A randomized, evaluator-blinded, parallel group, no-treatment controlled, multi-center study to evaluate the safety and effectiveness of Restylane-L® for correction of Infraorbital Hollows

Study products: *Restylane-L*

Clinical trial number (CTN): 43USTT1904

Sponsor: Q-Med AB, a Galderma affiliate.
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Investigators and Study Administrative Structure

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Senior Medical Expert:	PPD
PPD :	
Sponsor's Clinical Project Manager:	PPD
Sponsor's Statistician:	PPD

Further details on all participating Investigators and the complete administrative structure of the study are found in the study files. Note that administrative changes are to be documented in the study files without requiring a Clinical Study Protocol (CSP) amendment.

Sponsor Signatures

The CSP is electronically signed in the document management system within the Q-Med AB quality management system by the representatives listed below.

PPD **, Galderma R&D, LLC**

PPD

Senior Medical Expert, Q-Med AB

PPD

Statistician, Q-Med AB

PPD

Clinical Project Manager, Galderma R&D, LLC

PPD

Signed Agreement of the Clinical Study Protocol

CTN:	43USTT1904
Title of the CSP:	A randomized, evaluator-blinded, parallel group, no-treatment controlled, multi-center study to evaluate the safety and effectiveness of *Restylane-L*® for correction of Infraorbital Hollows

We, the undersigned, have read and understand the CSP specified above, and agree on the contents. The CSP, the clinical trial agreement (CTA) and the additional information given in the Instructions for use (IFU) and Report of Prior Investigations (ROPI) will serve as a basis for co-operation in this study.

Principal Investigator

Printed name	Signature	Date

Study site

Synopsis

Title of study:	A randomized, evaluator-blinded, parallel group, no-treatment controlled, multi-center study to evaluate the safety and effectiveness of *Restylane-L*® for correction of Infraorbital Hollows
Clinical Trial Number:	43USTT1904
Study population:	Subjects over 21 years of age with moderate or severe Infraorbital Hollows and with the intent to undergo correction of both infraorbital hollows.
Countries involved:	United States
Number of sites:	Approximately 18 sites: approximately half of the sites using needle for injection and the other sites using cannula for injection.
Number of subjects:	Approximately 329 subjects will be included ([redacted]) to treatment (using needle or cannula) or to no treatment group. Approximately 9 sites will be treating subjects using needle and approximately 9 sites will be treating subjects using cannula. Within each site subjects will be randomized to treatment versus no treatment. At least 36 subjects will be Fitzpatrick skin type (FST) IV - VI, with at least 18 of those subjects with FST V – VI. The aim is for equal distribution of subjects for the above referred Fitzpatrick skin types between sites using needle versus cannula.
Study Design:	This is a prospective, randomized, evaluator-blinded, no-treatment controlled, parallel group, multi-center US study. In the treatment group approximately 146 subjects will get injections using needle and approximately 136 subjects using cannula. Approximately 47 subjects will be randomized to no-treatment at baseline. Effectiveness and safety data will be collected for 12 months following the first injection. At the month 12 visit, the no-treatment comparator subjects will be offered an optional *Restylane-L*® treatment. The subjects who received *Restylane-L* at the baseline visit will also be offered an optional additional treatment if optimal aesthetic improvement is not maintained (as determined by the Treating Investigator and subject). For subjects receiving optional treatment at month 12, the effectiveness and safety data will be collected for another 6 months. A subject will be involved in the study for up to 19 months, including 30-day screening period and 6-month follow-up after optional treatment at month 12. The study visits are illustrated in Figure 1.

Primary Effectiveness Objective and Endpoint:	The primary objective of the study is to evaluate the effectiveness of *Restylane-L* (injected using needle or cannula) versus no-treatment control in the correction of Infraorbital Hollows. Endpoint: Responder rate based on the Blinded Evaluators' live assessment of the Galderma Infraorbital Hollows Scale (GIHS), at 3 months after baseline. A responder is defined as a subject with at least 1 point improvement from baseline, on both sides of the face concurrently.
Secondary Effectiveness Objective(s) and Endpoint(s):	To evaluate the effectiveness of *Restylane-L* (injected using needle or cannula) versus no-treatment control in the correction of Infraorbital Hollows. Endpoints: 1. Responder rate based on the Blinded Evaluators' live assessment of the GIHS, at 6, 9, and 12 months after baseline and at 3 and 6 months after optional treatment. A responder is defined as a subject with at least 1 point improvement from baseline, on both sides of the face concurrently, at each of the timepoints. 2. Proportion of subjects having at least "Improved" on the Global Aesthetic Improvement Scale (GAIS), as assessed live by the Subject and Treating Investigator separately at all follow-up visits after baseline. CCI [redacted]
Safety Objectives and Endpoints:	To evaluate Adverse Events (AEs) at all visits, and pre-defined, expected post-treatment events reported during the first 28 days after each treatment as recorded in the subject diary.
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Clinical Study Duration:	The planned clinical study duration (from FSFV to LSLV) is approximately 23 months. One month is defined as 4 weeks in the study. The planned duration of recruitment (from FSFV to LSFV) is approximately 4 months.
Duration of Subject Participation:	Clinical study participation for each subject is approximately 19 months, including 30 days screening period and 6 months follow-up after optional treatment at month 12.
Inclusion criteria:	The subjects must meet all the following criteria to be eligible for the study: 1. Subject is willing to comply with the requirements of the study including being photographed, following post-treatment care instructions, completing the diary, attending all study visits and providing a signed written informed consent. 2. Moderate or severe (Grade 2 or 3 on the GIHS) infraorbital hollows with no more than one grade difference between the left and right side at baseline as assessed by the blinded evaluator. 3. Visual function assessment tests without findings according to treating investigator. 4. Males or non-pregnant, non-breastfeeding females, over the age of 21. 5. Subject is willing to abstain from any other facial plastic surgical or cosmetic procedure(s) during the duration of the study (e.g. laser or chemical resurfacing, needling, facelift, radiofrequency). 6. Intent to undergo correction of both orbital hollows. 7. If the subject is a female of childbearing potential, she agrees to use an acceptable form of effective birth control for the duration of the study and is willing to take a urine pregnancy test (UPT) at the screening/enrollment visit and prior to treatment. Acceptable forms of effective birth control include: a) Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical caps) with spermicidal foam/gel/film/cream/suppository. b) Bilateral tubal ligation. c) Combined oral contraceptives (estrogens and progesterone), implanted or injectable contraceptives on a stable dose for at least 28 days prior to Day 1. d) Hormonal or copper intra uterine device (IUD) inserted at least 28 days prior to Day 1.

	e) Vasectomized partner (in monogamous relationship) for at least 3 months prior to screening. f) Strict abstinence (at least one month prior to baseline and agrees to continue for the duration of the study or use acceptable form or birth control). 8. Negative urine pregnancy test for females of childbearing potential at screening and all injection visits.
Exclusion criteria:	The presence of any of the following exclusion criteria excluded a subject from enrollment in the study: 1. Known/previous allergy or hypersensitivity to any injectable hyaluronic acid (HA) gel or to gram positive bacterial proteins. 2. Known/previous allergy or hypersensitivity to local anesthetics, e.g. lidocaine or other amide-type anesthetics. 3. Active or a history of recurrent or chronic infraorbital edema or rosacea or uncontrolled severe seasonal allergies. 4. Previous or present multiple allergies or severe allergies, such as manifested by anaphylaxis or angioedema, or family history of these conditions. 5. Previous superficial facial dermal therapies (i.e. microderm abrasion, superficial chemical peels) to the periorbital or malar region within the past 6 months or plans to receive such treatment during participation in the study. 6. Previous deep facial dermal therapies (i.e. facial ablative or fractional laser, deep chemical peels, non-invasive skin-tightening [e.g. Ultherapy, Thermage]) to the periorbital or malar region within the past 12 months or plans to receive such treatment during participation in the study. 7. Prior lower-eyelid surgery, including orbital or midface surgery, or has a permanent implant or fat grafting or fat injections in the mid-facial region or tattoo (including microblading of eyebrow or eyeliner) that could interfere with effectiveness assessments or plans to have it during the study. 8. Lower lid retraction or exophthalmos. 9. Pigmentation abnormalities around the eyes and/or dark circles under the eyes due to pigmentation changes and not from infraorbital hollow shadowing. 10. Ectropium, entropion, or trichiasis of the lower eyelid or eye diseases that lead to reddening and tendency of watering of the eye. 11. Has gained or lost $\geqslant$ 2 body mass index (BMI) units within the previous 90 days or has the intention to gain or lose a significant amount of weight during the study. 12. Received lower **periorbital and/or malar** region treatments with any absorbable or temporary fillers such as porcine-based collagen fillers, HA products, RADIESSE®, poly L-lactic acid (PLLA) or received mesotherapy treatment to the area within the past 24 months or plans to receive such treatments during participation in the study. 13. Received neurotoxin treatment to the periorbital region, Forehead Lines (FL), Lateral Canthal Lines (LCL) or glabella, within the past 6 months or plans to receive such treatment during participation in the study.

	14. Any current or history of uncontrolled retinal disease or detached retina or any other condition with the potential to cause a decline of visual acuity (e.g. uncontrolled diabetes). 15. Tendency to accumulate eyelid edema, has developed festoons, or has large and/or herniating infraorbital fat pads. 16. Skin or fat atrophy, other than age-related, in the mid-facial and/or perio-orbicular regions or has been diagnosed with a connective tissue disorder. 17. Skin laxity or sun damage beyond typical for the subject's age. 18. A history of recurrent herpetic eruption in the mid-facial region, excluding the lips, within 12 months. 19. Subjects typically experiencing occasional migraines (≥ 8 per year). 20. History of radiation damage, cancerous or pre-cancerous lesions (e.g. actinic keratosis) near the area close to be treated. 21. Scars or deformities, active skin disease, inflammation, or related conditions such as infection, perioral dermatitis, seborrheic dermatitis, eczema, rosacea, acne, psoriasis, and herpes zoster near or in the area to be treated. 22. Subjects with dental or oral status on visual inspection that, in the opinion of the Investigator, would make the subject unsuitable for inclusion, or Subjects with dental, oral or sinus surgery within past 12 months prior to the treatment visit or planned surgery, including dental implants, tooth extractions, orthodontia, during the study period. 23. Inflammation, active or chronic (e.g. in the mouth, dentals, head and neck region). 24. History of or active autoimmune disease or connective tissue diseases such as systemic lupus erythematosus, rheumatoid arthritis, polymyositis, dermatomyositis, or localized or systemic scleroderma. 25. Tendency to form keloids, hypertrophic scars, or any other healing disorder. 26. History of bleeding disorders or treatment with anticoagulants or inhibitors of platelet aggregation e.g. aspirin or other non-steroid anti-inflammatory drugs (NSAIDs), Omega-3, or vitamin E within 2 weeks before treatment. 27. Treatment with chemotherapy, immunosuppressive agents, immunomodulatory therapy (e.g., monoclonal antibodies, antiviral treatment for HIV or hepatitis); systemic or topical (facial) corticosteroids within 3 months before treatment (inhaled corticoids are allowed). 28. Any prescription skin-irritating topical preparations, or pigmenting agents (e.g., self-tanning or bleaching agents) in the periorbital area within the past 2 weeks. 29. Concomitant treatment with prescribed topical (facial) retinoids within 3 months, or systemic retinoids within 6 months before treatment,or plan to receive such treatment during participation in the study. 30. Any medical condition that in the opinion of the Investigator would make the subject unsuitable for inclusion (e.g., porphyria, methemoglobinemia, hemoglobinopathy, thalassemia, glucose-6-phoshate dehydrogenase deficiency, a chronic, relapsing or hereditary disease that may affect the general condition or may require frequent

	medical treatment, any abnormal screening laboratory value or ECG, or psychiatric disorders). 31. Women who are pregnant or breast feeding, or women of childbearing potential who are not practicing adequate contraception or planning to become pregnant during the study period. 32. Study site personnel, close relatives of the study site personnel (e.g. parents, children, siblings, or spouse), employees, or close relatives of employees at the Sponsor Company. 33. Participation in any other clinical study within 30 days before treatment.
Investigational product:	*Restylane-L* 0.5 mL syringe, co-packed 29G x ½" Thin Wall (TW) needle, or commercially available TSK Steriglide 25G x 1½" and TSK Steriglide 27G x 1½" cannulas. The co-packed needle should be used as incision needle with each cannula. The sterilized gel contains 20mg/mL stabilized HA and 3 mg/mL lidocaine hydrochloride in a physiological buffer.
Reference therapy:	No treatment control group
Treatment regimen and location of treated area:	One treatment at baseline and one optional touch-up treatment at 1 month. Subjects who received Restylane-L at the baseline visit will be offered an optional additional treatment at month 12 if optimal aesthetic improvement was not maintained (as determined by the Treating Investigator and subject). The no-treatment comparator subjects will also be offered an optional Restylane-L treatment at 12 months. Detailed information regarding the injection procedure, pre- and post-treatment care and patients instructions are provided in the IFU. Restylane-L will be placed at the junction of the lower eyelid and midface along the inferior orbital rim in the supraperiosteal plane. The injection technique is at the discretion of the Investigator. For needle serial puncture is recommended and for cannula fanning technique is recommended. Slow injection is recommended and overcorrection should be avoided. Approximately half of the sites will be selected to use needle for injection and the other sites will use cannula. Allowed maximum injection volume for initial injection, touch-up, and optional treatment is 1,0 mL per side at each treatment session. Prior to injection, Vision Function Assessment tests including the Visual Snellen visual acuity test, Extraocular muscle function test and Confrontation visual field, will be assessed by the treating investigator.
Effectiveness Assessment(s):	• Blinded evaluator GIHS • Treating Investigator GIHS • Treating Investigator GAIS • Subject reported GAIS CCI [redacted]
Safety Assessment(s):	Adverse Event reporting: AEs will be obtained from signs and symptoms reported by the subject or detected during each examination. Device deficiencies will be assessed at treatment visits.

	All incidences of visual disturbances, regardless of relationship to study product or seriousness, are considered Adverse Events of Special Interest (AESIs) and include but are not limited to the following: any change in vision, any loss of vision, blurry vision, double vision, pain in or around the eye, blind spot or shadow in the visual field, trouble moving eyes, any change in Snellen visual acuity including change of one line or greater. Vision Function Assessment tests will be performed prior to and 30 minutes post injection of the study product. A subject diary will be dispensed to all subjects for daily completion over the first 28 days after each treatment to record the following pre-identified symptoms: bruising, redness, pain, tenderness, lumps/bumps, itching, swelling. Any other symptoms outside the pre-identified should also be recorded in the diary. The diary will also include instructions for the subject to: • Contact an eye doctor (retinal specialist or ophthalmologist) if they experience changes in vision (i.e. vision loss, blurriness, double vision, pain in or around eye, blindness, blind spots, problems moving your eyes), change in skin color, or crusty/scabby skin around the eyelids • Call 911 and seek immediate medical attention if signs of stroke or subject experience dizziness, confusion, weakness, or numbness in face, arms or legs, changes to consciousness or alertness, difficulty speaking/speech impairment, face droop <u>Stopping rules</u> Enrollment and treatment in the study will be temporarily halted if an SAE occurs for a vascular embolic event that leads to skin necrosis, vision loss, or stroke, and is determined by the Investigator to be directly or possibly related to the investigational device or injection procedure. The SAE will be investigated by the Sponsor.
Statistical Methods:	<u>Analysis populations:</u> • Modified Intention-to-treat (mITT) population includes all subjects who are randomized and will be analyzed according to the randomization scheme; subjects with a GIHS month 3 assessment via a remote visit will be excluded from the mITT • Intention-to-treat (ITT) population will include all subjects who are randomized and will be analyzed according to the randomization scheme • Per-protocol (PP) population will include all subjects in ITT who complete 3 months after baseline visit without any deviations considered to have substantial impact on the primary effectiveness outcome • Safety population will include all subjects who were treated with *Restylane-L* or randomized to the control group, and will be analyzed according to as-treated principle <u>Primary effectiveness analysis:</u> Responder rate based on the GIHS, as assessed live by the Blinded Evaluator at Month 3 after baseline, will be the primary effectiveness endpoint. A responder will be defined as a subject with at least 1 point improvement from baseline on both sides of the face concurrently. For a significant result, the two-sided p-value of the comparison of responder rates between the treated and untreated subjects at Month 3, using the Cochran-Mantel-Haenszel (CMH) test stratified by injection tool, must be smaller than 0.05. The null hypothesis will be that there is no relationship between responder rate and treatment group (i.e. the responder rate is the same in both groups). The

alternative hypothesis will be that there is a relationship between responder rate and treatment group (i.e. the responder rate is different in the two groups).

