejected, two additional tests will be performed, as subgroup analyses, to investigate the effectiveness of two injection techniques (i.e., needle and cannula).

CCI

Primary analyses

The first hypothesis test of the primary analysis evaluates whether the response rate in treated subjects from TRT is significantly larger than 50%. The second hypothesis test evaluates whether the response rate in treated subjects from TRT is higher than the response rate in untreated subjects from the control group CTL. Both hypotheses will be tested using the lower limits of the 95% CIs (two-sided), based on Wilson scores. The lower limit of the 95% Wilson CI must exceed the margin of 50% responder rate to reject Hypothesis 1 (H_{10}). The lower limit of the 95% Newcombe CI must be greater than zero to reject Hypothesis 2 (H_{20}).

Using the Wilson and Newcombe CIs in these tests will allow for imputation of missing values of the primary effectiveness endpoint with a multiple-imputation approach. This procedure will replace missing MIHAS values at Week 8 for the $ITT_{(1)}$ population.

SAS PROC MI will be used to create multiple sets with imputed MIHAS scores per group. Baseline MIHAS, Week 4 MIHAS, pooled site (for pooling details, see subgroup analyses below) and touch-up (yes/no) will be included in the multiple-imputation model. For each data set, the Wilson CI will be computed and later combined using SAS PROC MIANALYZE. Then, the limits of the two resulting combined Wilson CIs for TRT and

CTL will be used to compute the Newcombe CI for the responder rate difference between the groups.

CCI

Subgroup analyses

If both alternative hypotheses in the primary analysis are accepted, additional hypotheses testing will be performed to evaluate whether treatment with cannula-injection technique and treatment with needle-injection technique are superior over control as displayed in CCI test Steps 3 and 4.

Furthermore, response rates for TRT, CTL as well as the difference of response rates between TRT and CTL, including corresponding 95% CIs will be provided for the following subgroups: baseline MIHAS, gender, and Fitzpatrick Skin Type (I-III vs. IV-VI).

13.4.1.2 Secondary Effectiveness Endpoints

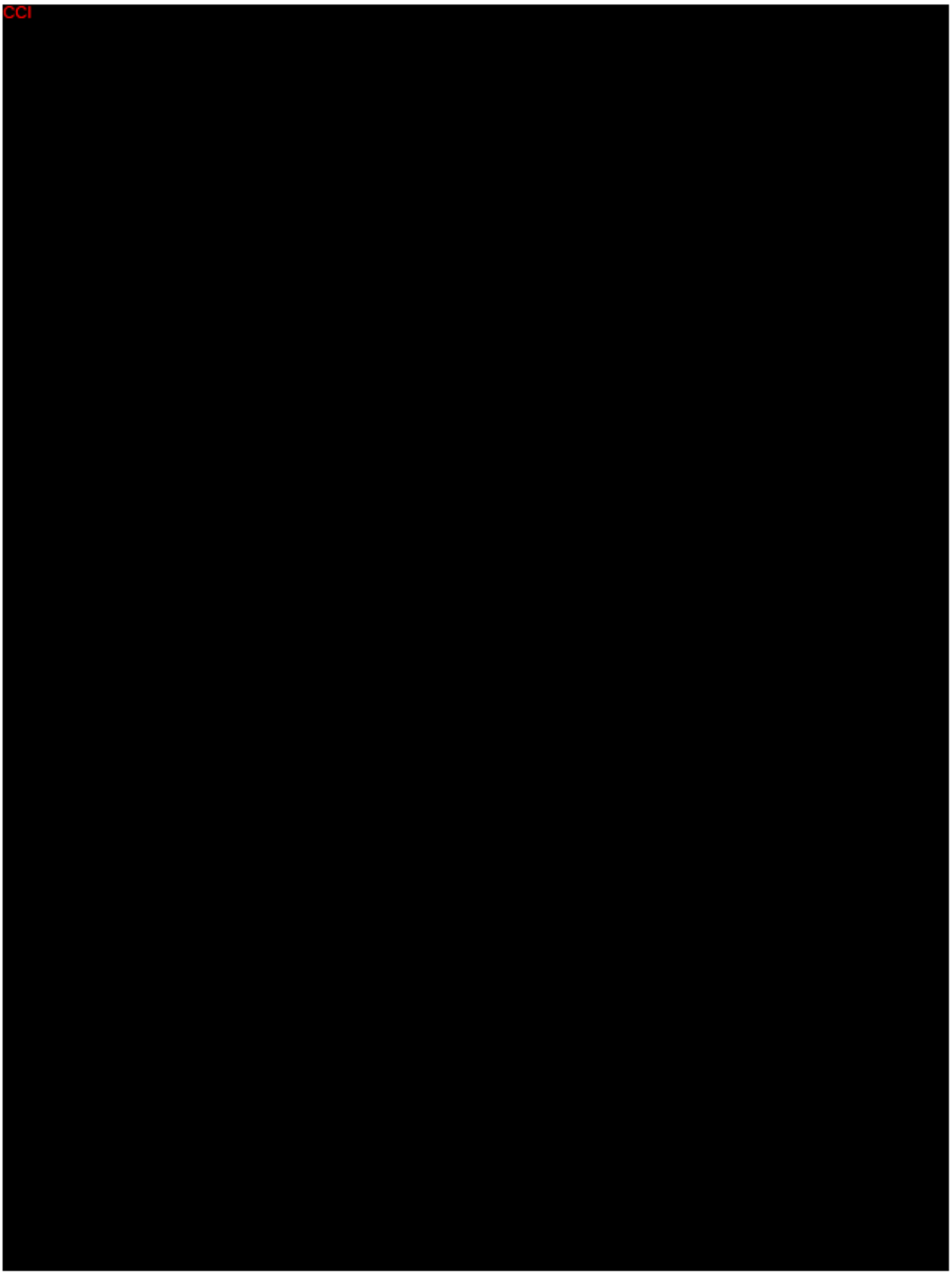
If not otherwise specified, secondary effectiveness analyses will be conducted based on observed cases for the $ITT_{(1)}$ and PP population for subjects of treatment groups TN and TC and of pooled treatment group TRT only.

