SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Injectable Dermal Filler

Device Trade Name: RHA Redensity® Eye Lido and RHA Redensity® Eye

Device Procode: LMH

Applicant's Name and Address: TEOXANE SA
Les Charmilles
Rue de Lyon, 105
CH - 1203 Geneva, Switzerland

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P170002/S050

Date of FDA Notice of Approval: May 12, 2026

RHA Redensity® was approved on December 22, 2021, under PMA panel-track supplement P170002/S012 and RHA Redensity® Mepi was approved on October 13, 2023, under panel-track supplement P170002/S026. Both were approved for injection into the dermis and superficial dermis for the correction of moderate to severe dynamic perioral rhytids, in adults aged 22 years or older. The SSEDs to support the indication of RHA Redensity® and RHA Redensity® Mepi for the correction of moderate to severe perioral rhytids are available on the CDRH website and is incorporated by reference here. The current supplement was submitted to expand the indication of these two products.

II. INDICATIONS FOR USE

RHA Redensity® Eye Lido is indicated for injection into the sub-dermis and supraperiosteum for the correction of moderate to severe tissue volume deficiencies in the infraorbital region, in adults aged 22 years or older.

RHA Redensity® Eye is indicated for injection into the sub-dermis and supraperiosteum for the correction of moderate to severe tissue volume deficiencies in the infraorbital region, in adults aged 22 years or older.

III. CONTRAINDICATIONS

- RHA Redensity® Eye Lido and RHA Redensity® Eye are contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.
- RHA Redensity® Eye Lido and RHA Redensity® Eye contain trace amounts of gram-positive bacterial proteins and is contraindicated for patients with a history of allergies to such material.
- RHA Redensity® Eye Lido and RHA Redensity® Eye should not be used in patients with previous hypersensitivity to local anesthetics of the amide type, such as lidocaine or mepivacaine.
- RHA Redensity® Eye Lido and RHA Redensity® Eye should not be used in patients with bleeding disorders.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in RHA Redensity® Eye Lido and RHA Redensity® Eye labeling.

V. DEVICE DESCRIPTION

RHA Redensity® Eye Lido and RHA Redensity® Eye are viscoelastic, sterile, non-pyrogenic, clear, colorless, and biodegradable gel implants. They are produced with sodium hyaluronate (NaHA) with a concentration of 15 mg/g obtained from bacterial fermentation using a *Streptococcus equi* bacterial strain, crosslinked with 1,4-butanediol diglycidyl ether (BDDE) and reconstituted in a physiological buffer (pH 7.3).

RHA Redensity® Eye Lido contains 0.3% lidocaine hydrochloride monohydrate to reduce pain on injection.

RHA Redensity® Eye contains 0.3% mepivacaine hydrochloride to reduce pain on injection.

RHA Redensity® Eye Lido gel is pre-filled in a 1.0 ml syringe and is supplied with two 30G ½ inch hypodermic needles.

RHA Redensity® Eye gel is pre-filled in a 1.0 ml syringe and is supplied with one 30G ½ inch hypodermic needle and one 25G 1 ½" cannula (with it 23G ¾" pre-hole needle).

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for tissue volume deficiencies in the infraorbital region: blepharoplasty that may include fat repositioning, fat grafting and different soft tissue fillers. These volume filling techniques can be used in conjunction with laser skin

resurfacing or botulinum toxin to reduce wrinkles in the area. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

RHA® products containing lidocaine have been sold in the United States since 2020 and RHA® products containing mepivacaine were launched late 2024. They have been approved for perioral rhytid and nasolabial fold indications. RHA® products with lidocaine are also commercially available in the European Union and registered in more than 45 countries around the world since 2015. They have been approved for a wide range of indications including for infraorbital hollows. No RHA® products containing lidocaine or mepivacaine have been removed from the marketplace for any reasons related to safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g. complications) associated with the use of the device.

Common treatment responses which can occur with the use of RHA® family of products, include bruising, discoloration, firmness (induration), itching, lumps/bumps (injection site mass), pain, redness, swelling and tenderness. All these common treatment responses were seen in the clinical studies.

In addition to the common treatment responses noted above, the following adverse events were reported from use in the various locations of the face, as part of the post-marketing surveillance on the use of RHA® family of products in and outside the United States. The following adverse events were reported on the use of RHA family of products worldwide with a prevalence equal or superior to one occurrence for 100,000 syringes: skin edema, injection site masses (lumps and bumps), skin swelling, skin induration, vascular complication (such as vessel compression/occlusion), pain, ecchymosis, erythema, skin discoloration and inflammatory reaction. Also, the injection of a dermal filler in the infraorbital region may result in a Tyndall effect, i.e. temporary blue hue of the skin caused by light scattering onto the gel.

Additionally, other less frequent adverse reactions have also been reported, including dermal filler overcorrection, allergic reaction, product misplacement, inflammatory nodules (papules), skin necrosis, granuloma, injection site movement impairment, paraesthesia, skin atrophy, injection site fibrosis, urticaria, device dislocation and injection site extravasation.

Delayed-onset inflammation near the site of dermal filler injections is one of the known adverse events associated with dermal fillers. Cases of delayed-onset inflammation have been reported to occur at the dermal filler treatment site following viral or bacterial

illnesses or infections, vaccinations, or dental procedures. Typically, the reported inflammation was responsive to treatment or resolved on its own.

Additionally, the following rare but serious adverse events that are associated with intravascular injection of other soft tissue filler material in the face have been reported in the literature: vision impairment (acute or permanent), blindness, cerebral ischemia or cerebral hemorrhage leading to stroke, skin necrosis, and damage to underlying facial structures.