The estimates of the responder rate in each treatment group will be presented as well as the difference in responder rates. Corresponding confidence intervals for responder rates and the difference in responder rates along with the p-value for the difference will also be presented.

Secondary effectiveness CCI :
Responder rates (defined as at least 1 point improvement from baseline on both sides of the face concurrently) based on the GIHS as assessed by the Blinded Evaluator at month 6, 9, and 12 after baseline and at 3 and 6 months after optional treatment will be analyzed in the same way as the primary effectiveness endpoint. No correction for multiplicity will be done; p-values obtained for any endpoint other than the primary will only be provided for ease of interpretation of the results.

All other secondary effectiveness analyses will be done descriptively, as appropriate.

Safety analysis will be descriptive only.

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Handling of drop-outs and missing data
Number of missing values will be summarized and reported as appropriate.
For mITT analysis of the Blinded Evaluator GIHS responder rate at month 3 after baseline (primary endpoint), CCI Impact of missing data on the primary endpoint will be evaluated by performing sensitivity analysis based on the baseline observation carried forward (BOCF) method, and the observed cases in the ITT set.

All other effectiveness endpoints will be evaluated based on the observed cases in ITT.

Descriptive statistics of all safety data will be performed on observed cases in the Safety population.

Sample size
Due to the public health emergency related to the COVID-19 pandemic during 2020, steps have been taken to ensure patient and practitioner safety in alignment with FDA Guidance dated May 11, 2020 (Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency). Most notably, in partnership with clinical sites and the IRB, optional remote assessment procedures for efficacy and safety endpoints has been implemented to ensure safety and respect localized and elective restrictions. Therefore, the sample size has been increased during the conduct of the study to ensure a

	sufficient number of subjects in the mITT population used in the assessment of the primary effectiveness endpoint. The study was initially planned to enroll a total sample size of approximately 238 subjects; approximately 204 randomized to treatment with Restylane-L (~102 injected using needle, and ~102 injected using cannula) and approximately 34 randomized to no treatment. Based on information on missing data and the number of remote visits performed at study sites so far, the study is now planned to enroll approximately 329 subjects; approximately 282 will be randomized to treatment with Restylane-L (~146 will be injected using needle, and ~136 will be injected using cannula) and approximately 47 will be randomized to no treatment in order to achieve the required number of mITT subjects in each stratum. <u>Previous data</u> Since the primary endpoint will be based on a new scale, no existing data is available.
	CCI [redacted]

Abbreviations and Definitions of Terms

AE	Adverse Event
AESI	Adverse Events of Special Interest
Blinded evaluator	An evaluator responsible for independent evaluation of treatment result(s). The evaluator must not be involved in the treatment of the subject.
CFR	Code of Federal Regulations
Childbearing Potential	A female (including pre-menopausal subjects) capable of becoming pregnant; this includes women on oral, injectable, or mechanical contraception or women whose male partners have been vasectomized or are utilizing mechanical contraceptive devices
CMH test	Cochran-Mantel-Haenszel test
CRO	Contract research organization
CSP	Clinical Study Protocol
CTA	Clinical trial agreement
CTN	Clinical trial number
CV	Curriculum vitae
Device deficiency	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance (includes malfunctions, use errors, and inadequate labelling)
DMP	Data management plan
eCRF	Electronic case report form
EOS	End of Study
ET	Early termination
FDA	United States Food and Drug Administration
FL	Forehead Lines
FSFV	First Subject First Visit, i.e. first subject who signs the informed consent form
FST	Fitzpatrick Skin Type
G	Gauge
GAIS	Global Aesthetic Improvement Scale
GCP	Good clinical practice
GDPR	General Data Protection Regulation
GIHS	Galderma Infraorbital Hollows Scale
TW	Thin walled (needles)
HA	Hyaluronic acid
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form

ICH	International Conference on Harmonization
IFU	Instructions for use
Investigational product	Medical device being assessed for safety or performance in a study. “Investigational product” is the same as “study device”, “investigational device”, or “investigational medical device.”
Institution	Any public or private entity or agency or medical or dental facility where a clinical study is conducted.
Investigator	The Principal Investigator (PI) or other qualified person, i.e. sub-Investigator, designated and supervised by the PI at a study site to perform critical study-related procedures or to make important study-related decisions as specified on the signature and delegation log
Investigator file	Essential documents relating to a clinical study as defined in applicable GCP guidance document and maintained by the Investigator.
CCI	[redacted]
IRB	Institutional review board
ISO	International Organization for Standardization
ITT	Intention-to-treat
LCL	Lateral Canthal Lines
LSFV	Last Subject First Visit
LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
NSAID	Non-steroidal anti-inflammatory drugs
PI	Principal Investigator; qualified person responsible for conducting the study at a study site
PP	Per protocol
PT	Preferred term
QA	Quality assurance
RA	Regulatory authority
Reference product	Medical device, therapy (e.g. active control), placebo or no treatment, used in the reference group in a study
ROPI	Report of Prior Investigations, i.e. compilation of the current clinical and non-clinical information on the investigational product, relevant to the clinical study
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDV	Source data verification
SEC	Self-evident change
SOC	System organ class

Sponsor file	Essential documents relating to a clinical study as defined in applicable GCP guidance document and maintained by the Sponsor.
Study files	The Investigator file and the Sponsor file
Study products	The investigational product and the reference product under study
Study site	Institution or site where the study is carried out
TC	Telephone Call
Touch-up	Repeated injection to be performed after treatment, if necessary to achieve optimal correction
Tx	Treatment
U-HCG	Urinary human chorionic gonadotropin
WHO	World Health Organization

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1. Ethical Considerations

1.1 Statement of ethical compliance

The study shall be conducted in compliance with the clinical trial agreement (CTA), the Clinical Study Protocol (CSP), good clinical practice (GCP), and applicable regional or national regulations. The study shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (1964, and its amendments in force at the initiation of the study) insofar as such revisions are consistent with US treaty obligations and in accordance with US law.

The study shall follow the international standard for clinical study of medical devices for human subjects, ISO14155:2011 as applicable for US regulations and the International Conference on Harmonization (ICH) guideline for GCP (E6) as applicable for medical device.

1.2 Application to institutional review board; IRB and/or regulatory authorities

It is the responsibility of the Principal Investigator (PI) to obtain approval of the CSP/CSP amendment(s) from the institutional review board (IRB). The study shall not begin until the required favorable opinion from the IRB has been obtained. The PI shall file all correspondence with the IRB in the Investigator file and copies of IRB approvals shall be forwarded to the Sponsor. Any additional requirements imposed by the IRB or regulatory authorities (RA) shall be followed.

The study requires application for approval from the US Food and Drug Administration (FDA). The study will not be started until the Sponsor has received written approval or until the statutory waiting period from the appropriate authority has elapsed. The Sponsor will provide the PI with a copy of the relevant document.

The collection, access to, processing, and transfer of protected health information or sensitive personal data shall be carried out in accordance with applicable rules and regulations.

2. Background Information

2.1 Indication and population description

Restylane-L is in this study intended for correction of infraorbital hollows in subjects over the age of 21.

The study will include at least 36 subjects with Fitzpatrick Skin Types (FST) IV-VI with at least 18 of those subjects with FST V-VI.

2.2 Study Product Profile

2.2.1 Investigational product description

The currently marketed *Restylane-L* 0,5 mL syringes will be used in the study. For injection either needle or cannula will be used.

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2.2.1.2 Clinical documentation

Please refer to the *Restylane-L* study-specific Instructions for Use (IFU) which summarizes the Adverse Events (AEs) experienced with HA injections along with precautions that can minimize these potential complications**.**

For intravascular complications or embolic event, the treating physician should provide prompt medical attention and follow relevant clinical practice guidelines [1] for handling these symptoms. The treating physician should also review the Intravascular Treatment Protocol provided separately in the Investigator file, as a supportive tool.

Please refer to the study ROPI for a description of performed clinical studies and clinical data from literature with *Restylane-L* in the periorbital area.

2.2.2 Reference product description

Not applicable. The reference in this study is a no-treatment control.

2.3 Study rationale and justification for design

A result of the aging process is development of noticeable concave deformity in the area under the eyes, resulting in a tired and noticeable aged appearance of the face. Although many anatomical and physiological contributing factors must be considered for the cause of infraorbital hollowing, subjects with an inherent level of volume loss may benefit from filler augmentation treatment of the infraorbital hollows.

The rationale of performing this study is to obtain evidence of safety and effectiveness of *Restylane-L* for correction of infraorbital hollows to support a future US marketing application.

The Galderma Infraorbital Hollows Scale (GIHS) was created to allow for a quantitative assessment of the infraorbital hollow area in clinical trials. In order for the GIHS to be considered a reliable and valid tool for assessing aesthetic improvements, live subjects were rated by an independent panel review at two sessions separated at least two weeks apart in order to assess the intra- and inter-rater reliability. Based on the validation results GIHS was determined to be fit-for-purpose to be used in the clinical setting to detect changes to treatment by improving the level of hollowing as a result of volume correction.

The purpose of this study is to evaluate the effectiveness of *Restylane-L* in the treatment for correction of infraorbital hollows by demonstrating superiority in responder rates (defined as at least 1 point improvement from baseline on the Galderma Infraorbital Hollows Scale (GIHS)) relative to no treatment. No treatment has been chosen as control as there are no other HA products approved in the US for the same intended use.

[1] Alam M, Gladstone H, Kramer EM, et al. ASDS guidelines of care: injectable fillers. Dermatol Surg. 2008; 34 (suppl 1): S115-S148.

The study will also assure that *Restylane-L* used in the infraorbital hollows will not impact the safety of the product in an ethnically diverse population by including at least 36 subjects with FST IV, V, or VI with at least 18 of those subjects with FST V-VI.

2.4 Risks and benefits

Restylane-L has been proven safe and well tolerated in animal studies as well as in human clinical trials, with high levels of aesthetic improvement and sustained optimal correction of moderate to severe, deep facial wrinkles and fold such as nasolabial folds and for lip augmentation in patients over the age of 21 . The safety or effectiveness of *Restylane* and *Restylane-L* for the treatment of anatomic regions nasolabial folds and lips have been established in controlled clinical studies.

The primary benefit of the study is a perceived improvement of the treated area. Infraorbital Hollows is a major concern for many individuals seeking periorbital rejuvenation. Prominent Infraorbital Hollows gives a fatigued appearance despite adequate rest, and is refractory to attempts at cosmetic concealment. *Restylane-L* is less invasive than surgical options and offers less down time from swelling and bruising, adding volume in the Infraorbital Hollows to improve the patient satisfaction and restoring the harmony of the periorbital area.

As all other injectable medical devices, *Restylane-L* has the potential to cause complications. Most events are related to the injection volume and injection technique, though some could be associated with properties or constitutes of the gel itself. After the injection with *Restylane-L*, some common injection-related reactions might occur, such as swelling, erythema, tenderness, pain, bruising, and itching. These reactions consist mainly of short-term minor or moderate symptoms starting early after treatment that generally resolve spontaneously within one to two weeks after injection. The intensity and duration of these events are usually considered tolerable by a majority of subjects.

Although most AEs occur within days to weeks following the implant procedure, some AEs such as swelling and serious infections/abscess have been reported several weeks to months after the injection. Vascular occlusion resulting in ischemia/necrosis and visual disturbances including blindness have been reported following injection of any soft tissue filler in the face especially in the nose, glabella, periorbital areas, nasolabial folds and cheek, with a time to onset ranging from immediate to a few weeks following injection. Vascular compromise may occur due to an inadvertent intravascular injection or as a result of vascular compression associated with implantation of any injectable product. This may manifest as blanching, discoloration, necrosis or ulceration at the implant site or in the area supplied by the blood vessels affected; or rarely as ischemic events in other organs due to embolisation. Isolated rare cases of ischemic events affecting the eye (leading to visual loss) and the brain (resulting in cerebral infarction) following facial aesthetic treatments have been reported. Reported treatments included anticoagulant, epinephrine, aspirin, hyaluronidase, steroid treatment, analgesics, antibiotics, local wound care, drainage, surgery and hyperbaric oxygen. Outcome of the events ranged from resolved to ongoing at the time of last contact. In many of the events requiring medical intervention, the patient was injected into the highly vascularized areas of the glabella, nose, and periorbital area.

According to published literature AEs are mostly described as injection site reactions minor such as including some degree of bruising, erythema, local swelling, contour irregularity, and color change.

Post-market surveillance reporting with device location defined as *Tear trough* alone or in combination with other locations (cheek, glabella, nasolabial folds, jaw lines, temple, eye lid,

or oral commission) are generally in line with the overall reporting pattern for *Restylane*. To date, no unacceptable risks have been identified for *Restylane-L* treatment. Any potential concerns related to the clinical study have been assessed and the remaining risks are disclosed in the study specific IFU.

Lidocaine can, in rare cases, give allergic reactions, and therefore subjects with known allergy or hypersensitivity to local anesthetics should not be included in the study.

Additional information about reported AEs and anticipated risks are included in the product specific IFUs and ROPI.

To mitigate these risks, only study Investigators qualified by education and experience, and who are skilled in the use of dermal fillers from their clinical practice and involvement in clinical research, and with a firm knowledge of the vascular anatomy and understanding of the depth and plane of injection as well as knowledge of the signs and symptoms and management of potential complications will be chosen in order to assure proper device implantation and management of study risk. Visual function assessments will be performed before and after gel injection; an Intravascular Treatment Protocol is available for reference would an intravascular event occur; and the subject diary includes instructions in case of severe intravascular events. The study protocol also defines a stopping rule, see section 8.5.8.

Based on the open-label clinical studies sponsored by the company as well as published literature and spontaneously reported Adverse Events from the market, it is concluded that there is reasonable assurance from a safety perspective for conducting an IDE clinical trial in the USA, using *Restylane-L* for injection into the infraorbital hollow (tear trough) area in subjects over the age of 21.

Given the anticipated low level of transient and acceptable AEs in connection with the injection, the protocol required safety assessments, and the training being provided on the injection technique, it was determined the risk-benefit assessment for use of *Restylane-L* for correction of infraorbital hollows offer a clinical benefit at reasonable risk.

3. Objective(s) and Endpoint(s)

3.1 Objectives and endpoints

3.1.1 Primary objective and endpoint

The primary objective of the study is to evaluate the effectiveness of *Restylane-L* (injected using needle or cannula) versus no-treatment control in the correction of Infraorbital Hollows.

Endpoint: Responder rate based on the Blinded Evaluators' live assessment of the Galderma Infraorbital Hollows Scale (GIHS), at 3 months after baseline.

A responder is defined as a subject with at least 1 point improvement from baseline, on both sides of the face concurrently.

3.1.2 Secondary objectives and endpoints

The secondary objectives are to evaluate the effectiveness of *Restylane-L* (injected using needle or cannula) versus no-treatment control in the correction of Infraorbital Hollows.

Endpoints:

1. Responder rate based on the Blinded Evaluators' live assessment of the GIHS, at 6, 9, and 12 months after baseline and at 3 and 6 months after optional treatment.