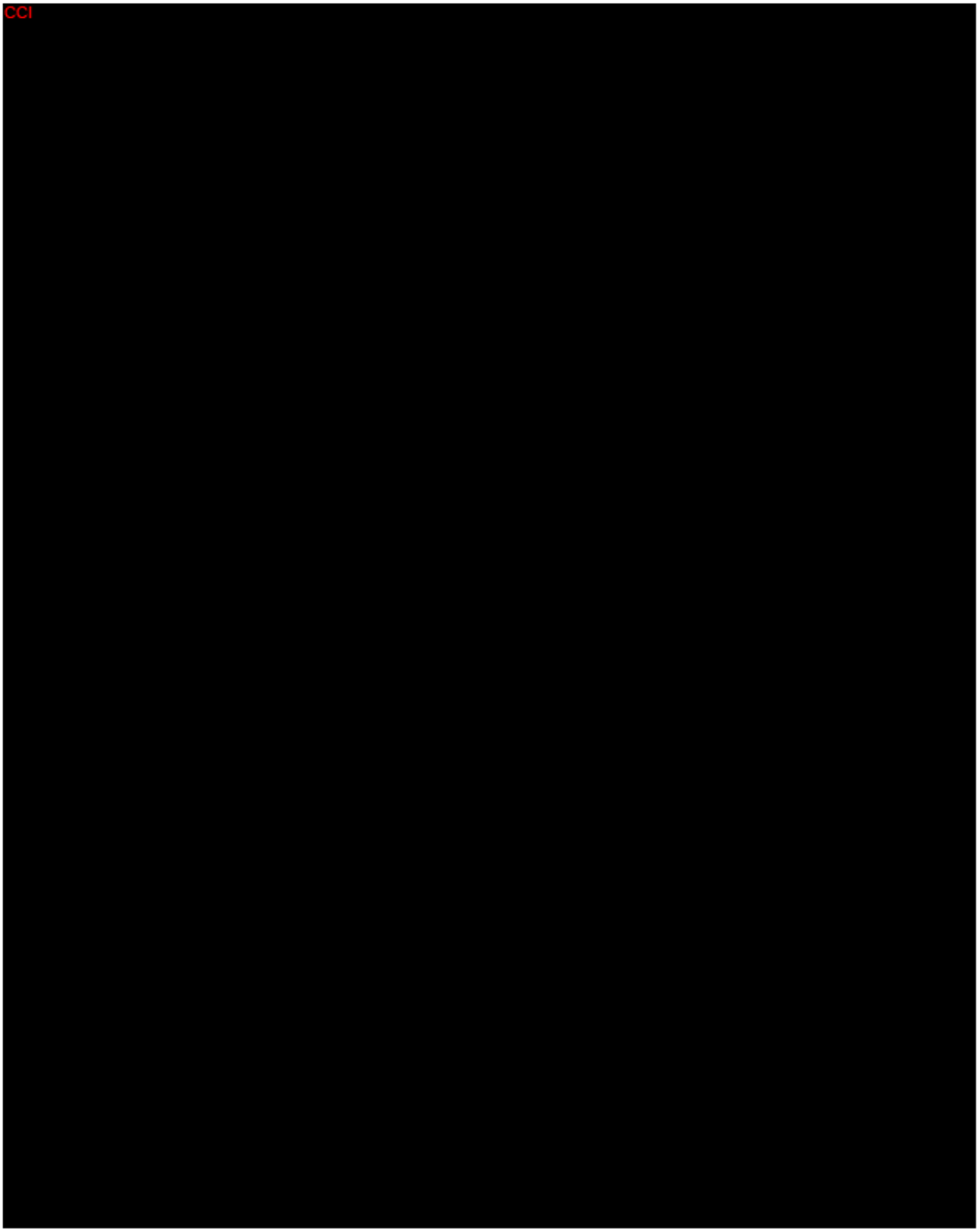
CCI

[redacted]

Subgroup analyses

In addition to the overall summary statistics defined above, summary statistics will also be provided for the same subgroups as analyzed