In many cases the symptoms resolved without any treatment. Reported treatments included the use of (in alphabetical order): analgesics, antibiotics, antihistamines, anti-inflammatories, anti-viral, corticosteroids, drainage, excision, implant dissolution (hyaluronidase), incision, massage and vasodilators. Outcomes for these reported events ranged from resolved to ongoing at the time of last contact.

For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF NON-CLINICAL STUDIES

A. Laboratory Studies

Table 1: Physical and Chemical Testing – Requirements for RHA Redensity® Eye Lido and RHA Redensity® Eye

Test	Purpose	Results
NaHA content	To confirm the NaHA concentration meets specifications	Passed
Sterility	To ensure the product is sterile	Passed
Bacterial Endotoxins	To confirm the endotoxins count in the device meets specifications	Passed
pH	To confirm the pH of the gel meet specifications	Passed
Residual crosslinker content	To confirm the residual crosslinker content of the gel meets specifications	Passed
Anesthetic content Lidocaine for RHA Redensity® Eye Lido Mepivacaine for RHA Redensity® Eye	To confirm the anesthetic concentration of the gel meets specifications	Passed
Impurities deriving from anesthetic	To confirm impurities in the gel meet specifications	Passed
Extrusion force	To confirm the extrusion force meets specifications	Passed
Rheology: mechanical properties of the gel	To confirm phase angle δ of the gel meets specifications	Passed
Appearance of the device	To control visually the absence of irregularities and defects in the device	Passed
Gel content	To ensure gel meets specifications	Passed

B. Biocompatibility Studies

Table 2: Summary of Biocompatibility Studies for RHA Redensity® Eye Lido and RHA Redensity® Eye

Test	Method	ISO Standard or USP	Results
Cytotoxicity	MTS Cytotoxicity Test Agarose Overlay Method	ISO 10993-5	Same cytotoxic potential as control*.
Sensitization	Guinea pig maximization study	ISO 10993-10	No delayed sensitization.
Intracutaneous reactivity	Intradermal injection in rabbits	ISO 10993-10**	Level of reactivity similar or slightly less than its control*. RHA Redensity® Eye Lido was non-irritant at 4 days or sooner. RHA Redensity® Eye was non-irritant in 72 hours or sooner.
Pyrogenicity	Rabbit pyrogen study	USP 36 NF 31 (RHA Redensity® Eye Lido) USP 41 NF 36 (RHA Redensity® Eye) ISO 10993-11	Non-pyrogenic.
Genotoxicity	Ames test (bacterial reverse mutation study)	ISO 10993-3	Non-mutagenic.
Genotoxicity	Mouse lymphoma assay (MLA)	ISO 10993-3	Non- mutagenic.
Genotoxicity	Mouse peripheral blood micronucleus test (for RHA Redensity® Eye Lido only)	ISO 10993-3	Non-genotoxic.
Acute systemic toxicity	Mice intraperitoneal study	ISO 10993-11	No evidence of acute systemic toxicity.
Subacute and subchronic systemic toxicity	Intradermal injection in Sprague-Dawley rats (for RHA Redensity® Eye Lido only)	ISO 10993-11	No toxicological concern.
Intradermal implantation	Intradermal implantation in rats	ISO 10993-6	The test article was classified as non-irritant. No adverse response microscopically or macroscopically. After 52 weeks, degradation had started.

(*) Note: The control device was an FDA approved Hyaluronic Acid soft tissue filler, with similar characteristics. The control product is legally marketed with similar indications for use

(**) Note: This standard has been updated in 2021 and now covers only sensitization tests, ISO 10993-23 is now covering irritation tests. However, in vivo intracutaneous tests were carried out based on a methodology which has not been modified. Therefore, results remain valid accordingly for irritation assays performed on RHA Redensity® Eye Lido and RHA Redensity® Eye products.

C. Stability studies

Stability data have been collected on three batches per product (RHA Redensity® Eye Lido and RHA Redensity® Eye) at 25°C ± 2°C and 60% ± 5% relative humidity (ICH long term storage conditions). The stability study was conducted through 36 months for RHA Redensity® Eye Lido and 24 months for RHA Redensity® Eye. As part of stability testing, products were characterized via microbiological, physical, and chemical specifications parameters, including lidocaine hydrochloride monohydrate content for RHA Redensity® Eye Lido and mepivacaine hydrochloride content for RHA Redensity® Eye, and lidocaine-related or mepivacaine-related degradation products. Conformance of all batches with all specifications was confirmed up to the end of the studies. Therefore, RHA Redensity® Eye Lido and RHA Redensity® Eye dermal fillers have a 36-month and 24-month shelf life respectively with recommended storage conditions up to 25°C (77°F).

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness when injecting RHA Redensity® Eye Lido into the sub-dermis and supraperiosteum layers of the infraorbital region for the correction of moderate or severe infraorbital hollows in adults aged 22 years or over in the U.S. under IDE # G200191. Data from this clinical study was the basis for the PMA approval decision. Those data were leveraged for RHA Redensity® Eye as they are identical products with a different anesthetic agent. Clinical study IDE G190055 demonstrated the non-inferiority of mepivacaine to lidocaine in the device. A summary of the clinical study with RHA Redensity® Eye Lido is presented below.

A. Study Design

Patients were treated between December 2, 2020 and February 10, 2023. The database for this PMA reflected data collected through August 16, 2024 and included 248 subjects treated. There were 11 investigational sites.