   A responder is defined as a subject with at least 1 point improvement from baseline, on both sides of the face concurrently, at each of the timepoints.

2. Proportion of subjects having at least "Improved" on the Global Aesthetic Improvement Scale (GAIS), as assessed live by the Subject and Treating Investigator separately at all follow-up visits after baseline.

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3.1.3 Safety objectives and endpoints

The safety objectives and endpoints are:

- To evaluate AEs at all visits, and pre-defined, expected post-treatment events reported during the first 28 days after treatment as recorded in the subject diary.

4. Design of the Study

4.1 General outline

This is a prospective, randomized, evaluator-blinded, no-treatment controlled, parallel group, multi-center US study to evaluate the effectiveness and safety of *Restylane-L* for correction of Infraorbital Hollows. Approximately 329 subjects will be included (CCI) to treatment (using needle or cannula) or to no treatment group. In the treatment group approximately 146 subjects will get injections using needle and approximately 136 subjects using cannula. Approximately 47 subjects will be randomized to no-treatment at baseline. The sites will be selected to use either needle or cannula for injection of all subjects randomized to treatment at their particular site. Approximately half of the sites will be using needle and the other using cannula for injection.

All randomized subjects' will have a GIHS score of 2 (Moderate) or 3 (Severe) with no more than one grade difference between the left and right side at baseline.

Investigator blinding will be accomplished by using a Treating Investigator to administer the treatments and a Blinded Evaluator, to whom randomization and treatment are concealed, to conduct the blinded assessments. In addition, the Blinded Evaluator should not be allowed to retrieve study supplies or be present during the opening of the study supplies or injection procedure. All documents with information regarding study products and randomization assignment should be kept in a separate binder not available to the Blinded Evaluator. Safety assessments will be performed by non-blinded personnel.

Eligible subjects randomized to receive treatment will be injected by the Treating Investigator at Day 1. Optional touch-up treatment may be administered after 1 month of initial treatment, if deemed necessary by Treating Investigator and subject to obtain optimal aesthetic improvment. Optimal aesthetic improvement is defined as at least 1 grade improvement, from baseline, on the GIHS and best correction that can be achieved as agreed by the Treating Investigator and the subject. If optional touch-up is performed, a 72 hours telephone call, 14 day and 1 month follow-up visits should be scheduled.

Effectiveness and safety data will be collected for 12 months following the first injection.

At the month 12 visit, the no-treatment comparator subjects will be offered an optional *Restylane-L* treatment. The subjects who received *Restylane-L* at the baseline visit will also be offered an optional additional treatment if optimal aesthetic improvement is not maintained (as determined by the Treating Investigator and subject). For subject receiving optional treatment at month 12 the effectiveness and safety data will be collected for another 6 months. A subject will be involved in the study for up to 19 months including 30 days screening and 6 months follow-up after optional treatment at month 12. The study visits are illustrated in Figure 1.

GALDERMA EST. 1981	Title **43USTT1904 CSP Infraorbital Hollows**	Doc id **MA-40833**

Effective date: 2021-12-15 20:29
Effective
Version: 10.0

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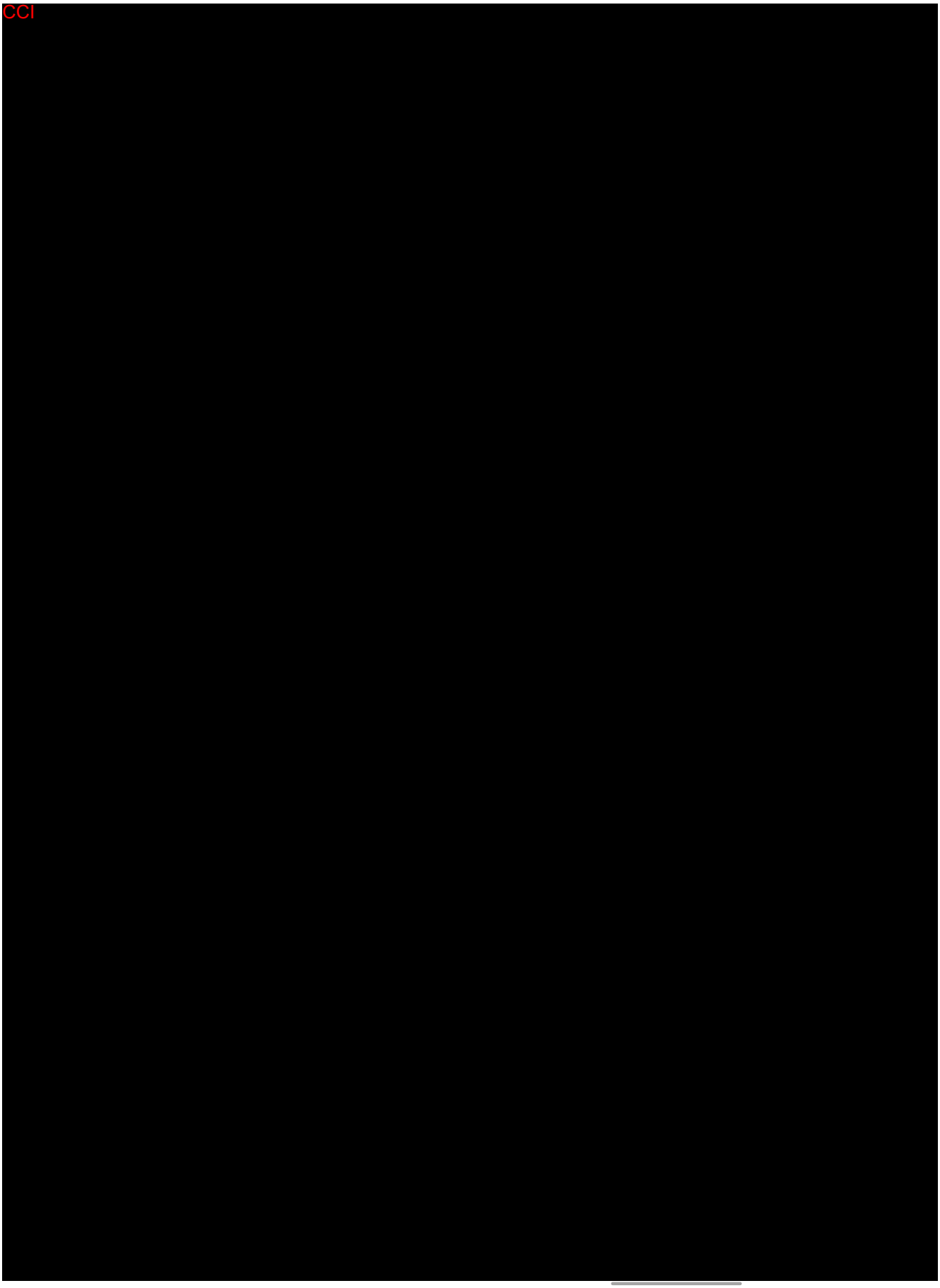

4.2 Number of subjects

Approximately 329 subjects will be enrolled in approximately 18 sites in the USA. The duration of the enrollment period is expected to 4 months. Approximately 15 to 25 subjects will be included and treated per site.

4.3 Duration of subject participation

The total duration of the study is approximately 19 months including 30 days screening period and 6 months follow-up after optional treatment at month 12. One month is defined as 4 weeks in the study.

End of study is when enrolment has reached the target number of subjects and all subjects have completed the last study visit.

4.4 Randomization and blinding

4.4.1 Randomization

Approximately 329 subjects will be randomized in a CCI ratio to treatment with *Restylane-L* or no treatment. Before starting the study, a computer generated randomization list will be prepared under the supervision of a designated statistician from the Sponsor. The randomization list will be stratified by FST group (I-III, IV, and V-VI). The FST I-III group will be further stratified by study site. The FST IV and FST V-VI groups will be further stratified at needle or cannula level (needle sites pooled into a needle stratum, and cannula sites pooled into a cannula stratum). Randomization numbers will be allocated in ascending sequential order to each subject. Randomization will be performed using an Interactive Response System by assigning each subject to *Restylane-L* or no treatment according to the randomization list.

4.4.2 Blinding

The Treating Investigator will not be blinded to study treatments.

A Blinded Evaluator, to whom randomization and treatment are concealed, will conduct the blinded assessments. The Blinded Evaluator is not allowed to be present during the injections or to discuss treatments with the Treating Investigator or subjects. No study related documents that contain information regarding the treatment of subjects should be available to the Blinded Evaluator.

Safety assessment will be performed by non-blinded personnel as treatment-related AEs are expected to occur during a few days after treatment, thereby revealing which subjects has received the study product.

4.4.3 Emergency unblinding

Not applicable as the treating Investigator is not blinded to treatment.

4.5 Medical history

History of relevant surgical events and medical conditions should be documented (including any prior dermatological procedures or implants) in the electronic case report forms (eCRF) using medical terminology.

4.6 Prior and concomitant therapies

4.6.1 Definition

Prior therapies are defined as therapies that have been used within 30 days preceding the Screening visit or within the timelines specified in the Inclusion/Exclusion criteria, and then stopped prior to the Screening visit.

Concomitant therapies are defined as follows:

- any existing therapies ongoing at the time of the Screening visit,
- any changes to existing therapies (such as changes in dose or formulation) during the course of the study, or
- any new therapies received by the subject since the Screening visit

4.6.2 Recording

Prior and concomitant therapies are to be recorded on the appropriate form in the eCRF.

Concomitant therapies are to be recorded, reviewed, and updated at each visit.

Any new concomitant therapy or modification of an existing therapy may be linked to an AE. A corresponding AE form must be completed to account for the change in therapy, except in some cases such as therapy used for prophylaxis, dose modification for a chronic condition.

4.6.3 Authorized concomitant therapies

Unless listed in prohibited concomitant therapies (section 4.6.4), all therapies are authorized.

4.6.4 Prohibited concomitant therapies

The following therapies are prohibited during the study because they may interfere with the efficacy and/or safety assessment of the study product(s) and/or injection procedure:

- Anticoagulants or inhibitors of platelet aggregation (e.g. aspirin, non-steroidal anti-inflammatory drugs [NSAIDs]), Omega-3 or Vitamin E should not be used within 2 weeks before any treatment to avoid increased bruising or bleeding at injection sites. Omega 3 and Vitamin E are acceptable only as part of a standard multivitamin formulation.
- The study product contains lidocaine, but additional local anesthesia may be used. Lidocaine should however be used with caution in subjects receiving other local anesthetics or agents structurally related to amide-type anesthetics, e.g. certain antiarrhythmics, as the systemic toxic effects can be additive.
- Concomitant treatment with chemotherapy, immunosuppressive agents, immunomodulatory therapy (e.g. monoclonal antibodies, antiviral treatment for HIV or Hepatitis) is prohibited.
- Any prescription skin-irritating topical preparations, or pigmenting agents (e.g., self-tanning or bleaching agents) in the periorbital area.
- Immunosuppressive medications or systemic steroids (except intranasal/inhaled steroids) or prescription topical steroids (face).
- Topical (facial) prescription retinoids or systemic retinoids.

- Superficial facial dermal therapies (e.g. microderm abrasion, superficial chemical peels) or aesthetic facial plastic surgery or cosmetic procedures (i.e., facial ablative or fractional laser, deep chemical peels, threads, non-invasive skin-tightening [e.g., Ultherapy, Thermage]**)** to the periorbital or malar region.
- Lower eyelid surgery, including orbital or midface surgery, or permanent implant or fat grafting in the midfacial region or tattoo (including microblading of eyebrow or eyeliner)
- Neurotoxin treatment to the periorbital region, LCL, forehead lines or glabella lines.
- Lower periorbital and/or malar region treatments with absorbable or temporary dermal fillers (e.g., collagen, fat, hyaluronic-acid products, calcium-hydroxylapatite, poly L-lactic acid products, etc.) and/or mesotherapy.
- Facial treatments with any permanent dermal fillers and/or permanent implant.
- Planned surgery including dental implants, tooth extractions, orthodontia are prohibited.
- Participation in any other clinical study during this study is prohibited.

If a prohibited therapy becomes a necessary treatment for the safety or best interest of the subject, the Sponsor Medical Expert should be notified, time permitting, to discuss possible alternatives prior to administration of a prohibited therapy.

If a subject receives prohibited therapy during the clinical study, the Sponsor should be notified to discuss the pertinence and the modalities for the subject to continue in the clinical study.

Table 1: Schedule of events

Procedure	Visit 1a	Visit 1b	Visit 2[4]	Visit 3[4]	Visit 4	Visit 4a[4]	Visit 4b[4]	Visit 4c[4]	Visit 5 -7	Visit 8 or EOS/ET	Visit 8a[4]	Visit 8b[4]	Visit 8c[4]	Visit 8d[4]	Visit 8e[4] EOS for optional Tx
	Visits may be combined if subject meets eligibility criteria		72 hrs after Tx (±24 hrs)	14 days after Baseline (±3 days)	1 month[10] after Baseline (+7 days)	72 hrs after Optional touch-up (±24 hrs)	14 days after Optional touch-up (±3 days)	1 month[10] after Optional touch-up (+7 days)	3, 6, & 9 months[10] after Baseline (±7 days)	12 months[10] (±7 days) after Baseline	72 hrs after optional Tx (±24 hrs)	14 days after optional Tx (±3 days)	1 month after optional Tx (+7 days)	3 months[10] after optional Tx (±7 days)	6 months[10] after optional Tx (+7 days)
	Screening Day -30 to 1	**Baseline/ Tx Day 1**	**TC**	**Follow-up**	**Follow-up Optional TU**	**TC**	**Follow-up**	**Follow-up**	**Follow-up**	**Follow-up Optional Tx**	**TC**	**Follow-up**	**Follow-up**	**Follow-up**	**Follow-up**
Informed Consent	X														
Med. Hx/prior therapies	X	X[1,2]													
Demographics	X														
Height/Weight[6]		X[1,6]		X[6]	X[6]		X[6]	X[6]	X[6]	X[6]		X[6]	X[6]	X[6]	X[6]
Inclusion/Exclusion Criteria	X	X[1,2]			X[1,5]					X[1,5]					
Urine pregnancy test[3]	X	X[1,2]			X[1,5]					X[1,5]					
Vision Function Assessments	X	X[2,8,9]		X	X[5,8,9]		X			X[5,8]		X			
Randomization		X													
Treatment with study product		X[9]			X[5,9]					X[5]					
Evaluate device deficiencies		X			X[9]					X[5]					
Dispense Subject Diary		X[9]			X[5]					X[5]					
Collect / Review Subject Diary			X[7]	X	X[9]	X[7]	X	X			X[7]	X	X		
2D Photography		X[1]		X	X[1]		X	X	X	X[1]		X	X	X	X
Concomitant Therapies	X	X[2]	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of AEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Treating Investigator Assessments															
GAIS					X[1]			X	X	X[1]			X	X	X
GIHS	X	X[1,2]			X[1]					X[1]					
Blinded Evaluator Assessments															
GIHS	X	X[1,2]							X	X[1]				X	X
Subject Assessments															
GAIS					X[1]			X	X	X[1]			X	X	X
CCI [redacted]															

[1]Prior to any planned treatment [2]Omitted if the screening and baseline visits occur on Day 1. Screening visit and baseline visit can be combined if no drug washout is needed [3]For females of childbearing potential [4]Visit is scheduled only if initial treatment, optional touch-up or optional treatment is performed [5]Omitted if optional touch-up or optional treatment is not performed [6]Subject self-reported. Height only needs to be collected at baseline [7]Review diary with subject over the phone [8]Performed prior and 30 minutes post injection of study product [9]For subjects randomized to study treatment [10] One month is defined as 4 weeks in the study	ET = Early Termination EOS = End of Study GIHS = Galderma Infraorbital Hollows Scale GAIS = Global Aesthetic Improvement Scale TC= Telephone call TU = Touch up Tx = Treatment

4.7 Visits

4.7.1 Visit 1 a: Screening (Day -30 to Day 1)

The following activities and screening assessments will be performed within 30 days prior to baseline/Day 1 visit:

- Obtain Informed Consent.
- Obtain demographic data: date of birth, gender, ethnicity, race, and FST. For determination of the FST, see Table 2.