for the primary effectiveness endpoint: baseline MIHAS, gender, and Fitzpatrick Skin Type (I-III vs. IV-VI).


CCI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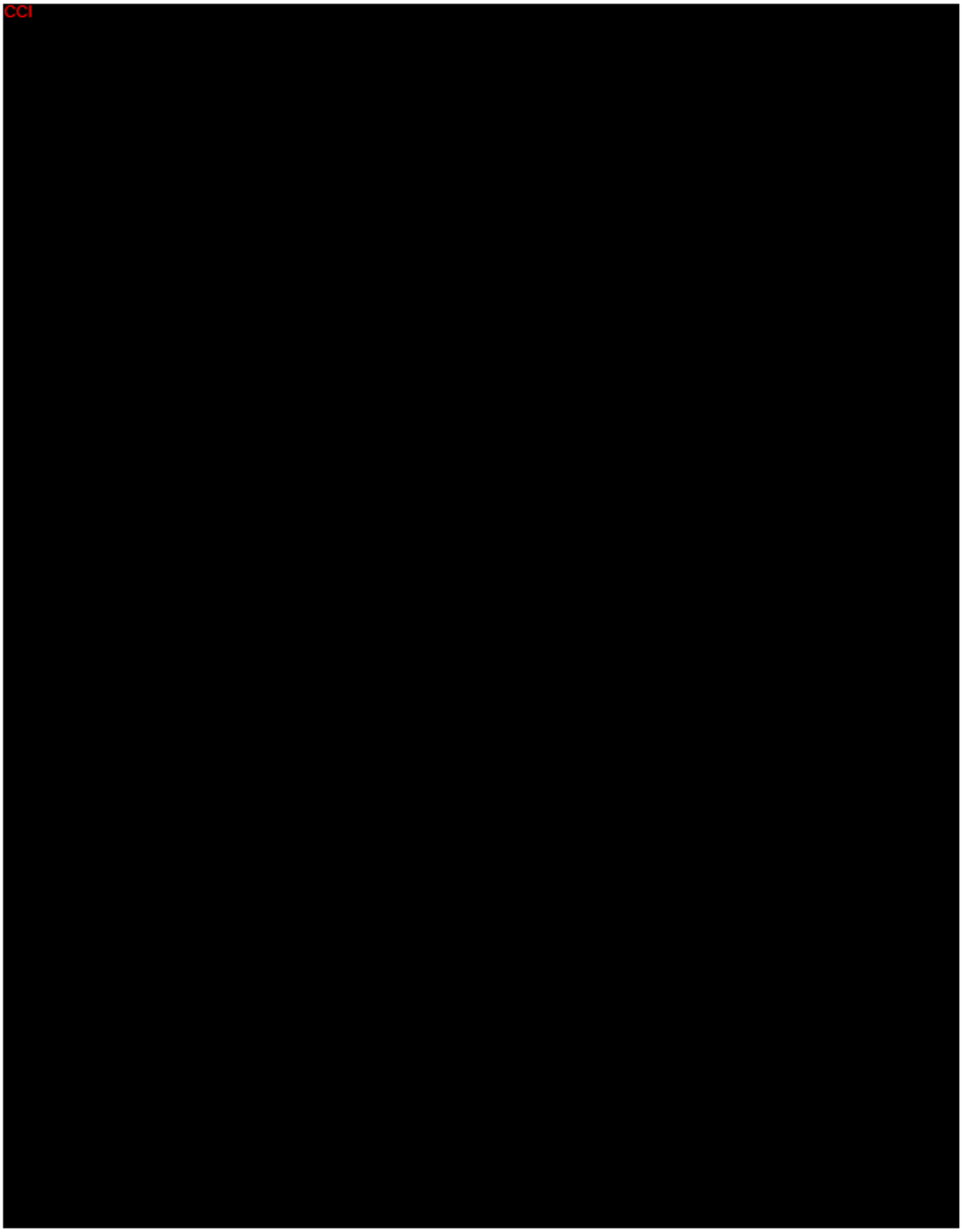