The study was a no-treatment control design with 183 subjects initially treated with RHA Redensity® Eye Lido and 65 subjects in the No-Treatment control group. After reaching the primary endpoint, the subjects in the No-Treatment control group were scheduled to receive treatment and followed the same study plan as those initially assigned to the treatment group.

The study was a multicenter, blinded-evaluator, randomized, prospective, no-treatment control clinical investigation to identify whether RHA Redensity® Eye Lido was superior to no treatment for the correction of moderate to severe tissue volume deficiencies in the infraorbital regions. Subjects meeting inclusion/exclusion criteria were randomized 3:1 ratio into the treatment or control group. Patients receiving RHA Redensity® Eye Lido were further divided by the method of administration: injection with a needle (30G ½") or a cannula (25G 1 ½"). There was an approximate 1:1 distribution between the subgroups.

The primary effectiveness endpoint using the Teoxane Infra-orbital Hollows Scale (TIOHS) was evaluated at 12 weeks after Visit 1. All patients were followed for 52 weeks after injection to evaluate the long-term safety and effectiveness of RHA Redensity® Eye Lido when injected into the infraorbital regions. Safety and effectiveness assessments were also evaluated for 12 weeks after retreatment.

The maximum volume of administration of RHA Redensity® Eye Lido was 1 mL per eye and per treatment.

The study duration was nearly 18 months and included repeat treatment.

1. Key Clinical Inclusion and Exclusion Criteria

Enrollment in the pivotal study was limited to subjects who met the following inclusion criteria:

- Outpatient, male or female of any race, 22 years of age or older. Female patients of childbearing potential must have had a negative urine pregnancy test (UPT) at Visit 1 and practice a reliable method of contraception throughout the study:
- Had infraorbital volume loss of grades 2 to 3 on the Teoxane Infra-orbital Hollows Scale (TIOHS) for both eyes (ranging from 0 = none to 4 = very severe). Bilateral symmetry was not required. The blinded live evaluator (BLE) and treating investigator (TI) must independently assess and agree that this criterion was met; however, concordance of fullness was not required. If the assessments of the TI and the BLE were the same or differ by exactly 1 point on the scale, this difference was considered acceptable. The BLE assessment was used for the Baseline for the primary endpoint.
- Was willing to abstain from facial aesthetic procedures/therapies that could interfere with study evaluations (e.g., other fillers, botulinum toxin injections, laser, or chemical resurfacing, facial plastic surgery) for the duration of the study

Patients were not permitted to enroll in the study if they met any of the following exclusion criteria:

- Had either one of the following assessments during the vision tests: Snellen acuity test worse than 20/40 (with corrections, if applicable); abnormal confrontational visual field test; or abnormal ocular motility test
- Had known hypersensitivity or previous allergic reaction to any component of the study or the control device

- Had known sensitivity to local anesthetics of the amide type, including known or suspected lidocaine hypersensitivity, history of multiple severe allergies, or history of anaphylactic shock
- Compromised immunity, including but not limited to, poorly controlled diabetes mellitus (all types), autoimmune disease, or treatment with systemic corticosteroids, standard immunosuppressants, or biologics that may increase the risk of injection as judged by the TI.
- Was planning to undergo during the study or had undergone any type of facial, plastic, nonablative, or reconstructive surgery (e.g. blepharoplasty, face lift, or rhinoplasty) within 6 months before randomization. Subject was also excluded if residual swelling is present or complete healing has not occurred within at least 6 months of the treatment received.
- Had previously undergone or was planning to undergo prohibited treatment/procedures during certain time periods in the treated area or upper part of the face (above the lower orbital rim).
    - Semi-permanent dermal filler (e.g., calcium hydroxylapatite, poly-L-lactic acid) ≤24 months before randomization
    - Bioresorbable facial dermal filler (hyaluronic acid, collagen, or autologous fat) ≤ 12 months before randomization
    - Botulinum toxin injection ≤ 6 months before randomization
    - Permanent filler injection (e.g., polymethylmethacrylate, silicone) at any time in the past
- Had prior lower eyelid surgery, including orbital or midface surgery, or has a permanent implant or graft in the midfacial region that could interfere with effectiveness assessments or plans to have it during the study
- Had an orbital fat prolapse that might be linked to high weight variability (loos or gain), excessive lower eyelid skin laxity, ectropion, entropion, or previously/currently treated with fat injections ≤12 months before randomization
- Had triangular malar mounds or fluid bags
- Had ongoing cutaneous injection at the site of injection at randomization
- Had known susceptibility to keloid formation, hypertrophic scarring, or clinically significant skin pigmentation disorders as judged by the TI
- Had a history of connective tissue disease (rheumatoid arthritis, scleroderma, systemic lupus erythematosus)
- Had a need for clinically significant, as judged by the TI, and continuous medical treatment within 2 weeks prior to Visit 1

- Had any significant concomitant skin disease or ocular condition that may interfere with the study assessment as judged by the TI.
- Had known prolonged bleeding times because of disease or anticoagulant medication (including warfarin or low-dose aspirin). If food supplements with potential anticoagulant or antiplatelet effect (e.g., fish oil, omega-3, vitamin E, herbal supplements with garlic, or gingko biloba) were taken, the subject must have stopped them and waited 1 week or until bleeding times returned to normal before injecting. Supplements should not have been used for 1 week after the injection
- Has eye tattoos, scars, lumps, or severe asymmetry that would interfere with visualization of the eye region for the effectiveness assessments as per TI discretion.
- Had received any investigational product within 90 days prior to Visit 1 or planned to participate in another investigation during the course of the study
- Had medical or psychiatric conditions that may increase the risk associated with study participation or may interfere with the interpretation of study results or compliance of the subject and would make the subject inappropriate for entry into this study, as judged by the TI
- Had clinically significant alcohol or drug abuse, or history of poor cooperation or unreliability, as judged by the TI
- Was study staff or a close relative to study staff (e.g., parents, children, siblings, or spouse).