Table 2: Fitzpatrick Skin Types (FST)

Skin type	Skin color	Skin characteristics
I	White; very fair; red or blond hair; blue eyes; freckles	Always burns, never tans
II	White; fair; red or blond hair; blue, hazel or green eyes	Usually burns, tans with difficulty
III	Cream white; fair with any eye or hair color; very common	Sometimes mild burn, gradually tans
IV	Brown; typical Mediterranean Caucasian skin	Rarely burns, tans with ease
V	Dark brown; Middle Eastern skin types	Very rarely burns, tans very easily
VI	Black	Never burns, tans very easily

FST is a skin classification system that categorizes different skin colors, and their reactions to ultraviolet light.[2]

- Record the subject's medical history (including any prior dermatological procedures or implants) and prior or concomitant therapies.
- For all females of childbearing potential, perform UPT prior to treatment. Test result must be negative for the subject to be eligible for treatment.
- Assess GIHS – Treating Investigator and Blinded Evaluator
- Assess eligibility (inclusion and exclusion criteria).
- Schedule the Baseline/Day1 (initial treatment) visit or proceed to Day 1 activities if subject meets all eligibility criteria.

4.7.2 Visit 1b: Baseline/Day 1 (Initial Treatment)

The screening visit and baseline visit (Day 1) may be performed on the same day if a subject is deemed eligible by the Treating Investigator.

If Screening visit and Baseline/Day 1 visit are not performed on the same day, the following procedures should be repeated at the Baseline/Day 1 visit:

- Review for changes in medical history and concomitant therapies.
- Re-confirm eligibility criteria.

[2] Fitzpatrick T.B. (1988). The validity and practicality of sun-reactive skin types I through VI. Arch. Dermatol. 124, 869–871.

- Perform UPT for all females of childbearing potential (prior to treatment). Test result must be negative for the subject to be eligible for study treatment.
- Assess GIHS – Treating Investigator and Blinded Evaluator
- Evaluate the subject for AEs since screening visit.

Once the subject is deemed eligible for study treatment by the Treating Investigator, the following procedures should be completed:

- Record subject's height and weight.
- Obtain pre-treatment photographs of the infraorbital hollows.
- Randomize the subject to treatment (using needle or cannula according to what is agreed per site) or to no treatment. For subject randomized to treatment:
    - Perform Vision Function Assessments prior to injection.
    - Subjects will be injected with the study product.
    - Record all concomitant medications/procedures used during the injection session.
    - Record the number of syringes used and the volume of study product injected during the injection session.
    - Evaluate for device deficiencies. If deficiencies are noted, complete form as specified in section 8.6
    - Following 30 minutes after injection, perform Vision Function Assessments
    - Evaluate post-treatment AEs by Treating Investigator
    - Dispense Subject Diary and instruct subject on Diary completion. Remind the subject to bring the diary to next on-site study visit.
    - Schedule the 72 hours (±24 hours) follow-up phone call (Visit 2) and Visit 3, 14 days (±3 days) after the Baseline visit (Visit 1b) for subjects randomized to treatment.
- Schedule Visit 4, 1 month (+7 days) after the Baseline visit (Visit 1b).

4.7.3 Visit 2: Follow up 72 hour (±24 hours) telephone call after Baseline/Day 1

Visit conducted for subjects randomized to treatment only.

- Interview subject regarding any concomitant therapies.
- Interview subject regarding any AEs that have occurred since receiving treatment. If AEs are reported, notify the Investigator immediately and determine whether subject should return to the site for an unscheduled visit. The Investigator should assess all reported AEs in a timely manner.
- Interview subject regarding the Diary completion and reported events since receiving treatment. Remind subject to complete the Diary daily and bring it to the next on-site visit.
- Remind subject of the next scheduled on-site visit.

4.7.4 Visit 3: Follow up visit 14 days (± 3 days) after Baseline/Day 1

- Interview subject regarding any concomitant therapies and record subject's weight.
- Interview subject and evaluate any AEs, and post-treatment AEs by Treating Investigator (if randomized to treatment) that have occurred since the last visit.
- Obtain photographs.
- Perform Vision Function Assessments.
- Interview subject regarding the Diary completion and reported events since receiving treatment. Remind subject to complete the Diary daily and bring it to the next on-site visit.
- Remind subject of the next scheduled on-site visit.

4.7.5 Visit 4: Follow-up visit 1 month (+ 7 days) after Baseline/Day 1/ Optional touch-up

- Interview the subject regarding concomitant therapies and record subject's weight.
- Interview subject and evaluate any AEs, and post-treatment AEs by Treating Investigator (if randomized to treatment) that have occurred since the last visit.
- Obtain photographs (if treatment is given, ensure photos are taken prior to injection)
- Assessments to be performed, prior to optional touch-up:
    - GIHS – Treating Investigator
    - GAIS – Treating Investigator and Subject

CCI [redacted]

- Schedule Visit 5, 3 months (± 7 days) after the Baseline visit (Visit 1b).

For subjects randomized to treatment

- Collect and review Subject Diary for subjects randomized to treatment:
    - Review diary entries for completeness and legibility.
    - If the subject handwrites entries on the diary pages, review these entries with the subject and clarify as needed. Record all clarifications on the subject's source documents and record the Diary data into the eCRF.
- Assess whether optimal aesthetic result has been achieved by subjects randomized to treatment (as agreed by the Treating Investigator and subject) and determine whether optional touch-up is appropriate.
    - Subject must meet eligibility criteria for touch-up to be provided.
    - Touch-up should not be provided if the subject has a disease or condition described in the exclusion criteria, or an ongoing treatment-related AE that in the opinion of the Treating Investigator would be worsened by a touch-up.

If touch-up is to be performed:

- Prior to any treatment being provided, perform UPT for all females of childbearing potential. The test result must be negative for a subject to receive the touch-up treatment.
    - Perform Vision Function Assessments prior to injection.
    - Subjects will be injected with the study product.
    - Record all concomitant medications/procedures used during the injection session.
    - Record the number of syringes used and the volume of study product injected during the injection session.
    - Evaluate for device deficiencies. If deficiencies are noted, complete form as specified in Section 8.6.
    - Following 30 minutes after injection, perform Vision Function Assessments.
    - Dispense new Subject Diary and remind subject on Diary completion. Remind the subject to bring the diary to next on-site study visit.
    - Schedule the 72 hours (± 24 hours) follow-up phone call (Visit 4a), Visit 4b, 14 days (± 3 days) and Visit 4c, 1 months (+ 7 days) after optional touch-up.

4.7.6 Visit 4a: Follow-up 72 hour (± 24 hours) telephone call after optional touch-up performed

This visit should only be conducted for subjects who received a touch-up treatment at Visit 4.

- Interview subject regarding any concomitant therapies.
- Interview subject regarding any AEs that have occurred since receiving treatment. If AEs are reported, notify the Investigator immediately and determine whether subject should return to the site for an unscheduled visit. The Investigator should assess all reported AEs in a timely manner.
- Interview subject regarding the Diary completion and reported events since receiving treatment. Remind subject to complete the Diary daily and bring it to the next on-site visit.
- Remind subject of the next scheduled on-site visit.

4.7.7 Visit 4b: Follow up visit 14 days (± 3 days) after optional touch-up performed

This visit should only be conducted for subjects who received a touch-up treatment at Visit 4.

- Interview subject regarding any concomitant therapies and record subject's weight.
- Interview subject and evaluate any AEs, and post-treatment AEs by Treating Investigator (if randomized to treatment) that have occurred since the last visit.
- Obtain photographs.
- Perform Vision Function Assessments.

- Interview subject regarding the Diary completion and reported events since receiving treatment. Remind subject to complete the Diary daily and bring it to the next on-site visit.
- Remind subject of the next scheduled on-site visit.

4.7.8 Visit 4c: Follow up visit 1 month (+ 7 days) after optional touch-up performed

This visit should only be conducted for subjects who received a touch-up treatment at Visit 4.

- Interview subject regarding any concomitant therapies and record subject's weight.
- Interview subject and evaluate any AEs, and post-treatment AEs by Treating Investigator that have occurred since the last visit.
- Collect and review Subject Diary:
    - Review diary entries for completeness and legibility.
    - If the subject handwrites entries on the diary pages, review these entries with the subject and clarify as needed. Record all clarifications on the subject's source documents and record the Diary data into the eCRF.
- Assess GAIS – Treating Investigator and Subject
- Obtain photographs
- Remind subject of the next scheduled on-site visit.

4.7.9 Visits 5-7: Follow-up visit 3 months, 6 months and 9 months (± 7 days), after Baseline/Day 1

- Interview the subject regarding concomitant therapies and record subject's weight.
- Interview subject and evaluate any AEs that have occurred since the last visit.
- Obtain photographs
- Assessments to be performed:
    - GIHS – Blinded Evaluator
    - GAIS assessment for all subjects – Treating Investigator and Subject

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- Schedule follow up visits for 6 months, 9 months and 12 months (± 7 days) after the Baseline visit (Visit 1b).

4.7.10 Visit 8: Follow-up visit 12 months (± 7 days) after Day 1 / Optional treatment / End of Study (EOS) / Early Termination Visit (ET)

- Interview the subject regarding concomitant therapies and record subject's weight.
- Interview subject and evaluate any AEs that have occurred since the last visit.
- Obtain photographs (if treatment is given, ensure photos are taken prior to injection)

- Assessments to be performed, prior to optional treatment:
  - GIHS - Treating Investigator and Blinded Evaluator
  - GAIS – Treating Investigator and Subject

CCI [redacted]

For subjects receiving optional treatment

- Assess whether optimal aesthetic result has been achieved by subjects randomized to treatment (as agreed by the Treating Investigator and subject) and determine whether optional treatment or if initial treatment is appropriate.
  - Subject must meet eligibility criteria for treatment to be provided.
  - Treatment should not be provided if the subject has a disease or condition described in the exclusion criteria, or an ongoing treatment-related AE that in the opinion of the Treating Investigator would be worsened by a treatment.

If treatment is to be performed:

- Prior to any treatment being provided, perform UPT for all females of childbearing potential. The test result must be negative for a subject to receive the touch-up treatment.
  - Perform Vision Function Assessments prior to injection.
  - Subjects will be injected with the study product.
  - Record all concomitant medications/procedures used during the injection session.
  - Record the number of syringes used and the volume of study product injected during the injection session.
  - Evaluate for device deficiencies. If deficiencies are noted, complete form as specified in Section 8.6.
  - Following 30 minutes after injection, perform Vision Function Assessments.
  - Dispense new Subject Diary and remind subject on Diary completion. Remind the subject to bring the diary to next on-site study visit.
  - Schedule the 72 hours (± 24 hours) follow-up phone call (Visit 8a), Visit 8b, 14 days (± 3 days) and Visit 8c, 1 months (+ 7 days) after optional treatment (Visit 8).

For subjects who do not receive an optional treatment:

- Complete end of study form in the eCRF.

4.7.11 Visit 8a: Follow-up 72 hour (± 24 hours) telephone call after optional treatment

This visit should only be conducted for subjects who received a treatment at Visit 8.

- Interview subject regarding any concomitant therapies.

- Interview subject regarding any AEs that have occurred since receiving treatment. If AEs are reported, notify the Investigator immediately and determine whether subject should return to the site for an unscheduled visit. The Investigator should assess all reported AEs in a timely manner.
- Interview subject regarding the Diary completion and reported events since receiving treatment. Remind subject to complete the Diary daily and bring it to the next on-site visit.
- Remind the subject of the next on-site visit.

4.7.12 Visit 8b: Follow up visit 14 days (± 3 days) after optional touch-up performed

This visit should only be conducted for subjects who received a treatment at Visit 8.

- Interview subject regarding any concomitant therapies and record subject's weight.
- Interview subject and evaluate any AEs, and post-treatment AEs by Treating Investigator (if randomized to treatment) that have occurred since the last visit.
- Obtain photographs.
- Perform Vision Function Assessments.
- Interview subject regarding the Diary completion and reported events since receiving treatment. Remind subject to complete the Diary daily and bring it to the next on-site visit.
- Remind subject of the next scheduled on-site visit.

4.7.13 Visit 8c: Follow up visit 1 month (+7 days) after optional treatment

This visit should only be conducted for subjects who received a treatment at Visit 8.

- Interview subject regarding any concomitant therapies and record subject's weight.
- Interview subject and evaluate any AEs, and post-treatment AEs by Treating Investigator that have occurred since the last visit.
- Collect and review Subject Diary:
  - Review diary entries for completeness and legibility.
  - If the subject handwrites entries on the diary pages, review these entries with the subject and clarify as needed. Record all clarifications on the subject's source documents and record the Diary data into the eCRF.
- GAIS assessment – Treating Investigator and Subject
- Obtain photographs
- Schedule Visit 8d, 3 months (± 7 days) after optional treatment (Visit 8).

4.7.14 Visit 8d: Follow up visit 3 months (± 7 days) after optional treatment

This visit should only be conducted for subjects who received a treatment at Visit 8.

- Interview subject regarding any concomitant therapies and record subject's weight.
- Interview subject and evaluate any AEs that have occurred since the last visit.

- Assessments to be performed:
  - GIHS – Blinded Evaluator
  - GAIS – Treating Investigator and Subject

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- Obtain photographs
- Schedule Visit 8e, 6 months (+ 7 days) after optional treatment (Visit 8).

4.7.15 Visit 8e: Follow up visit 6 months (+7 days) after optional treatment

This visit should only be conducted for subjects who received a treatment at Visit 8.

- Interview subject regarding any concomitant therapies and record subject's weight.
- Interview subject and evaluate any AEs that have occurred since the last visit.
- Assessments to be performed:
  - GIHS – Blinded Evaluator
  - GAIS – Treating Investigator and Subject

CCI [redacted]

- Obtain photographs
- Remind subjects to contact the study site if any new AE occurs after study exit as subjects will be asked to return to the study site and be evaluated and receive treatment, if applicable.
- Complete end of study form in the eCRF

5. Subjects

5.1 Subject information and informed consent

The PI or his/her authorized designee must always use the IRB-approved subject information and informed consent form and it must not be changed without prior discussion with the Sponsor and approval from the applicable IRB.

It is the responsibility of the PI or his/her authorized designee to give each subject prior to inclusion in the study, full and adequate verbal and written information regarding all aspects of the clinical study that are relevant to the subject's decision to participate throughout the study, e.g. explain the purpose and procedures of the study, the duration and number of expected participants, possible risks involved, and the opinion of the IRB. The subject shall be informed that the participation is confidential and voluntary and that the subject has the right to withdraw from the study at any time, without any consequences to his/her future medical care, treatment or benefits to which the subject is otherwise entitled. The information shall be provided in a language clearly and fully understandable to the subject. The subject shall be given sufficient time to read and understand the informed consent form and to consider participation in the study. Before any study-related activities are performed, the informed

consent form shall be personally signed and dated by the subject and the PI or his/her authorized designee responsible for conducting the informed consent. The consent includes information that data will be collected, recorded, processed, and may be transferred to other countries. The data will not contain any information that can be used to identify any subject.

Photographs collected during the study will be analyzed and stored in a database by the Sponsor and its representatives in order to evaluate the effect of the treatment in the study. The subjects will be recognizable on the photographs, but their names will not be disclosed.

All signed informed consent forms shall be filed in the Investigator file. The subject shall be provided with a copy of the signed and dated informed consent form and any other written information.

The Investigator shall ensure that important new information is provided to new and existing subjects throughout the study.