CCI

[redacted]

13.4.2 Safety Analyses

All safety endpoints will be summarized for observed values in the SP by injection technique (groups NED and CAN) and overall (TOTT), if not otherwise stated. Adverse events for the untreated control group (CTL) until Week 8, will be listed and summarized separately showing number of subjects with AEs and number of AEs by system organ class (SOC) and preferred term (PT).

All AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version in effect at the time the database is locked.

In the eCRF, AEs will be reported with their onset and further worsening, if required. For analysis, each documented worsening of an AE will be aggregated with the previous corresponding AE record. The start date of the AE will be the date of the record reporting the onset of the AE and the stop date will be the stop date of the last worsening records or ongoing, if not yet resolved. For seriousness, intensity, causal relationship, and outcome the worst attributes will be analyzed. All other AE attributes will be appropriately cumulated from all reported records.

There is one exception, where an aggregation with the previous record(s) is not allowed: if the previous AE record(s) started before the first treatment and the worsening record started (worsened) at or after date of first treatment. In this case, only the AE record(s) starting at or after treatment will be aggregated and regarded as treatment emergent adverse events (TEAE; see below).

TEAEs are defined as AEs with onset at or after the first administration of study treatment (Section 12.1.1). Only TEAEs and TESAEs will be analyzed. This will be done by

treatment cycle (see treatment cycles in Section 13.4.1.3). Hereby the following assignments will be made:

- For subjects of groups TN or TC, TEAEs will be grouped into two treatment cycles according to the AE onset date, as follows:
  - For subjects without retreatment:

    An AE is considered treatment emergent for **Cycle 1** if the start date of the AE is on or after the date of the initial treatment injection and before end of the study.
  - For subjects with retreatment:

    An AE is considered treatment emergent for **Cycle 1** if the start date of the AE is on or after the date of the initial injection and before the date of the retreatment.

    An AE is considered treatment emergent for **Cycle 2** if the start date of AE is on or after the date of the retreatment and before end of the study.
- For subjects of groups DTN and DTC, an AE is considered treatment emergent for **Cycle 1** if the start date is on or after the date of delayed treatment at Week 8.

All other AEs are considered to be non-TEAEs (i.e., all AEs with start date prior to initial injection).

An overall AE summary table will be provided by treatment cycle or overall as appropriate, displaying the following content:

- Any AEs;
- Any non-TEAEs;
- Any TEAEs;
- Any related TEAEs;
- Any TESAEs;
- Any related TESAEs;
- Any TEAEs leading to discontinuation from study; and/or
- Any TEAEs leading to discontinuation of study treatment.