2. Follow-up Schedule

All patients were scheduled to return for follow-up examination at 2, 4, 8 and 12 weeks after the initial visit. Patients in the No-Treatment control group then crossed over and received injection and returned for follow-up examination at 2, 4, 8 and 12 weeks after their injection. All patients continued the study and returned for follow-up examinations at 24, 36 and 52 weeks after their injection. At which time, all patients were offered retreatment or exited the study. If patients received retreatment, they were scheduled to return for follow-up examinations at 2, 4 and 12 weeks after retreatment before exiting the study.

All site visit windows were ±3 days except the visits at 24, 36 weeks after treatment and the visit 12 weeks after retreatment which were ±7 days.

Pre-injection, patients performed visual assessments (Snellen visual acuity, confrontational visual field test and ocular motility test) and blink and

closure tests. The TI and the BLE assessed the TIOHS grade of each eye and the patient completed *the Appraisal of lower eyelid* domain of the validated FACE-Q© patient-reported outcome measurement and part A of the Periorbital Subject Assessment Questionnaire (PSAQ) at Baseline.

Postinjection and at every visit, the objective parameters measured during the study included: TIOHS and GAIS assessments by the TI; FACE-Q, GAIS, PSAQ and subject satisfaction assessments by the patient; TIOHS and GAIS assessments by the BLE starting at the primary endpoint and thereafter.

Adverse events and complications were recorded at all visits.

The key timepoints are shown below in Table 3 and Table 4 summarizing safety and effectiveness.

Table 3: Treatment Schedule

	Treatment group RHA Redensity® Eye Lido		**No-Treatment group up to primary endpoint**		**No-Treatment group After primary endpoint(2)**	
Phase 1	V1 – Visit 1 – Initial injection	Phase 1a	V1	Phase 1a	V1b	Phase 1b
	V2 – Visit 2 – 2 weeks		V2		V2b	
	V3 – Visit 3 – 4 weeks		V3		V3b	
	V4 – Visit 4 – 8 weeks		V4		V4b	
	V5 – Visit 5 – 12 weeks Primary endpoint		V5		V5b	
Phase 2	V6 – Visit 6 – 24weeks		N/A		V6	
	V7 – Visit 7 – 36 weeks				V7	
	V8 – Visit 8 – 52 weeks[1] Exit visit or retreatment				V8	
	V9 – Visit 9 – 2 weeks after retreatment				V9	
	V10 – Visit 10 – 4 weeks after retreatment				V10	
	V11 – Visit 11 – 12 weeks after retreatment Exit visit				V11	

([1]) Retreatment offered to all subjects

([2]) No-Treatment group received treatment after the first 12 weeks of their participation in the study and followed the same schedule as the Treatment group. V1/V1b means that the population of the Treatment group and the No-Treatment group after they had received treatment was pooled.

Table 4: Treatment Schedule and Assessments

		RHA Redensity® Eye Lido (Tx) / No-Treatment (No-Tx)		Safety Assessments	Effectiveness Assessments
		Phase 1a **Tx group** **No-Tx group**	**Phase 1b** **No-Treatment group only**		
Initial treatment	V1/V1b	0 weeks Initial treatment for Tx group only	12 weeks after V1 Initial treatment	AEs If received Tx: Tyndall effect Blink / closure test Visual assessments CTR diary Pain VAS after injection	BLE: TIOHS TI: TIOHS Patient: FACE-Q, PSAQ (part A only)
	V1call/ V1b call	3 days after tx – phone call Tx group only	3 days after tx – phone call	AEs CTR diary	N/A
	V2	2 weeks	2 weeks after tx	AEs If received Tx: Tyndall effect Blink / closure test Visual assessments CTR diary	TI: TIOHS
	V3	4 weeks	4 weeks after tx	AEs If received Tx: Tyndall effect Blink / closure test Visual assessments CTR diary	TI: TIOHS, GAIS Patient: FACE-Q, GAIS, PSAQ, Subject satisfaction
	V4	8 weeks	8 weeks after tx	AEs If received Tx: Tyndall effect Blink / closure test Visual assessments	TI: TIOHS, GAIS Patient: FACE-Q, GAIS, PSAQ, Subject satisfaction
Phase 1a: Primary endpoint	V5	**12 weeks**	12 weeks after tx	AEs If received Tx: Tyndall effect Blink / closure test Visual assessments	BLE: TIOHS, GAIS TI: TIOHS, GAIS Patient: FACE-Q, GAIS, PSAQ, Subject satisfaction
Phase 2					
	V6	24 weeks after tx		AEs Tyndall effect Blink / closure test Visual assessments	BLE: TIOHS, GAIS TI: TIOHS, GAIS Patient: FACE-Q, GAIS, PSAQ, Subject satisfaction
	V7	36 weeks after tx		AEs Tyndall effect Blink / closure test Visual assessments	BLE: TIOHS, GAIS TI: TIOHS, GAIS Patient: FACE-Q, GAIS, PSAQ, Subject satisfaction