5.2 Inclusion criteria

The subjects must meet all the following criteria to be eligible for the study:

1. Subject is willing to comply with the requirements of the study including being photographed, following post-treatment care instructions, completing the diary, attending all study visits and providing a signed written informed consent.
2. Moderate or severe (Grade 2 or 3 on the GIHS) infraorbital hollows with no more than one grade difference between the left and right side at baseline as assessed by the blinded evaluator.
3. Visual function assessment tests without findings according to treating investigator.
4. Males or non-pregnant, non-breastfeeding females, over the age of 21.
5. Subject is willing to abstain from any other facial plastic surgical or cosmetic procedure(s) during the duration of the study (e.g. laser or chemical resurfacing, needling, facelift, radiofrequency).
6. Intent to undergo correction of both orbital hollows.

Inclusion criteria 7 - 8 apply to female subjects only

7. If the subject is a female of childbearing potential, she agrees to use an acceptable form of effective birth control for the duration of the study and is willing to take a urine pregnancy test (UPT) at the screening/enrollment visit and prior to treatment. Acceptable forms of effective birth control include:
   a) Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical caps) with spermicidal foam/gel/film/cream/suppository.
   b) Bilateral tubal ligation.
   c) Combined oral contraceptives (estrogens and progesterone), implanted or injectable contraceptives on a stable dose for at least 28 days prior to Day 1.
   d) Hormonal or copper intra uterine device (IUD) inserted at least 28 days prior to Day 1.
   e) Vasectomized partner (in monogamous relationship) for at least 3 months prior to screening.
   f) Strict abstinence (at least one month prior to baseline and agrees to continue for the duration of the study or use acceptable form or birth control).

8. Negative urine pregnancy test for females of childbearing potential at screening and all injection visits.

5.3 Exclusion criteria

The presence of any of the following exclusion criteria excluded a subject from enrollment in the study:

1. Known/previous allergy or hypersensitivity to any injectable hyaluronic acid (HA) gel or to gram positive bacterial proteins.
2. Known/previous allergy or hypersensitivity to local anesthetics, e.g. lidocaine or other amide-type anesthetics.
3. Active or a history of recurrent or chronic infraorbital edema or rosacea or uncontrolled severe seasonal allergies.
4. Previous or present multiple allergies or severe allergies, such as manifested by anaphylaxis or angioedema, or family history of these conditions.
5. Previous superficial facial dermal therapies (i.e. microderm abrasion, superficial chemical peels) to the periorbital or malar region within the past 6 months or plans to receive such treatment during participation in the study.
6. Previous deep facial dermal therapies (i.e. facial ablative or fractional laser, deep chemical peels, non-invasive skin-tightening [e.g. Ultherapy, Thermage]) to the periorbital or malar region within the past 12 months or plans to receive such treatment during participation in the study.
7. Prior lower-eyelid surgery, including orbital or midface surgery, or has a permanent implant or fat grafting or fat injections in the mid-facial region or tattoo (including microblading of eyebrow or eyeliner) that could interfere with effectiveness assessments or plans to have it during the study.
8. Lower lid retraction or exophthalmos.
9. Pigmentation abnormalities around the eyes and/or dark circles under the eyes due to pigmentation changes and not from infraorbital hollow shadowing.
10. Ectropium, entropion, or trichiasis of the lower eyelid or eye diseases that lead to reddening and tendency of watering of the eye.
11. Has gained or lost ≥ 2 body mass index (BMI) units within the previous 90 days or has the intention to gain or lose a significant amount of weight during the study.
12. Received lower periorbital and/or malar region treatments with any absorbable or temporary fillers such as porcine-based collagen fillers, HA products, RADIESSE®, poly L-lactic acid (PLLA) or received mesotherapy treatment to the area within the past 24 months or plans to receive such treatments during participation in the study.
13. Received neurotoxin treatment to the periorbital region, Forehead Lines (FL), Lateral Canthal Lines (LCL) or glabella, within the past 6 months or plans to receive such treatment during participation in the study.

14. Any current or history of uncontrolled retinal disease or detached retina or any other condition with the potential to cause a decline of visual acuity (e.g. uncontrolled diabetes).
15. Tendency to accumulate eyelid edema, has developed festoons, or has large and/or herniating infraorbital fat pads.
16. Skin or fat atrophy, other than age-related, in the mid-facial and/or perio-orbicular regions or has been diagnosed with a connective tissue disorder.
17. Skin laxity or sun damage beyond typical for the subject's age.
18. A history of recurrent herpetic eruption in the mid-facial region, excluding the lips, within 12 months.
19. Subjects typically experiencing occasional migraines (≥ 8 per year).
20. History of radiation damage, cancerous or pre-cancerous lesions (e.g. actinic keratosis) near the area close to be treated.
21. Scars or deformities, active skin disease, inflammation, or related conditions such as infection, perioral dermatitis, seborrheic dermatitis, eczema, rosacea, acne, psoriasis, and herpes zoster near or in the area to be treated.
22. Subjects with dental or oral status on visual inspection that, in the opinion of the Investigator, would make the subject unsuitable for inclusion, or Subjects with dental, oral or sinus surgery within past 12 months prior to the treatment visit or planned surgery, including dental implants, tooth extractions, orthodontia, during the study period.
23. Inflammation, active or chronic (e.g. in the mouth, dentals, head and neck region).
24. History of or active autoimmune disease or connective tissue diseases such as systemic lupus erythematosus, rheumatoid arthritis, polymyositis, dermatomyositis, or localized or systemic scleroderma.
25. Tendency to form keloids, hypertrophic scars, or any other healing disorder.
26. History of bleeding disorders or treatment with anticoagulants or inhibitors of platelet aggregation e.g. aspirin or other non-steroid anti-inflammatory drugs (NSAIDs), Omega-3, or vitamin E within 2 weeks before treatment.
27. Treatment with chemotherapy, immunosuppressive agents, immunomodulatory therapy (e.g., monoclonal antibodies, antiviral treatment for HIV or hepatitis), systemic or topical (facial) corticosteroids within 3 months before treatment (inhaled corticoids are allowed).
28. Any prescription skin-irritating topical preparations, or pigmenting agents (e.g., self-tanning or bleaching agents) in the periorbital area within the past 2 weeks.
29. Concomitant treatment with prescribed topical (facial) retinoids within 3 months, or systemic retinoids within 6 months before treatment,or plan to receive such treatment during participation in the study.
30. Any medical condition that in the opinion of the Investigator would make the subject unsuitable for inclusion (e.g., porphyria, methemoglobinemia, hemoglobinopathy, thalassemia, glucose-6-phoshate dehydrogenase deficiency, a chronic, relapsing or

hereditary disease that may affect the general condition or may require frequent medical treatment, any abnormal screening laboratory value or ECG, or psychiatric disorders).

31. Women who are pregnant or breast feeding, or women of childbearing potential who are not practicing adequate contraception or planning to become pregnant during the study period.
32. Study site personnel, close relatives of the study site personnel (e.g. parents, children, siblings, or spouse), employees, or close relatives of employees at the Sponsor Company.
33. Participation in any other clinical study within 30 days before treatment.

5.4 Subject number

Prior to any study procedures being conducted, the subject must sign the informed consent form. Each subject who has signed the informed consent form will be assigned a screening number. Upon randomization, each subject will be assigned a subject number that will be allocated in ascending order within each center. A screen failure is a subject who signed the informed consent but never enrolled (i.e. was randomized and/or received treatment) in the study. For screen failures, the subject source documents should indicate which assessments have been made and the reason why the subject was determined to be a screen failure. A screen failure should not be re-entered in the study. A subject is considered enrolled when they have signed the Informed Consent Form (ICF) and are randomized and/or treated.

For the duration of the clinical study, each subject will be identified using the subject number for all documentation and discussion. A subject identification log is required to be kept in the Investigator file.

5.5 Withdrawal of subjects

An investigator may decide to discontinue a subject from the clinical study for safety reasons.

Although the importance of completing the entire clinical study should be explained to the subject by the clinical study personnel, any subject is free to discontinue participation in this clinical study at any time and for whatever reason, specified or unspecified, and without any prejudice. No constraints are to be imposed on the subject, and when appropriate, a subject may be treated with other conventional therapy when clinically indicated.

When a subject does not complete the clinical study, he/she will be fully assessed, if such assessment is possible. The procedures designated for the Early Termination (ET) visit should be completed for all subjects discontinuing the clinical study and the appropriate eCRF should be completed.

All discontinuations and the reason for discontinuation are to be documented by the investigator on the Exit form.

For discontinuation due to and AE, the Adverse Event form is to be completed. The investigator should also ensure that the subject receives suitable therapy for the AE.

A subject who has been randomized cannot be replaced by another subject if he/she discontinues the clinical study for any reason.

Pregnancies occurring during the screening period are considered as screening failures; they should be recorded as such in the eCRF and no pregnancy form is to be completed.

In case of a pregnancy occurring after the baseline visit, follow the procedures described in section 8.5.12. The subject may remain in the study, but no invasive procedure should be conducted.

The Sponsor may also decide to prematurely terminate or suspend a subject's participation in the clinical study.

Potential reasons for discontinuation are defined below:

The withdrawal criteria are:

- **Medical Reasons** If the subject suffers from a medical condition and/or Adverse Events that, in the judgment of the Investigator makes it medically necessary to withdraw the subject. The specific rationale for Investigator-initiated withdrawal of a subject for medical reasons should document the specific condition for withdrawing the subject.
- **Withdrawal by Subject:** Includes consent withdrawal, subject relocation, schedule conflicts. A subject can withdraw their consent to participate in the study at their own request or be withdrawn from participation in the study at the request of their legally authorized representative at any time for any reason.
- **Lost to follow-up:** If a subject does not return for a scheduled visit, reasonable effort shall be made to contact that subject, confirm with three documented phone calls and a certified letter (delivery receipt requested) without answer before declaring the subject lost to follow-up.
- **Other:** This category is to be used for a subject who discontinues due to a reason other than as specified in the pre-defined categories above. Explain the reason for discontinuation.

If reason for discontinuation is "withdrawal by subject" or "other", the subject will be questioned to rule out the possibility of an AE. If the AE led to discontinuation then "Adverse Event" should be chosen as the reason for discontinuation, rather than "withdrawal by subject" or "other".

If an AE which, according to the Investigator's assessment, is related to the use of any of the study products and is still ongoing at the time of the withdrawal, the Investigator shall follow-up the subject until the AE resolves, is assessed by the Investigator to be "chronic" or "stable" or subject is lost to follow up. Follow-up information shall be reported on the AE follow-up form.

6. Study Products

The term "study products" refers to *Restylane-L*. The study product will be provided by the Sponsor.

6.1 Investigational product

The investigational device (i.e. study product) is *Restylane-L* injectable gel. The sterilized gel contains 20mg/mL stabilized HA and 3 mg/mL lidocaine hydrochloride in a physiological buffer. Each syringe contains 0.5 mL gel.

Restylane-L is supplied sterile, 0.5 mL filled in a disposable glass syringe with a luer lock fitting. *Restylane-L* is co-packed with one sterilized Thin Wall (TW) needle as indicated on the carton (29 G x ½").

6.2 Additional products and materials

The sponsor will provide Urine Pregnancy Tests, cotton wisps, and monofilaments to each study site.

Topical or local anaesthesia may be used at the discretion of the treating Investigator before the treatment. If used, the anaesthesia shall be supplied by the study site. Type of anaesthesia, administration route, product name, and quantity used must be recorded in the eCRF.

Small blunt tip commercially available cannulas TSK Steriglide 25G x 1½" and TSK Steriglide 27G x 1½" will be supplied by the study sites (for sites using cannula). The co-packed needle should be used as incision needle with each cannula.

6.3 Labelling and storage

Labelling will be performed according to United States Code of Federal Regulations (CFR) 21 CFR 812.5: Labelling of investigational devices. The carton will be labeled with the lot number as well as expiration date and the CTN and the following:

"CAUTION - Investigational Device. Limited by US Law to Investigational Use."

The syringes should be stored in their original packaging at a temperature up to 25°C (77°F), protected from sunlight and freezing. Opened packages or partially used devices should not be reused. Detailed product information is provided in the IFU.

6.4 Product accountability

The study products will be released to the Investigator or his/her authorized designee after study approvals have been received from the FDA and IRB and the CTA has been signed by all parties.

The Investigator must ensure that the study products are kept in a secure location, with access limited to those authorized by the Investigator.

The study products must be traceable from the manufacturer to their use in subjects until return or disposal. It is therefore important that the Investigator maintain accurate product accountability records, i.e. documentation of the physical location of all study products, deliveries, and return of study products between the Sponsor and the Investigator, and documentation of administration of product to the subject.

When the study is completed, all unused or expired study product at each study site should be returned to the Sponsor representative for destruction, or be destroyed locally at the site if documented as agreed with Sponsor.

Any malfunctioning study products should be reported as described in section 8.6.

Products deliberately or accidentally destroyed during shipment or at a study site should be accounted for and documented. Used syringes, needles, and any unused material must be discarded immediately after the treatment session and must not be reused due to risk for contamination of the unused material and the associated risks including infections according to standard procedures at the site. Disposal of hazardous material, i.e. syringes and needles must conform to applicable laws and regulations. The study products must not be used outside the study.

6.5 Treatment

The investigational product is reserved for use by Treating Investigators who are experienced in infraorbital injection procedures. Before treatment the subject will be informed about the expected post-treatment events that should be recorded in the Subject Diary and potential risks involved with the treatment and when to contact the Investigator in case of emerging symptoms. The investigator must be trained on, and have at hand, the relevant clinical practice guidelines[1] and the actions to be taken if visual disturbances occur. The investigator should also have reviewed the Intravascular Treatment Protocol supportive tool provided separately in the Investigator file.

6.5.1 Pre-Treatment procedure

A visual function assessment should be performed prior to injection of the investigational product, see section 8.2.

The study product contains lidocaine hydrochloride, but additional topical or local anesthesia or ice pack may be used at the discretion of the Treating Investigator to enhance the experience of the subject. Any additional topical or local anesthesia used should be recorded in the source documentation and on the eCRFs

6.5.2 Treatment Regimen (dose and interval)

Detailed information regarding the injection procedure, pre- and post-treatment care and patients instructions are provided in the IFU.

Restylane-L is to be placed in the supraperiosteal plane. The infraorbital treatment area is at the junction of the lower eyelid and midface where a volume deficit has formed. This area is bordered by the nasal sidewall medially, the temporal region of the bony orbit laterally, the bulk of the lower eyelid superiorly, and the superior aspect of the mid-face inferiorly.

The injection technique is at the discretion of the Investigator. For needle serial puncture is recommended and for cannula fanning technique is recommended. The injection should be performed with a constant low-to-moderate pressure on the plunger. Slight elevation of the skin should be observed without significant blanching of the skin. To avoid visible lumps and/or discoloration, avoid injection of *Restylane-L* superficially. When the injection is complete, the treated area may be gently massaged, if necessary.

[1] Alam M, Gladstone H, Kramer EM, et al. ASDS guidelines of care: injectable fillers. Dermatol Surg. 2008; 34 (suppl 1): S115-S148.

Allowed maximum injection volume for initial injection, touch-up and end of study treatment is 1,0 mL per side at each treatment session. Slow injection is recommended and overcorrection should be avoided.

For the optional treatment at 12 months sites will continue to use needle or cannula for injection based on the initial selection for each particular site.

6.5.3 Post-treatment care

Post treatment procedures with ice pack or gentle massage are allowed as per investigator normal procedure. Ice pack can be applied for a short period if the treated area is swollen. Gentle massage can be applied for any irregularities.

After the injection, some common injection-related reactions might occur. These reactions include erythema, swelling, pain, itching, bruising or tenderness at the implant site. Typically, resolution is spontaneous within one week after injection into the skin.