For TEAEs, related TEAEs, TESAEs, and related TESAEs, number of subjects with TEAEs and number of TEAEs will be summarized by SOC and PT, by treatment cycle or overall as appropriate.

In addition, the following TEAE incidences will be shown by treatment cycle or overall as appropriate:

- TEAEs, number of subjects with TEAEs by PT;
- TEAEs by worst intensity, number of subjects with TEAEs by SOC and PT;
- TEAEs by worst causal relationship, number of subjects with TEAEs by SOC and PT;
- TEAEs by worst outcome, number of subjects with TEAEs by SOC and PT; and
- TEAEs by maximum duration, number of subjects with TEAEs by SOC and PT (duration categories: 1 to 3 days, 4 to 7 days, 8 to 14 days, 15 to 28 days, and > 28 days).

Duration of TEAEs will be calculated by the difference of start and stop date plus 1 day.

Moreover, the AE overview table as well as incidences of related TEAEs (by PT and SOC) will be provided for the following subgroups, by treatment cycle:

- Touch-up (yes/no) (applies to Cycle 1 only);
- Gender; and
- Fitzpatrick skin types (I, II, III and IV, V, VI).

Incidences, maximum duration, and maximum severity of CTRs will be summarized for the initial treatment as well as for its corresponding touch-up injection (if applicable), delayed treatment and its corresponding touch-up injection (if applicable), and retreatment (if applicable) for the single treatment groups TN, TC, DTC and DTN. Additionally, CTR data may be summarized (as applicable) by pooling the initial injection data from the TRT and DTRT groups and pooling the touch-up data from the TRT and DTRT groups. Maximum duration will be calculated as the difference between the first date of CTR reporting and the last date of CTR reporting plus 1 day. Additional rules for handling missing eDiary entries will be specified in the SAP. Maximum duration categories will be defined as follows: 1 to 3 days, 4 to 7 days, 8 to 14 days, and 15 to 28 days.

Listings for all AEs, as well as subsets including non TEAEs, AEs leading to discontinuation, SAEs, and deaths will be provided. Device deficiencies will also be listed.

13.4.3 Other Subject Data

All demographic, baseline characteristics, and subject disposition data will be presented using standard descriptive statistics. Demographic data will be summarized for all screened subjects and the SP, $ITT_{(1)}$, $ITT_{(2)}$, and PP populations. The remaining baseline data will be summarized descriptively only for the $ITT_{(1)}$, $ITT_{(2)}$, and PP populations, as applicable.

Subject disposition (i.e., number of subjects screened, randomized, and treated, as well as the number of subjects in each analysis population) will be summarized by various groups (i.e., TN, TC, TRT, CTL, DTN, DTC, DTRT, NED, CAN, TOTT). Additionally, the number of subjects expected at a visit and attended a visit will be summarized.

Frequencies of concomitant treatments will be given based on different Anatomical Therapeutic Chemical (ATC) Classification System code levels for the SP. Indications for concomitant therapies will not be coded and will only be listed.

Medical history and concomitant diseases will be coded using the MedDRA dictionary and reported by SOC and PT levels for the SP.

13.5 Special Statistical/ Analytical Issues

13.5.1 Subject Discontinuation and Missing Data

Methods intended for handling of missing primary effectiveness endpoint data are described in Section 13.4.1.1.

Handling of missing scores of FACE-Q Satisfaction with Eyes scores is described in Section 13.4.1.2. Handling of missing scores of FACE-Q Appraisal of Lower Eyelids is described in Section 13.4.1.3.

For remaining endpoints, observed cases will be analyzed, if not otherwise specified.

Additional rules for handling missing eDiary entries will be specified in the SAP.

13.5.2 Interim Analyses

No interim analyses are planned.

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

13.5.3 Other Planned or Subgroup Analyses

Subgroup analyses are described for the primary effectiveness endpoint in Section 13.4.1.1 and for the secondary effectiveness endpoints in Section 13.4.1.2.

Subgroup analyses for safety are described in Section 13.4.2.

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.
- 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).

In the event of a pandemic disease outbreak (e.g., new 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 IECs/IRBs are possible at any time, even after the end of the study. 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 IEC/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 are detailed in a separate photography user manual.

This study will be monitored regularly by a qualified monitor from the sponsor/CRO/or designee according to GCP guidelines and the respective SOPs (see Section 14.1).