		RHA Redensity® Eye Lido (Tx) / No-Treatment (No-Tx)		Safety Assessments	Effectiveness Assessments
		Phase 1a Tx group No-Tx group	Phase 1b No-Treatment group only		
Retreatment Or exit visit	V8	52 weeks after tx		AEs Tyndall effect Blink / closure test Visual assessments If re-Tx: before and after visual assessments CTR diary Pain VAS after injection	BLE: TIOHS, GAIS TI: TIOHS, GAIS Patient: FACE-Q, GAIS, PSAQ, Subject satisfaction
	V8Call	3 days after re-tx– phone call		AEs CTR diary	N/A
	V9	2 weeks after re-tx		AEs Tyndall effect Blink / closure test Visual assessments CTR diary	BLE: TIOHS, GAIS TI: TIOHS, GAIS Patient: FACE-Q, GAIS, PSAQ, Subject satisfaction
	V10	4 weeks after re-tx		AEs Tyndall effect Blink / closure test Visual assessments CTR diary	BLE: TIOHS, GAIS TI: TIOHS, GAIS Patient: FACE-Q, GAIS, PSAQ, Subject satisfaction
Exit visit	V11	12 weeks after re-tx		AEs Tyndall effect Blink / closure test Visual assessments	BLE: TIOHS, GAIS TI: TIOHS, GAIS Patient: FACE-Q, GAIS, PSAQ, Subject satisfaction

Abbreviations: AE: Adverse Event; BLE: Blinded Live Evaluator; CTR: Common Treatment Response (30-day diary); GAIS: Global Aesthetic Improvement Scale; TI: Treatment Investigator; PSAQ: Periorbital Subjects Assessment Questionnaire; TIOHS: Teoxane Infraorbital Hollows Scale; Tx: Treatment; re-Tx: retreatment; VAS: Visual Analog Scale; Face-Q questionnaire used in the study: Appraisal of Lower Eyelids

3. Clinical Endpoints

With regards to safety, patients reported injection site pain, completed visual assessments, blink and closure tests and reported their symptoms on a 30-Day patient Common Treatment Response (CTR) diary (after each injection). The TI assessed and reported all Adverse Events.

The TI assessed all AEs and recorded details of seriousness, severity, duration, and action taken with study device, as well as relationship to the study device. For statistical analysis, the maximal severity reported for the AE was used, even if the AE presented as being less severe at some point during the event.

With regards to effectiveness the infraorbital hollows improvement was assessed based on the validated Teoxane Infra-orbital Hollows Scale

(TIOHS[1]) (Table 5) by BLE and the TI. In addition to the TIOHS assessments, the BLE and the TI also assessed the patient using the GAIS (Global Aesthetic Improvement Scale).

With regards to effectiveness from a patient's perspective, the patient completed the following assessments: GAIS, FACE-Q Appraisal of Lower Eyelids, Periorbital Subject Assessment Questionnaire (PSAQ) and Subject Satisfaction questionnaire.

Table 5: Teoxane Infra-Orbital Hollows Scale (TIOHS)

Category	Grade	Description
None	0	No visible infraorbital hollowing. Absence of medial and lateral volume loss in this area. Smooth lid-cheek junctions
Minimal	1	Mild infraorbital hollowing with limited loss of volume medial to the mid-pupillary line. Smooth lid-cheek junction
Moderate	2	Moderate infraorbital hollowing extending laterally beyond the mid-pupillary line with moderate loss of volume in at least ¾ of the lower orbital rim. Some volume loss will be present at the lid-cheek junction. May have volume deficiency in the medial cheek with flattening of the central upper cheek.
Severe	3	Severe infraorbital hollowing with moderate volume loss in the entire lower orbital rim. Full depression following creating a deeply defined groove at the lid-cheek junction.
Very Severe	4	Very severe infraorbital hollowing with severe loss of volume along the entire lower orbital rim. A very marked groove will be present along the lid-cheek junction.

With regard to success/failure criteria, the effectiveness of RHA Redensity® Eye Lido would be demonstrated if 1) the TIOHS responder rate of subjects treated with RHA Redensity® Eye Lido was statistically superior to the responder rate for subjects of the No-Treatment group 12 weeks after randomization as assessed by the BLE; and 2) the mean change from Baseline of the modified FACE-Q *Appraisal of lower eyelids* of subjects treated with RHA Redensity® Eye Lido was statistically superior to the raw score for subjects of the No-Treatment group 12 weeks after randomization as assessed by the subject.

1 Carey W., Trévidic P., Benedetto A., Maffert P. and Antunes S. - *Creation and Validation of Photonumeric Scale for Assessment of Infraorbital Hollows* – Dermatologic Surgery – August 2023 – Volume 49 – Number 8 –777:782.

B. Accountability of PMA Cohort

At the time of the database lock, of the 248 patients enrolled in the PMA study, 83% (205/248) were followed for 52 weeks following their treatment before being offered retreatment. 95 of them (38%) exited the study at this visit and 110 received retreatment and continued the follow-up. 108 patients (44%) were available for analysis at the final visit, 12 weeks after retreatment. Overall, 203 of the 248 patients (82%) completed the study.

A total of 281 subjects were screened and 248 were enrolled. Out of these enrolled subjects:

- 248 subjects (100%) were assigned to the Safety Population (SAFT)
- 248 subjects (100%) to the intent-to-treat (ITT) population
- 218 subjects (87.9%) to the per protocol (PP) population (16 subjects (8.7%) in RHA Redensity® Eye Lido group and 14 subjects (21.5%) in No-Treatment control group).