Post-injection Vision Function Assessment tests including the Snellen visual acuity test, Extraocular muscle function test and Confrontation visual field, by the treating investigator will be repeated 30 minutes after injection, see section 8.2.

Acetaminophen may be taken if instructed by the physician. Any medication or therapy used by the subject must be recorded in the CRF.

The subject must avoid exposing the treated area to heat (sun bathing, sauna, steam baths, etc.) or extreme cold until any signs of initial swelling and redness have disappeared.

6.5.4 Post-trial provisions

In time, the implant will be degraded in the body and additional treatments will be necessary to maintain the aesthetic result. Subjects will be offered optional treatment at the 12 months follow-up visit. The same procedure as described in section 6.5.1 and 6.5.2 should be followed. After the final study visit, the Sponsor will not supply any more treatments to the subjects, even if the result does not persist.

6.5.5 Treatment compliance

Not applicable; the treatment will be administered by the injector at the investigational site.

7. Effectiveness Assessments

7.1 General information

The methods for collecting efficacy data are described in the following sections. To minimize inter-observer variability, every effort should be made to ensure that preferably the same individual who made the initial baseline determinations completes all corresponding follow-up evaluations.

7.2 Galderma Infraorbital Hollows Scale (GIHS)

The GIHS is a 4 point scale for assessment of Infraorbital Hollows (Appendix 2). Each score in the GIHS is exemplified by Photographic images of the scale. The blinded evaluator and treating investigator will perform live assessment of the subject´s left and right Infraorbital Hollow separately.

The blinded evaluator will perform GIHS assessments at:

- screening and baseline
- 3, 6, 9 and 12 months after randomization
- 3 and 6 months after optional treatment. The evaluator is considered unblinded as these assessments are performed for all subjects receiving the optional treatment.

The treating investigator will perform GIHS assessment at:

- screening and baseline
- 1 and 12 months after randomization

7.3 Global Aesthetic Improvement Scale (GAIS)

The 7-graded GAIS will be used to live assess the aesthetic improvement of the Infraorbital Hollows by the Treating Investigator and the subject, by comparing to a photograph taken at the baseline visit before the first treatment. The Treating Investigator and the subject will, independently of each other, respond to the question: "How would you describe the aesthetic improvement of your tear troughs today compared to the photograph taken before treatment?" by using the respective categorical scale below.

GAIS will be assessed at 1, 3, 6, 9 and 12 months after randomization, at 1 month after optional touch-up and at 1, 3, and 6 months after optional treatment.

Table 3: **Global Aesthetic Improvement Scale (GAIS)**

Rating (Treating Investigator and Subject	Definition (only for Treating Investigator)
Very Much Improved	Optimal aesthetic result for the implant for this subject.
Much Improved	Marked improvement in appearance from the initial condition, but not completely optimal for this subject.
Improved	The appearance is improved from the initial condition.
No Change	The appearance is essentially the same as baseline.
Worse	The appearance is worse than the initial condition.
Much Worse	Marked worsening in appearance from the initial condition.
Very Much Worse	Obvious worsening in appearance from the initial condition.

The Treating Investigator and Subject shall independently rate their assessment for aesthetic change comparing the appearance at follow-up visits to baseline photographs (obtained prior to injection at baseline

7.7 Photography

Photographs will be taken prior to treatments with study product and at every follow-up visit in order to document treatment effect. Photographs may also be taken to document AEs at the Treating Investigator's discretion. Baseline photographs may be used as a reference in the GAIS assessment by the Treating Investigator and subject. Site personnel will be thoroughly trained in the photographic equipment and techniques before study start.

Camera equipment will be provided by the Sponsor or their designee and standardized photographs should be achieved. Further details regarding photography procedure will be specified in a separate user guide.

8. Safety Assessments

8.1 Assessment of AEs by direct question to subject and evaluation of subject

Safety evaluations for this study include an interview of the subjects at each visit to obtain information about any medical occurrence that meets the definition of an AE. Each subject should be questioned about AEs at each study visit following the screening visit. The question should be asked: "Since your last clinical visit have you had any health problems?" Information on AEs can also be obtained from signs and symptoms detected during each examination by the Investigator or designee, which should include visual inspection of the treatment area.

AEs must be documented in the source document and eCRF without regard for cause or relation to investigational product. If in the process of the interview, additional information regarding

medical history or pre-planned medical or surgical procedures is revealed, it must be documented in the source document(s) and eCRF.

It is the responsibility of the Investigator to determine severity of the AE and relatedness of the event to the study product.

8.1.1 Adverse Events of special interest

All incidences of visual disturbances, regardless of relationship to study product or seriousness, are considered Adverse Events of Special Interest (AESIs) and include but are not limited to the following: any change in vision, any loss of vision, blurry vision, double vision, pain in or around the eye, blind spot or shadow in the visual field, trouble moving eyes, any change in Snellen visual acuity including change of one line or greater.

AESIs should be reported (using the Adverse Event Clarification Form) within 24 hours of awareness to the Sponsor (following the instructions in section 8.5.6) via email to drugsafetypv@advancedclinical.com . Appropriate follow up should be conducted in order to determine the cause, severity, seriousness, outcome, and relationship to the study product or procedures.

8.2 **Vision function assessment**

Vision function assessments will be performed both prior to and 30 minutes post injection of the study product at baseline and optional touch-up and optional treatment. These assessments include Snellen visual acuity, extraocular muscle function, and confrontation visual field testing.

8.2.1 Snellen visual acuity test

A Snellen Eye Chart will be used to assess visual acuity for distance vision. Visual Acuity will be conducted using the subject's best distance correction (e.g. contacts or eye glasses) at a distance of approximately 6 feet from the chart. Each eye will be measured separately by either using an occluder or having the subject cover each eye. The subject will be asked to start reading the letters at the top of the chart working their way to the bottom. The smallest row of letters that the subject can read will indicate their visual acuity listed on the chart. Snellen Visual Acuity will be recorded in their source documentation and eCRF. If there is one or more visual acuity line changes during the course of study, these should be reported to the Sponsor within 24 hours of awareness as an AESI. These events should be reviewed and assessed by the Investigator as an Adverse Event.

8.2.2 Extraocular muscle function test

Extraocular muscle function testing examines the function of the eye muscles. This test observes the movement of the eyes in six specific directions to evaluate weakness or other problem in the extraocular muscles. The subject will be asked to sit or stand with their head up and looking straight ahead. The assessor will hold a pen or other object approximately 16 inches in front of the subject's face. The assessor will then move the object in several directions and ask the subject to follow it with their eyes, without moving their head. Normal or Abnormal will be recorded in the source documentation and eCRF. Changes in movement of the eyes during the course of the study should be reviewed and assessed by the Investigator for a potential Adverse Event.

8.2.3 Confrontation visual field

The Confrontation Visual Field test will be used to assess the subject's peripheral vision. The examiner will sit facing the subject, about 3 to 4 feet away from the subject and ask the subject to fix their gaze on the examiner's eye. The examiner will hold their arms straight out to the side and bring their hands into the subject's visual field from the sides in each quadrant. The subject will signal as soon as the hand is seen. Each quadrant will be recorded as normal or abnormal in the source documentation and eCRF. Changes in the visual field of the eyes during the course of the study should be reviewed and assessed by the Investigator for a potential Adverse Event

8.3 **Subject Diary Data**

The subject shall evaluate local tolerability in a 28 days diary, starting on the day of each treatment. The presence and maximum intensity of pre-defined, expected post-treatment events, i.e. bruising, redness, pain, tenderness, lumps/bumps, itching and swelling shall be assessed for the treated area. The Subject Diary will also have an area for the subject to report any other symptoms outside the pre-identified. Especially symptoms like change in vision change in skin color or crusty/scabby skin around the eyelids, dizziness, confusion, weakness or numbness in arms or legs, changes to consciousness or alertness, difficulty speaking/speech impairment, face droop, headache and fever should be recorded. The diary will also include instructions for the subject to:

- Contact an eye doctor (retinal specialist or ophthalmologist) if they experience change in vision (i.e. vision loss, blurriness, double vision, pain in or around eye, blindness, blind spots, problems moving your eyes), change in skin color or crusty/scabby skin around the eyelids
- Call 911 and seek immediate medical attention if signs of stroke or subject experience dizziness, confusion, weakness or numbness in face, arms or legs, changes to consciousness or alertness, difficulty speaking/speech impairment, face droop

The Investigator or study staff should review the diary for completion and clarify any events as needed. For events that are ongoing at the time of diary completion, the Investigator should follow them and record resolution in the subject's study file and eCRF. Diary data will be analyzed and displayed separately from AE data.

CCI [redacted]

8.4 **Laboratory assessments**

Pregnancy Test

For all women of childbearing potential, including those currently using contraception, a urine pregnancy test is required prior to receiving any study treatment (Day 1, optional touch-up, or o treatment). **The test result must be negative for the subject to receive any treatment with study product.** The test result will be documented in the subject's file and eCRF.

8.5 Adverse Events

8.5.1 Definition of an Adverse Event

An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons[I], whether or not related to the study product.

This definition includes:

a) events related to the investigational product or the reference product

b) events related to the procedures involved

8.5.2 Definition of a Serious Adverse Event

A Serious Adverse Event (SAE) is an AE that:

a) led to death,

b) led to serious deterioration in the health of the subject, that either resulted in

1. a life-threatening[II] illness or injury, or
2. a permanent impairment of a body structure or body function, or
3. in-patient or prolonged hospitalization[III], or
4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

c) led to fetal distress, fetal death, or a congenital abnormality or birth defect

In cases of doubt, whether an AE fulfils a serious criterion or not, there should be a predisposition to report as a SAE rather than not report as such (see section 8.5.7).

8.5.3 Definition of unanticipated adverse effect

An unanticipated adverse device effect is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, the investigational product, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence, or any other unanticipated serious problem associated with a device that relates to the right, safety or welfare of the subject (see US requirement CFR 812.3 (s).

8.5.4 Recording instructions

Each subject should be questioned about AEs at each study visit following signing of informed consent. The question asked should be: ”Since your last clinical visit; have you had any health problems?”. Information on AEs can also be obtained from signs and symptoms detected

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[I] For users or other persons, this definition is restricted to events related to the investigational product.

[II] The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. (Source: ICH-E2A clinical safety data management: definitions and standards for expedited reporting).

[III] Planned hospitalization for a pre-existing condition, or a procedure required by the CSP, without serious deterioration in health, is not considered a SAE. (Source: ISO14155:2011).

during each examination or from a laboratory test, observations made by the study site personnel, subject diaries, or spontaneous reports from the subjects or their relatives.

When an AE is related to a device deficiency (refer to section 8.6), including technical device malfunction, the AE shall be recorded on the AE form/module in the eCRF and the technical complaint shall be reported separately on the clinical study complaint form provided separately in the Investigator file.

Investigators, or other study site personnel, shall record all AEs in the eCRF, including:

a) Event term (recorded in standard medical terminology and avoiding abbreviations)
b) Affected area
c) Start date (first day with symptoms)
d) Stop date (last day with symptoms)
e) Intensity (mild, moderate, or severe according to definition in section 8.5.4.1)
f) Seriousness (serious or not serious, according to definition in section 8.5.4.2)
g) Causal relationship to study product or study product injection procedure (yes or no)
h) Action taken (none, medication treatment, non-pharmacological treatment, or other procedures/tests, subject withdrawn)
i) Outcome of the AE (ongoing, recovered, recovered with sequelae, death, chronic/ stable, not recovered at the end of the study)

The AE form/module in the eCRF must be signed and dated by the Investigator.

The pre-defined, expected post-treatment events shall be assessed separately. These events shall be collected by direct questioning to subjects in a diary used daily for 28 days after each treatment.

8.5.4.1 Intensity

Intensity will be recorded for each reported AE. The following definitions of intensity are to be used:

Mild:	Awareness of symptoms or signs, but easily tolerated (acceptable*)*
Moderate:	Enough discomfort to interfere with usual activity (disturbing)
Severe:	Incapacity to work or to do usual activity (unacceptable)

If the intensity changes within one day, the maximum intensity of the AE during that day shall be recorded.

8.5.4.2 Causal relationship and seriousness

Each AE, serious as well as non-serious, shall be assessed by the Investigator for causal relationship with the study product and its use (the injection procedure) and for seriousness (Yes or No) of the event.

A two-point scale (Yes or No response) shall be used for the causality assessments. The Investigators shall be asked to indicate a response to each of the following questions in the eCRF:

- "Do you consider that there is a reasonable possibility that the event may have been caused by the study product?", and
- "Do you consider that there is a reasonable possibility that the event may have been caused by the study product injection procedure?"

If any of these questions is answered Yes, the AE is considered related.

Each AE will also be assessed for causal relationship and seriousness by the Sponsor, in order to fulfil regulatory requirements.

8.5.5 Reporting of Adverse Events

Adverse Event reporting on each subject shall start once a subject is enrolled (i.e., randomized and/or treated) in the study. All other events that occur after the subject signs the ICF but before enrollment will be recorded in the subject's medical history. The reporting shall continue during each follow-up visit (including telephone contacts and extra visits between planned visits) until the last scheduled visit in the study.

All AEs, non-serious as well as serious, are to be reported as an AE in the *e*CRF.

8.5.6 Reporting of Adverse Events of special interest (AESIs)

AESIs should be reported (using the AE Clarification Form) within 24 hours of awareness to the Sponsor at the email address drugsafetypv@advancedclinical.com. In case of difficulty to obtain all the required information within 24 hours, an initial report can be submitted with follow up information provided within 24 hours of awareness of the new information.

The following information should be provided when reporting an AESI:

- Subject identification (subject number and initials)
- Event description including observed symptoms
- Medical history related to event
- Event onset date and time
- Depth of injections
- Interventions implemented to treat event
- Event outcome (with resolution date and time if applicable)
- Relatedness to study product or procedure
- Seriousness of event
- Study treatment information (number of injections, date of injections, name of product injected, volume injected, etc.)

If the Investigator assesses an AESI to be serious, an SAE report should be submitted as specified in section 8.5.7.

Upon receipt of the AESI report, the Medical Monitor and Sponsor will review the information provided, assess the event, and report to RA within 24 hours and to the IRB as applicable.

8.5.7 Reporting of serious Adverse Events

The Investigator shall report any **SAE** to the Sponsor **immediately but not later than 24 hours of awareness of the event**. This initial report can be made via e-mail or submitted via the eCRF.

In case of difficulty to obtain all the required information within 24 hours, an initial report can be submitted, with the following information as a minimum, irrespective of whether some of it is regarded as preliminary:

- Subject identification (age, gender, initials, subject number)
- Adverse Event description
- Date when AE occurred
- Name of PI
- Name of study product

Follow-up information and data missing in the initial SAE reporting shall be gathered as soon as possible and reported to the Sponsor immediately but not later than 24 hours of awareness of the new data. Complete and adequate information on each SAE is required. All attempts to obtain this information, including dates for follow-up activities, must be documented by the Investigator.

Supporting documentation to be provided with the SAE report:

- Concomitant therapies form/list
- AE form/list
- Medical history form/list
- Any other relevant supporting documentation (e.g. hospital notes, death certificate, autopsy reports etc.)

E-mail for SAE reporting: drugsafetypv@advancedclinical.com

E-Fax number for SAE reporting: +888–493–0910

For non-urgent complementary information that is not possible to send by e-mail or fax, please use surface mail.

Surface mail for providing complementary information:

Advanced Clinical
ATTN: Pharmacovigilance and Safety Monitoring
Building 2, Ground Floor
Guildford Business Park
Guildford Surrey GU2 8XH
United Kingdom

The SAE form must be signed and dated by the Investigator. If the initial 24-hour SAE report does not contain full information or if it is made without using the SAE form the fully completed and signed SAE form shall be e-mailed or faxed to the Sponsor. A copy of the fully completed SAE form shall be kept at the site. The blinded evaluator should perform live effectiveness assessments only and not discuss the treatment or any potential Adverse Events with the patient.