14.2.2 Source Documentation Requirements

All data collected from a subject during the course of a clinical investigation should be retained in the respective source documentation (e.g., subject file). This includes a copy of the letter sent to the subject's primary physician about the subject's participation in the investigation (provided the subject has a primary physician and has agreed to the primary physician being informed). The source documentation must also contain a descriptive statement on the informed-consent procedure. The investigator must also confirm by written statement in the source documentation that all inclusion criteria and all exclusion criteria were checked prior to inclusion of the subject. In addition to this statement, the subject's meeting or non-meeting of the and eligibility criteria have to be traceable on the basis of the documentation in the subject's file. The childbearing potential of female subjects must be noted in the source documentation. The site will keep a source data location list, which will outline for the different (electronic) data categories (e.g., demographics, medical history, and adverse events, etc.) which document serves as source for these data (e.g., subject file, subject eDiary).

If an investigational site is using an electronic system for documenting source data, a member of the site staff must print out the source data after each visit. The paper print-outs must be overlapping, if possible (i.e., must contain at least the last row of data from the subject's previous visit). If it is not possible to obtain overlapping paper print-outs, the completeness of source data must be ensured by other suitable means. The print-out must be signed and dated by a member of the site staff who can confirm the accuracy and completeness of data in the paper print-out. The monitor should also sign and date after verifying the source data. The paper print-out should be stored in the Investigator Site File. If source data information is entered retrospectively, this must be done directly on the paper print-out and should be initialed and dated. The same applies to any corrections of initial data.

If the site is using a validated computer system including audit trail with an adequate access for the monitor (i.e., the monitor can only access the data of the investigation subjects), then no such paper print-outs are required. The monitor should perform spot-checks in the electronic system to confirm that the process of generating paper print-outs by site staff is comprehensive and reliable.

14.2.3 Data Management

Systems (e.g., eCRF, eDiary) used for electronic data capture fulfill all requirements from 21 CFR Part 11.

Data required for reporting according to this protocol are to be recorded in the web-based eCRFs, ClinCase, 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. By electronically signing the eCRF, the investigator will confirm that all investigations have been completed and conducted in compliance with the protocol.

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 site staff. The audit trail in the EDC system will document all changes. Edit checks generate automatic queries during data entry when applicable. Manual queries to be answered by site staff can be raised during source-data verification and/or during medical, safety, and/or data management review. After all data are entered and all queries are resolved, the database will be closed. If any data changes are required after database close, these changes will be documented according to the respective SOP. Further details of the data management process will be described in the data management plan.

Photographs will be archived by the central photography vendor in system separate from the database (see Section 14.3). eDiary data 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 Section 16.6.

In the event of a pandemic disease outbreak (e.g., new 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 study nurses, coordinators, and investigators.

- Depending on the content of data clarifications, the necessity for source data review will be assessed by the sponsor.
- Self-evident corrections of obvious query responses will be allowed. These will be documented thoroughly (e.g., using a list of self-evident corrections to be approved before Database Lock).
- If applicable, risk-based assessment of closing long open queries will be done considering their impact on trial conclusion and data validity.
- Assessment will be completed to determine if data clarifications and/or eCRF pages are to be signed by staff that is not yet on the delegation log. The delegation log is to be updated, if applicable.

14.2.4 Auditing

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

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

Study documents may not be destroyed by study-site personnel prior to the end of the required retention period as specified by local regulations. The 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 study protocol, study data, and information related the study or the sponsor's products or research programs are to be kept confidential and may not be disclosed without the consent of the sponsor. The investigators have the responsibility to provide complete study data, records, and reports for inspection by the appropriate regulatory authorities, the sponsor, or the IEC/IRB, as appropriate.

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

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 U.S. law. Study registration may include a list of study 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 (1) 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.

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

If an immediate deviation from the protocol is required to eliminate an immediate hazard to subjects, the investigator must contact the sponsor 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.

15 REFERENCE LIST

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4. Pincus T, Bergman M, Sokka T, Roth J, Swearingen C, Yazici Y. Visual analog scales in formats other than a 10 centimeter horizontal line to assess pain and other clinical data. J Rheumatol. 2008;35(8):1550-8.

16 APPENDICES