The PP population are all subjects in the ITT who completed up to Visit 5 (primary endpoint visit at 12 weeks) with no major protocol deviation that could affect effectiveness assessment). Of the 30 subjects (5.2%) who were excluded from the PP:

- 13 had a major protocol deviation: 6 (2.4%) subjects had their Visit 5 visit out of windows, 5 (2.0%) subjects missed Visit 5, and 2 (0.8%) subjects did not meet the inclusion criteria.
- 17 subjects discontinued the study before Visit 5: 5 (2.0%) in the RHA Redensity® Eye Lido treatment group and 12 (4.8%) in the No-Treatment control group

For the pooled population, of the 65 subjects in the No-Treatment group, 13 did not reach Visit 5 to crossover and receive RHA Redensity® Eye Lido treatment and 2 of the 50 who reached Visit 5 did not receive treatment at that visit. Therefore, there were 233 subjects as part of the safety population (SAFT) for the pooled data set.

The overall Safety population includes all subjects who were assigned to the treatment or No-Treatment control groups and completed Visit 1. The Safety population of the pooled data set consists of all subjects who received at least one treatment with the study device.

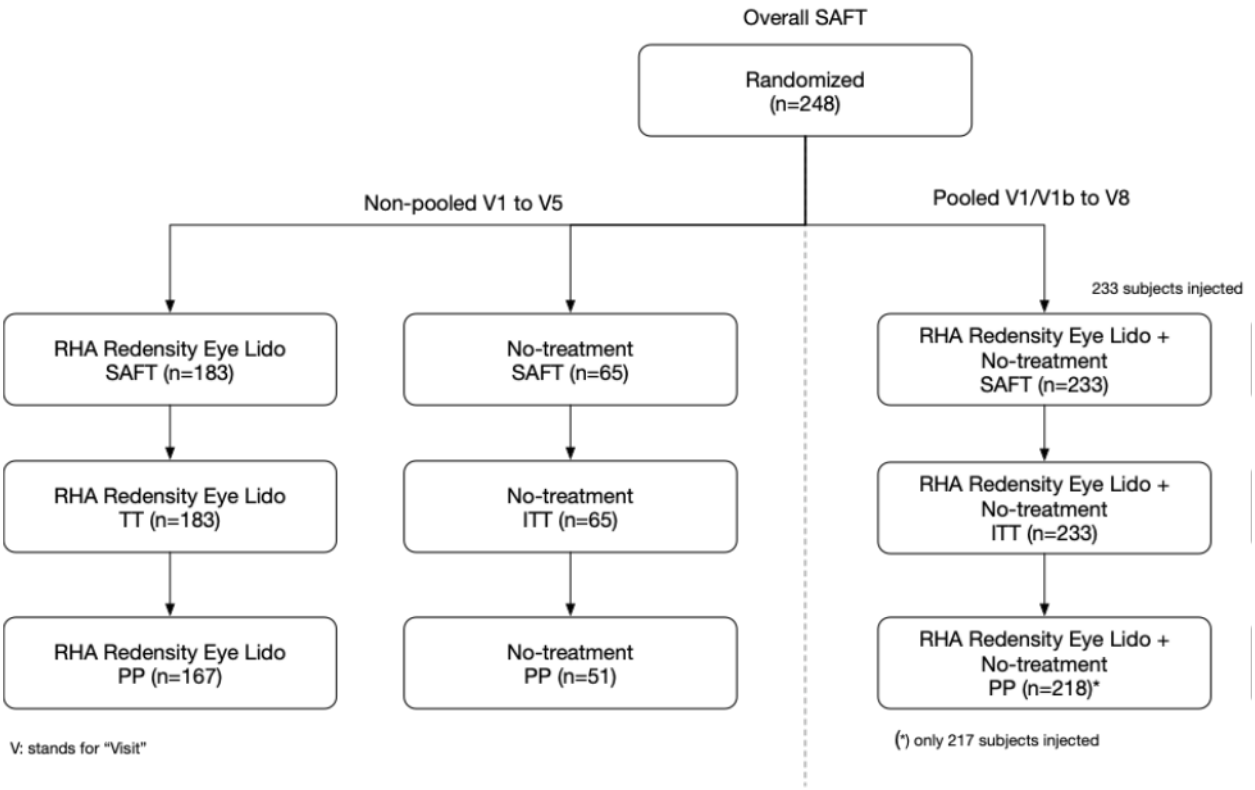


Figure 1: Subject Population

Table 6: Subject Accountability and Disposition (ITT population)

	RHA Redensity® Eye Lido	**No-Treatment control**
Screened	281	
Enrolled	248	
Safety population	183	65
ITT population	183	65
PP population	167	51
Number of subjects who completed the study	160 (87.4%)	43 (66.2%)
Number of subjects at primary endpoint visit (V5 – 12 weeks)	173 (94.5%)	52 (80.0%)
Number of subjects at V8 (52 weeks)	160 (87.4%)	45 (69.2%)
Number of subjects who received retreatment at V8	88 (48.1%)	22 (33.8%)
Number of subjects withdrawn from study	23 (12.6%)	22 (33.8%)
Reason for discontinuation		
A subject or legal representative withdrawal	11 (6.0%)	12 (18.5%)
Investigator withdrawal	2 (1.1%)	1(1.5%)
Lost to follow-up	7 (3.8%)	6 (9.2%)
Sponsor decision	1 (0.5%)	0 (0%)
Other	2 (1.1%)	3 (4.6%)

All percentages are based on the number of subjects by group in the ITT population.

C. Study Population Demographics and Baseline Parameters

a) Demographics

The demographics of the study population were typical for a pivotal study performed in the United States.