In addition, the PI shall report SAEs to the responsible IRB without undue delay. The PI is responsible for checking what reporting procedures are applicable for his/her IRB regarding SAEs and final report of the outcome of the study and to comply with such reporting procedures during the study period.

The Sponsor is responsible for reporting to the RA, if applicable and according to national regulations.

8.5.8 Stopping Rule

Enrollment and treatment into the study will be temporarily halted if the Sponsor receives a SAE for a vascular embolic event that lead to skin necrosis, vision loss, or stroke and is determined by the Investigator to be directly or possibly related to the study device or injection procedure. The SAE will be investigated by the Sponsor. If the Sponsor's investigation concludes:

- The SAE was unanticipated, directly related to the study product or device injection procedure, and presents an unreasonable risk to study subjects, the study will be terminated and the Investigators notified. The IRB and RA will also be notified if the study is prematurely terminated due to safety concerns.
- If the SAE does not meet the above criteria, then enrollment in the study will continue.

8.5.9 Reporting of unanticipated adverse device effects

The Investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during the study as soon as possible (see US requirement 21 CFR 812:150 (a.), for contact details, see section 8.5.7.

8.5.10 Follow-up of unresolved events ongoing at termination of the study

All serious as well as non-serious AEs with a causal relationship to the study product or treatment procedure and ongoing at study end, shall be followed up after the subject's participation in the study is over. Such events shall be followed-up after the last study visit until resolved, assessed as chronic or stable, or subject is lost to follow up. Follow-up information shall be reported on the AE follow-up form.

8.5.11 Reporting and follow-up of events occurring after subject termination of the study

All Adverse Events with a causal relationship to the study products or treatment procedure that the Investigator becomes aware of, serious as well as non-serious, with onset after the study termination (subject's last study visit) shall be reported to the Sponsor by email to safety.q-med@galderma.com. The Investigator shall follow the subject until the event as resolved.

8.5.12 Pregnancy

Pregnancy itself is not regarded as an AE.

If there is a pregnancy during the study period the subject must be withdrawn from any following study treatment, but should continue to be followed within the study and the outcome of pregnancy must be reported even if the delivery occurs after study completion.

A pregnancy confirmed during the study period must be reported by the Investigator on a pregnancy report form immediately upon acknowledge be submitted to the Sponsor according to contact details specified in section 8.5.7. The report can be prospective or retrospective. Follow-up shall be conducted to obtain outcome information on all prospective reports.

Cases that led to fetal distress, fetal death or a congenital abnormality or birth defect are to be regarded as SAEs and shall be reported on the exposure *in utero* report form to the Sponsor immediately but no later than 24 hours after the Investigators awareness. These events shall be handled as SAEs during data processing. Other complications during the pregnancy that are related to the pregnant woman and fulfils any serious criteria, such as pre-eclampsia requiring hospitalization, shall be reported and handled as SAEs. Elective abortions without complications shall not be reported as AEs.

8.5.13 Anticipated Adverse Events

Information regarding anticipated AEs for *Restylane-L* is included in the study specific IFU.

8.6 Device deficiencies

8.6.1 Definition of a device deficiency

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

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

8.6.2 Recording instructions

When a device deficiency is discovered, Part A of the clinical study complaint form shall be completed by the Investigator. The type of complaint shall be described and injury to the subject or user or unintended exposure to study product shall be reported as applicable. If an injury has occurred, an AE or an SAE form shall be completed as applicable (refer to sections 8.5.5 and 8.5.7). If no SAE was experienced as a result of the device deficiency the Investigator shall assess whether or not the device deficiency could have led to an SAE if:

- Suitable action had not been taken,
- Intervention had not been made or,
- Circumstances had been less fortunate

In Part B of the clinical study complaint form the Sponsor will make the same assessment.

8.6.3 Reporting of device deficiencies

The Investigator shall send the completed clinical study complaint form to the Sponsor.

E-mail for device deficiencies reporting: drugsafetypv@advancedclinical.com

Fax number for device deficiencies reporting: +888–493–0910

[IV] Inadequacy of device safety refers to properties of the device which could have or have led to an AE.

A device deficiency that led to a SAE and any device deficiency that could have led to a SAE shall be reported to the Sponsor within 24 hours after the Investigator's awareness (for contact information, see section 8.5.7).

If the Investigator or the Sponsor assesses that the device deficiency could have led to a SAE the Sponsor is responsible for reporting the device deficiency to RA and the PI is responsible for reporting it to the IRB.

The deficient study product shall be kept by the study site until the Sponsor has confirmed whether the product shall be returned to Sponsor for further study or if it can be destroyed at the study site.

9. Data Handling and Management

9.1 Data management

Data management based on GCP refers to the activities defined to achieve safe routines to enter clinical data information into a database, efficiently and avoiding errors. The data management routine includes procedures for database set-up and management, data entry and verification, data validation, and documentation of the performed activities including information of discrepancies in the process. The data management process will be described in detail in the data management plan (DMP).

The database, the data entry screens and program will be designed in accordance with the CSP and the CRF template. Data validation will be performed by computerized logical checks and manual review. Drugs and events will be coded in accordance with World Health Organization (WHO) Drug and medical dictionary for regulatory activities (MedDRA) dictionaries as specified in the DMP. Safety data (SAE and if applicable AE of special interest) in the clinical database will be reconciled against the data in the safety database.

When all efforts have been made to ensure that the data recorded in the eCRFs and entered in the database is as correct and complete as possible, the clinical database will be locked. Study data will be transferred to SAS datasets, which thereafter will be write-protected. Statistical analyses will be generated in SAS using data from the locked datasets.

9.2 Electronic case report forms

A 21 Code of Federal Regulations Part 11-compliant electronic data capture application will be used to collect, modify, maintain, archive, retrieve, and transmit study data. An eCRF is required and should be completed electronically for each screen failure as well as enrolled subjects.

The eCRF includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Study data should be entered directly from the source documents, which are to be defined at each site before inclusion of the first subject.

Authorized study site personnel designated by the Investigator should complete data collection. Appropriate training and security measures should be completed with all authorized investigation site personnel prior to the study being initiated and any data being entered into the system for any subject.

The study data is the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate RA, without written

permission from the Sponsor. At the end of the study, electronic data are kept at the Sponsor and a copy (provided by the vendor) at the study site as part of the Investigator file.

Any delegation of collection of data should be specified in a signature and delegation log.

9.2.1 Data entry

All data shall be entered in English. The eCRFs should always reflect the latest observations on the subjects participating in the study. Therefore, the eCRFs shall be completed as soon as possible during or after the subject's visit. The subject's identity must always remain confidential, i.e. the name and address of the subjects must not be registered in the eCRFs or in the database. The Investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available, not applicable or unknown, the Investigator shall indicate this in the eCRF. The Investigator shall electronically sign off the study data. By signing, the Investigator takes responsibility for the accuracy, completeness, and legibility of the data reported to the Sponsor in the eCRF.

9.2.2 The query process

The monitor shall review the eCRFs and evaluate them for completeness and consistency. Each eCRF shall be compared with the respective source documents to ensure that there are no discrepancies between critical data. All entries, corrections, and alterations shall be made by the PI or his/her authorized designee. The monitor cannot enter data in the eCRFs. Once study data have been submitted to the central server via the eCRF, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who made the change, together with time and date will be logged. Roles and rights of the site personnel responsible for entering study data into the eCRF shall be determined in advance. If discrepant data is detected during review of the data, either by the Sponsor or by its representatives, the responsible data manager or monitor shall raise a query in the electronic data capture application. The query shall state the question or data to be changed and shall be resolved in the system by the PI or his/her authorized designee. The appropriate study site personnel shall answer the queries in the eCRF. This will be audit trailed by the electronic data capture application meaning that the name of study site personnel, time, and date is logged.

9.2.3 User identification

Electronic CRF records will be automatically appended with the identification of the creator, by means of their unique UserID. Specified records shall be electronically signed by the Investigator to document his/her review of the data and acknowledgement that the data are accurate. This will be facilitated by means of the Investigator's unique UserID and password; date and time stamps will be added automatically at time of electronic signature. If an entry in an eCRF requires change, the correction shall be made in accordance with the relevant software procedures.

9.2.4 Audit trail

All changes will be fully recorded in a protected audit trail and a reason for the change shall be stated. Once all data have been entered, verified, and validated, the database will be locked.

9.3 **Source documents**

Source documents are all documents used by the Investigator or hospital that relate to the subject's medical history, that verifies the existence of the subject, the inclusion and exclusion

criteria, and all records covering the subject's participation in the study. They include laboratory notes, memoranda, material dispensing records, subject files, etc.

The Investigator is responsible for maintaining source documents. These should be made available for inspection by the monitor at each monitoring visit. The Investigator must submit a completed eCRF for each subject for whom signed informed consent has been collected. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the CTN and subject number. Any personal information, including name, should be removed or rendered illegible to preserve individual confidentiality.

9.4 Record keeping and access to source data

The Investigator/Institution should permit study-related monitoring, audits, IRB review, and RA inspections and should provide direct access to the source data/medical record including the identity of all participating subjects (sufficient information to link records, i.e. eCRF, medical records, original signed informed consent forms and detailed records of study product accountability). The records should be retained by the Investigator as required by local legislation and international guidelines. Any transfer of responsibility for storage of the records should be documented and the Sponsor should be informed in writing.

The Sponsor should verify that each subject has consented in writing to direct access to the original medical record/source data (by the use of written subject information and signed informed consent). The data recorded in the eCRFs will be checked for consistency with the source documents/medical record by the monitor during monitoring (source data verification; SDV). In order to be able to perform SDV, information about each subject's participation in the study has to be detailed in the medical record.

9.5 Document and data retention

All records pertaining to the conduct of the study, including signed eCRFs, informed consent forms, study product accountability records, source documents, and other study documentation must be retained for as long as is specified in the CTA. Measures should be taken to prevent accidental or premature destruction of these documents (e.g. protection against damage and unauthorized access, preferably by storage in a fire-proof cabinet).

It is the Investigator's responsibility to inform the Sponsor in writing if the Investigator file is moved or if the responsibility for the documents is transferred to someone else.

10. Statistical Methods

10.1 General

A comprehensive Statistical Analysis Plan (SAP) with detailed description of all statistical analyses will be developed before database lock.

All study data will be listed in subject data listings.

All statistical analyses, including summary tables and data listings, will be performed using SAS. Confidence intervals (CIs) will be two-tailed and constructed at a confidence level of 95%. Statistical tests will be performed at a significance level of 5%, and p-values will be two-sided, unless otherwise specified.

Continuous endpoints will be summarised using descriptive statistics, e.g. number of subjects (n), mean, median, standard deviation, minimum and maximum values. Categorical endpoints

will be presented in frequency tables with number and percentage of observations for each level.

10.2 Analysis populations

The following populations will be defined:

• Modified Intention-to-treat (mITT)	Includes all subjects who are randomized and will be analyzed according to the randomization scheme; subjects with a GIHS month 3 assessment via a remote visit will be excluded from the mITT.
• Intention-to-treat (ITT)	Includes all subjects who are randomized and will be analyzed according to the randomization scheme
• Per protocol (PP)	Includes all subjects in ITT who complete 3 months after baseline visit without any deviations considered to have substantial impact on the primary effectiveness
• Safety	Includes all subjects who were treated with *Restylane-L* or randomized to the control group, and will be analyzed according to as-treated principle

The mITT will be used for the primary effectiveness analysis. All secondary effectiveness endpoints will be analyzed based on the ITT population, CCI [redacted] Safety analysis is performed based on the safety population set.

The disposition of subjects will be presented in tables and/or figures as appropriate. The number of screened, treated, completed, and withdrawn subjects will be presented, as well as number of subjects in each analysis population set.

10.3 Demographics, baseline assessments, and subject characteristics

Demographic endpoints, baseline assessments, and subject characteristics will be presented based on the ITT analysis set using descriptive statistics by treatment, as appropriate.

10.4 Effectiveness analysis

10.4.1 Primary effectiveness analysis:

Responder rate based on the GIHS as assessed live by the Blinded Evaluator at month 3 after baseline will be the primary effectiveness endpoint. A responder will be defined as a subject with at least 1 point improvement from baseline on both sides of the face concurrently. For a significant result, the two-sided p-value of the comparison of responder rates between the treated and untreated subjects at month 3, using the Cochran-Mantel-Haenszel (CMH) test stratified by injection tool, needs to be smaller than 0.05.

The null hypothesis will be that there is no relationship between responder rate and treatment group (i.e. the responder rate is the same in both groups). The alternative hypothesis will be that there is a relationship between responder rate and treatment group (i.e. the responder rate is different in the two groups).

The estimates of the responder rate in each treatment group will be presented as well as the difference in responder rates. Corresponding confidence intervals for responder rates and the difference in responder rates along with the p-value for the difference will also be presented.

CCI [redacted]

10.4.2 Secondary effectiveness analysis:

Responder rates (defined as at least 1 point improvement from baseline on both sides of the face concurrently) based on the GIHS as assessed by the Blinded Evaluator at month 6, 9, and 12 after baseline and at 3 and 6 months after optional treatment will be analyzed in the same way as the primary effectiveness endpoint. No correction for multiplicity will be done; p-values obtained for any endpoint other than the primary will only be provided for ease of interpretation of the results.

All other secondary effectiveness analyses will be done descriptively as appropriate.

10.5 Safety analysis

Number and percentage of subjects reporting each pre-defined, expected, post-treatment symptoms, as collected in the 28 days diary, will be presented in total and by maximum severity. Number of days with the event will be presented by treatment group and category: 1, 2-7, 8-13, and 14-28.

All AEs will be coded according to MedDRA and summarized by system organ class (SOC), preferred term (PT) and treatment.

A summary of all AEs will be provided, which will include:

- number of subjects with at least one AE and number of events (in total as well as serious AEs)
- number of subjects with at least one related AE and number of events (in total as well as serious AEs)
- number of subjects with at least one mild, moderate and severe AE and number of events (in total as well as serious AEs)
- number of subjects with at least one unrelated AE and number of events (in total as well as serious AEs)
- number of subjects who did not have an AE

The number of subjects with AEs related to study product or injection procedure as well as the number of events will be summarized by SOC, PT and maximum severity. In addition, for related AEs the number of days to onset and the duration of event will be summarized by SOC and PT using mean, SD, min, max and median. Action taken for related AEs will also be summarized. Serious AEs will be listed. AEs with onset >21 days after most recent treatment will be listed.

Non-related AEs will be summarized by SOC, PT and intensity.

To evaluate consistency of AEs across different subgroups, AEs will also be summarized by subgroups defined as described below.

Safety analysis will be descriptive only.

10.6 Subgroup analyses

10.6.1 Effectiveness

The GIHS and GAIS endpoints will be analyzed in the needle group and the cannula group separately, using the same analysis method as for the primary analysis for GIHS, and descriptively for GAIS (control subjects will be pooled). CCI [redacted]

CCI [redacted]

CMH tests will be used for comparison of responder rates, as well as confidence intervals of the differences in responder rates. These will be displayed in graphs.

10.6.2 Safety

In order to evaluate the safety of treatment using needle and cannula respectively, AE data will be summarized by needle, cannula and no treatment separately.

CCI [redacted]

10.7 Handling of drop-outs and missing data

Number of missing values will be summarized and reported as appropriate.

For mITT analysis of the Blinded Evaluator GIHS responder rate at month 3 after baseline (primary endpoint), CCI [redacted]. Impact of missing data on the primary endpoint will be evaluated by performing sensitivity analysis based on the baseline observation carried forward (BOCF) method, and the observed cases.

All other effectiveness endpoints will be evaluated based on the observed cases in ITT.

Descriptive statistics of all safety data will be performed on observed cases in the Safety population.

10.8 Interim analysis

Not applicable.

10.9 Data monitoring committee

Not applicable.