The study population included female and male subjects who were ≥ 22 years old. The study ensured that subjects meeting the inclusion criteria were representative of gender and ethnicity of the U.S. population who may use RHA Redensity® Eye Lido implant for the treatment of infraorbital region. Subjects had a mean age of approximately 50 years, and most subjects were female (approximately 88.7% (220/248) of study subjects). The majority of subjects were white (84.7% - 210/248), with 8.9% (22/248) of subjects identifying as Black or African American. 25.8% (64/248) of subjects were of Hispanic or Latino ethnicity. Fitzpatrick Skin Types were appropriately represented with all predefined minimal sample size thresholds being attained for subjects with skin types IV-VI, with approximately 66.1% (164/248) and 33.9% (84/248) of subjects had skin types I-III and IV-VI, respectively (and 7.6% (19/248) of subjects having skin types V/VI).

Table 7: Demographic Characteristics at Baseline (ITT population)

Variable	Sample Characteristics / Category	RHA Redensity® Eye Lido (N = 183)	No-Treatment (N = 65)	Total (N = 248)
Age [years]	n (missing)	183 (0)	65 (0)	248 (0)
	Mean (SD)	50.0 (10.65)	48.2 (11.11)	49.5 (10.78)
	Median	51.0	49.0	51.0
	Min to Max	24 to 73	23 to 73	23 to 73
	22 – ≤ 51[(a)]	92 (50.3%)	38 (58.5%)	130 (52.4%)
	> 51[(a)]	91 (49.7%)	27 (41.5%)	118 (47.6%)
Sex	n (missing)	183 (0)	65 (0)	248 (0)
	Male	23 (12.6%)	5 (7.7%)	28 (11.3%)
	Female	160 (87.4%)	60 (92.3%)	220 (88.7%)
Ethnicity	n (missing)	183 (0)	65 (0)	248 (0)
	Hispanic or Latino	49 (26.8%)	15 (23.1%)	64 (25.8%)
	Not Hispanic or Latino	130 (71.0%)	49 (75.4%)	179 (72.2%)
	Not available	4 (2.2%)	1 (1.5%)	5 (2.0%)
Race[2]	n (missing)	183 (0)	65 (0)	248 (0)
	Not allowed by local law/Unknown	4 (2.2%)	1 (1.5%)	5 (2.0%)
	American Indian or Alaska Native	2 (1.1%)	1 (1.5%)	3 (1.2%)
	Asian	6 (3.3%)	0	6 (2.4%)
	Black or African American	17 (9.3%)	5 (7.7%)	22 (8.9%)
	Native Hawaiian or Other Pacific Islander	3 (1.6%)	0	3 (1.2%)
	White	152 (83.1%)	58 (89.2%)	210 (84.7%)

Variable	Sample Characteristics / Category	RHA Redensity® Eye Lido (N = 183)	No-Treatment (N = 65)	Total (N = 248)
Fitzpatrick Skin Type	n (missing)	183 (0)	65 (0)	248 (0)
	I-III	121 (66.1%)	43 (66.2%)	164 (66.1%)
	IV-VI	62 (33.9%)	22 (33.8%)	84 (33.9%)
	V/VI	14 (7.7%)	5 (7.7%)	19 (7.6%)

Abbreviations: N = number of subjects; SD = standard deviation
All percentages are based on the number of subjects by group with non-missing information for each variable.
(a) 51 corresponds to the median age of the total ITT population.
[1] For female, being not of childbearing potential is defined as postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy, or hysterectomy).
[2] A subject can be counted in several categories.

b) Extent of exposure

The number of treatment sessions is described in Table 8 below. All subjects who received retreatment were injected with RHA Redensity® Eye Lido.

Table 8: Number of Treatment Sessions – Safety Population

Treatment	RHA Redensity® Eye Lido Needle (N=116)	RHA Redensity® Eye Lido Cannula (N=117)	RHA Redensity® Eye Lido Total (N=233)
Initial treatment	116 (100%)	117 (100%)	233 (100%)
Retreatment	48 (41.4%)	62 (53.0%)	110 (47.2%)
Number of subjects receiving 1 treatment (i.e., only initial treatment)	68 (58.6%)	55 (47.0%)	123 (52.8%)
Number of subjects receiving 2 injections (initial and retreatment)	48 (41.4%)	62 (53.0%)	110 (47.2%)

All percentages are based on the number of subjects by group in the population.

For each individual subject, the method of administration was the same at initial and retreatment. Method of administration was a 1:1 ratio between needle and cannula with 116 subjects injected with a needle and 117 subjects injected with a cannula.

Among the SAFT population (248 subjects), 233 subjects received an initial treatment with RHA Redensity® Eye Lido (94.0%, 233/248) and of those, 110 subjects received a retreatment at 52 weeks after their initial treatment (47.2%, 110/233).

The mean (SD) volume injected for both eyes after initial treatment was 1.52 (0.526) mL. The mean volume injected at retreatment was lower, it was 0.91 mL (0.472) on average.

c) Administration method and depth of injection

The majority of subjects (83.6%, 97/116) who received needle injections were administered into the supraperiosteum. Additionally, 14.6% (17/116) were injected both into the sub-dermis and supraperiosteum layers. Only 1.7% (2/116) were injected solely into the sub-dermis.
The distribution was more balanced for subjects injected with a cannula. The majority of subjects injected with a cannula were injected into both the sub-dermis and supraperiostum (53.0%, 62/117) and the rest was relatively balanced into the other 2 categories: 28.2% (33/117) of subjects injected into the sub-dermis only and 18.8% (22/117) of subjects injected into the supraperiosteum only.