10.10 Withdrawals and deviations

All withdrawn subjects will be listed individually, including at least subject number, date and reason for withdrawal, and last visit performed.

Subjects with CSP deviations will be listed individually, including subject number and observed deviation. Depending on the seriousness of the deviation, subject might be excluded from the PP population, which shall be documented prior to database lock.

Deviations from the statistical plan will be documented in the Clinical Study Report.

10.11 Sample size

Due to the public health emergency related to the COVID-19 pandemic during 2020, steps have been taken to ensure patient and practitioner safety in alignment with FDA Guidance dated May 11, 2020 (Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency). Most notably, in partnership with clinical sites and the IRB, optional remote assessment procedures for efficacy and safety endpoints has been implemented to ensure safety and respect localized and elective restrictions. Therefore, the sample size has been increased during the conduct of the study to ensure a sufficient number of subjects in the mITT population used in the assessment of the primary effectiveness endpoint.

The study was initially planned to enroll a total sample size of approximately 238 subjects; approximately 204 randomized to treatment with *Restylane-L* (~102 injected using needle, and ~102 injected using cannula) and approximately 34 randomized to no treatment.

Based on information on missing data and the number of remote visits performed at study sites so far, the study is now planned to enroll approximately 329 subjects; approximately 282 will be randomized to treatment with *Restylane-L* (~146 will be injected using needle, and ~136 will be injected using cannula) and approximately 47 will be randomized to no treatment in order to achieve the required number of mITT subjects in each stratum.

CCI [redacted]

11. Protection of personal data

All processing of personal data must be carried out in accordance with national legislation concerning the protection of personal data. The Institution and the Investigator are responsible for complying with all requirements pursuant to national legislation in which the Institution and the Investigator are located. The Sponsor will ensure that all requirements for data processing are fulfilled.

The Investigator understands that clinical studies conducted under an IDE are exempt from the study subject identifier confidentiality provisions of the Health Insurance Portability and Accountability Act of 1996 (HIPAA), and the study subject should be made aware of this exception in the informed consent. The Institution and Investigator are jointly responsible for providing sufficient information to all subjects to enable them to give their informed consent not only to the participation in the investigation, but also to the processing of Personal Data. Such information includes information regarding the purposes of the processing, the length of time during which Personal Data will be stored, the right of access to stored Personal Data and the right to correction or purging of incorrect or obsolete Personal Data. A subject may also withdraw his or her consent at any time.

A subject who withdraws his or her consent to the processing of Personal Data must be considered to have withdrawn from the investigation, but the data collected until the consent was withdrawn may be used in the statistical analyses.

Authorized representatives from the Sponsor or a RA may visit the investigational site to perform audits/inspections, including source data verification, i.e., comparing data in the subjects' medical records and the eCRF. Data and information will be handled with strict confidentiality.

The study shall include collection and processing of personal data as specified in the Regulation (EU) 2016/679 (General Data Protection Regulation, GDPR) on the protection of individuals with regard to the processing of personal data. For the purposes of the study, Sponsor will be considered the data controller, and Institution and PI will both be considered data processors.

12. Quality Control and Quality Assurance

12.1 Quality control

On-site monitoring of the study will be arranged by the Sponsor according to GCP guidelines to verify that the rights and well-being of the subjects are protected, the reported data are accurate, complete, verifiable from source documents, and that the conduct of the study complies with the approved CSP, subsequent amendment(s), GCP and the applicable regulatory requirements.

Any CSP deviation shall be documented appropriately, verified, discussed, and collected by the monitor and appropriate actions will be taken. The PI is responsible for promptly reporting any deviations from the CSP that affects the rights, safety or well-being of the subject or the scientific integrity of the study, including those that occur under emergency circumstances, to the Sponsor as well as the IRB if required by national regulations. Deviations will be reviewed to determine the need to amend the CSP or to terminate the study.

12.2 Quality assurance

The study site may be subject to quality assurance audit by the Sponsor as well as inspection by appropriate RA. It is important that the PI and other relevant study site personnel are available during the monitoring visits, possible audits, and inspections, and that sufficient time is devoted to the monitoring process.

Each participating member of the study site team shall provide a curriculum vitae (CV) or equivalent that demonstrates their qualifications to conduct the study.

It is the responsibility of the PI to ensure that all personnel involved in the study are fully informed of all relevant aspects of the study, including detailed knowledge of and training in all procedures to be followed. All Investigators and other responsible persons shall be listed together with their function in the study on the signature and delegation log.

12.3 Changes to the clinical study protocol

The PI and other site personnel involved in the study must not implement any changes to the CSP without agreement with the Sponsor and prior review and documented approval from the IRB and RA, if applicable, except where necessary to eliminate an immediate hazard to the subjects. All changes to the final CSP must be documented in a dated and version-controlled written protocol amendment.

13. Financing, Indemnification, and Insurance

The CTA outlines the compensation and payment terms of the study. The CTA must be signed before the first subject is screened in the study. If there are differences between the CTA and the CSP regarding certain rights and obligations, the CTA is the prevailing document.

The Sponsor´s obligations in this clinical study are covered by Galderma's global general liability program. An insurance certificate will be provided upon request. The Institution/PI is obligated to maintain insurance coverage for their obligations in the clinical study according to the CTA.

14. Publication Policy

The PI's, Institution's, and Q-Med AB's obligations regarding intellectual property rights, confidentiality, and publications are described in detail in the CTA.

The aim is to submit the results of this study for publication in the public database ClinicalTrials.gov and to a medical journal for a first joint publication of the results. Everyone who is to be listed as an author of the results of this multicenter study shall have made a substantial, direct, intellectual contribution to the work. Authorship will be based on (1) substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and (2) drafting the work or revising it critically for

important intellectual content; and (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved[V]. Conditions 1, 2, 3, and 4 must all be met in order to be designated as author. Those who do not meet all four criteria will be acknowledged. Among the authors that fulfil the above mentioned criteria, one author will be appointed by Q-Med AB to take primary responsibility for the overall work as primary author.

15. Suspension or Premature Termination

The Sponsor will suspend or terminate the study when so instructed by the IRB or RA, or if it is judged that the subjects are subjected to unreasonable risks, or for valid scientific or administrative reasons, or for business reasons.

The Sponsor may also decide to close a single study site due to unsatisfactory subject enrolment or non-compliance with the CSP, GCP, or applicable regulatory requirements.

In the event of premature termination, Q-Med AB will provide information on the handling of currently enrolled subjects who have not completed the study.

[V] Defining the role of authors and contributors, compiled by the International Committee of Medical Journal Editors (ICMJE) (http://www.icmje.org).

16. References

1. Alam M, Gladstone H, Kramer EM, et al. ASDA guidelines of care: injectable fillers. Dermatol Surg. 2008; 34 (suppl 1): S115-S148.
2. Fitzpatrick T.B. (1988). The validity and practicality of sun-reactive skin types I through VI. Arch. Dermatol. 124, 869–871.

Appendix 1 Declaration of Helsinki

WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

Appendix 2 Galderma Infraorbital Hollows Scale (GIHS)

The following validated scale will be used to assess Infraorbital Hollows assessed by Blinded evaluator and Treating Investigator.

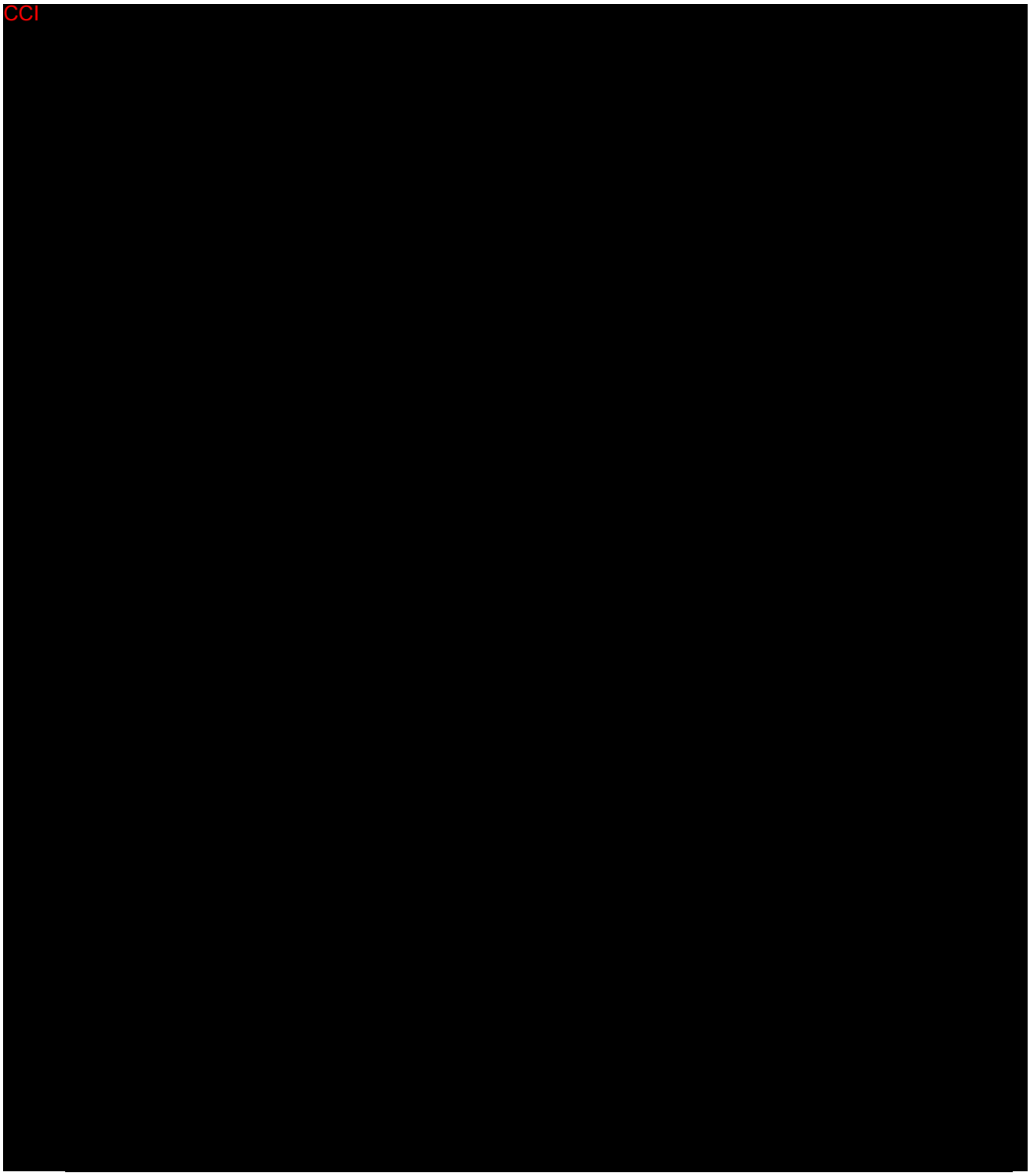
GALDERMA EST. 1981	Title **43USTT1904 CSP Infraorbital Hollows**	Doc id **MA-40833**

Effective date: 2021-12-15 20:29

Effective

Version: 10.0

CCI



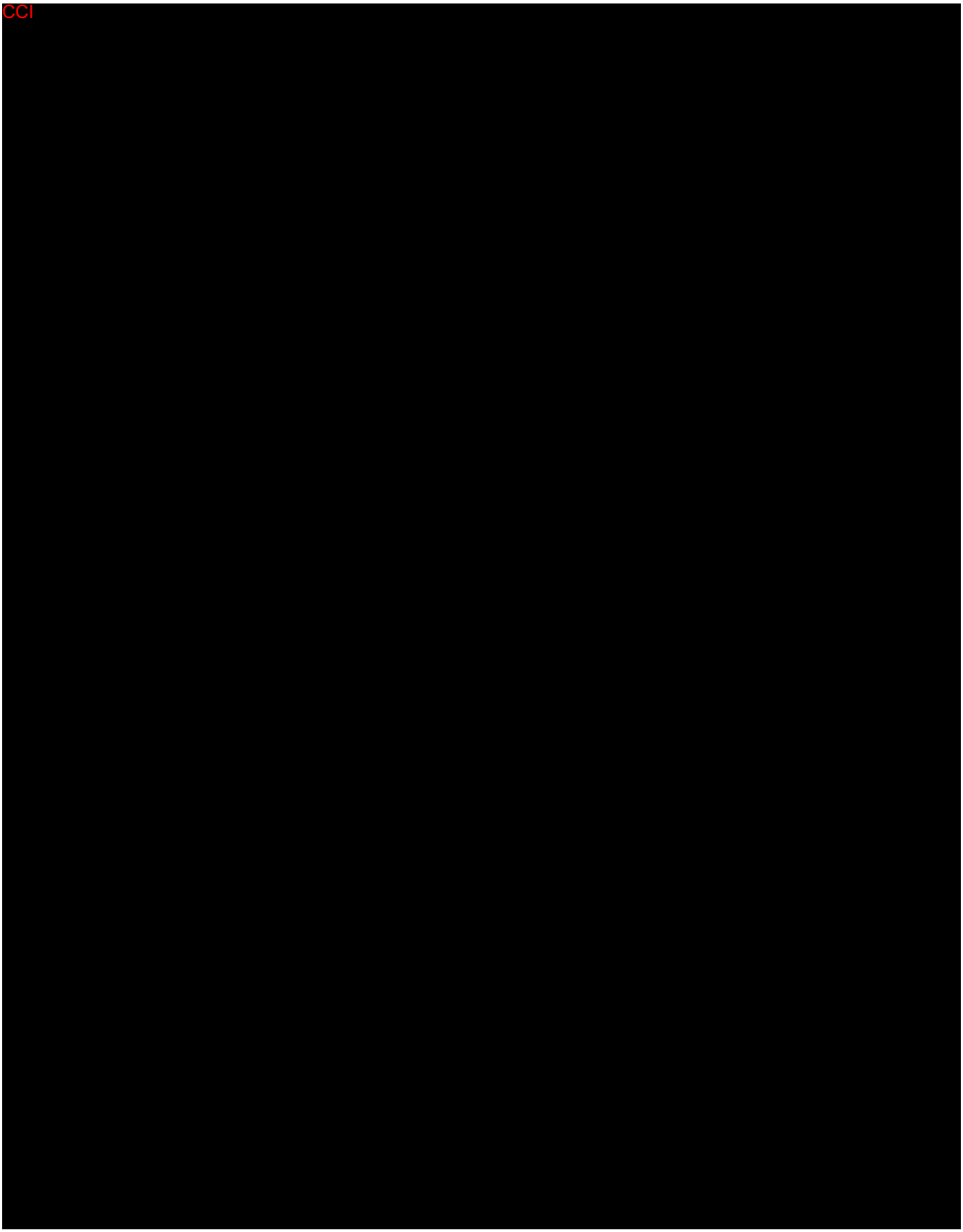
GALDERMA EST. 1981	Title **43USTT1904 CSP Infraorbital Hollows**	Doc id **MA-40833**

Effective date: 2021-12-15 20:29

Effective

Version: 10.0

CCI



Appendix 5 Summary of changes to the clinical study protocol

Summary of Changes in Clinical Study Protocol 43USTT1904 from Version 9.0 to Version 10.0

Section in the clinical study protocol	Rational for changes	Description of changes
Synopsis, and section 3.1.2	CCI	[redacted]
Synopsis, sections 10.4.1, 10.4.2, and 10.6.1		

GALDERMA EST. 1981	Title **43USTT1904 CSP Infraorbital Hollows**	Doc id **MA-40833**

SIGNATURES PAGE

Date	Signed by
2021-12-15 07:46	PPD
Justification	Approved by Technical Expert

2021-12-15 10:57	PPD
Justification	Approved by Technical Expert

2021-12-15 14:56	PPD
Justification	Approved by Project Manager

2021-12-15 20:29	PPD
Justification	Approved by Owner