Table 9: Method of Injection and Injection Depth – Safety Population

Treatment		Needle (N=116)	Cannula (N=117)	Total (N=233)
Initial treatment	# of subject injected	116	117	233
Depth	Sub-dermis	2 (1.7%)	33 (28.2%)	35 (15.0%)
	Supraperiosteum	97 (83.6%)	22 (18.8%)	119 (51.1%)
	Both	17 (14.7%)	62 (53.0%)	79 (33.9%)
Technique	Anterograde linear threading	12 (10.3%)	4 (3.4%)	16 (6.9%)
	Retrograde linear threading	4 (3.4%)	91 (77.8%)	95 (40.8%)
	Multipuncture technique	96 (82.8%)	0	96 (41.2%)
	Other	4 (3.4%)	22 (18.8%)	26 (11.2%)
Retreatment	# of subject injected	48	62	110
Depth	Sub-dermis	4 (8.3%)	18 (29.0%)	22 (20.0%)
	Supraperiosteum	35 (72.9%)	20 (32.3%)	55 (50.0%)
	Both	9 (18.8%)	24 (38.7%)	33 (30.0%)
Technique	Anterograde linear threading	4 (8.3%)	3 (4.8%)	7 (6.4%)
	Retrograde linear threading	1 (2.1%)	46 (74.2%)	47 (42.7%)
	Multipuncture technique	36 (75.0%)	0	36 (32.7%)
	Other	7 (14.6%)	13 (21.0%)	20 (18.2%)

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the Safety pooled population (i.e., population from the Treatment group + population of the No-Treatment group after their received treatment after the primary endpoint). It is based on a cohort of 233 subjects available for up to 52 weeks after initial treatment.

The common treatment responses for this study are presented below in Table 10 to Table 12. Adverse device effects are reported in Table 13 to Table 16.

Safety of the RHA Redensity® Eye Lido implant when injected into the infraorbital region was evaluated through a 30-Day patient Common Treatment Response (CTR) diary which was completed after each injection, AE assessments at each visit, visual assessment at each visit and measurement of injection site pain.

a) Common Treatment Responses after initial treatment

CTR data for initial treatment are presented in Table 10 for the needle and cannula subgroups. CTRs for retreatment were of the same proportions.

After initial injection at Visit 1/1b was administered to 233 subjects, 223 CTR diaries were retrieved, and 181 subjects experienced at least 1 CTR (181/223 [81.2%]). The incidence of subjects experiencing at least 1 CTR was slightly higher in the needle subgroup (89.1%, 98/110) than in the cannula subgroup (73.5%, 83/113).

Overall, the most common CTR after the initial injection at Visit 1/1b was "tenderness" in 57.4% of subjects (128/223), followed by "swelling" in 57.0% of subjects (127/223), "bruising" in 54.7% of subjects (122/223), "lumps/bumps" in 49.3% of subjects (110/223), "firmness" in 44.4% of subjects (99/223), "redness" in 35.9% of subjects (80/223), "discoloration" in 35.9% of subjects (80/223), "pain" in 18.8% of subjects (42/223), and "itching" in 11.2% of subjects (25/223) was the least frequent.

After the initial injection at Visit 1/1b, the maximum severity of CTRs reported by the subjects in their diaries were distributed as follows:

- None: 18.8% (42/223) of subjects did not experience any CTRs
- Mild: 51.1% (114/223) of subjects experienced mild CTRs as maximum severity
- Moderate: 25.6% (57/223) of subjects experienced moderate CTRs as maximum severity
- Severe: 4.5% (10/223) of subjects experienced severe CTRs as maximum severity

Most severe CTRs were reported when injected with a needle (9 of the 10 severe CTRs) and the most frequent severe CTRs reported was bruising which is consistent and anticipated when injecting with a needle compared to a cannula.

69.1% of subjects (154/223) experienced a CTR that lasted 1-3 days and 25.6% of subjects (57/223) experienced CTRs that lasted between 15 and 30 days. The incidence rates by number of days were similar between needle

and cannula subgroups following the initial injection. Of the 813 CTRs, 70.2% (576/813) had resolved by day 7.

By the end of the diary, nearly all CTRs had resolved (95.7% [807/843]). On the last day of the diary, 12.1% (27/223) of subjects were experiencing a CTR. The most frequent CTR was lumps/bumps (33.3% [12/36]). All CTRs on the last day of the diary were automatically elevated to an Adverse Event and their severity assessed by the TI and all were assessed as "mild".

Table 10: CTRs Incidence Rate – Initial Treatment (V1/V1b) – Safety Population

CTR	Needle	Cannula	Total
Number of subjects	116		117
Number of CTR diaries retrieved	110		113
≥1 CTR	98 (89.1%)	[81.9- 93.6%]	83 (73.5%)
Redness	54 (49.1%)	[39.9- 58.3%]	26 (23.0%)
Pain	21 (19.1%)	[12.8- 27.4%]	21 (18.6%)
Tenderness	60 (54.5%)	[45.2- 63.5%]	68 (60.2%)
Firmness	51 (46.4%)	[37.3- 55.6%]	48 (42.5%)
Swelling	73 (66.4%)	[57.1- 74.5%]	54 (47.8%)
Lumps/Bumps	60 (54.5%)	[45.2- 63.5%]	50 (44.2%)
Bruising	79 (71.8%)	[62.8- 79.4%]	43 (38.1%)
Itching	15 (13.6%)	[8.4- 21.3%]	10 (8.8%)
Discoloration	48 (43.6%)	[34.7- 53.0%]	32 (28.3%)

Abbreviation: CTR = Common Treatment Response. All percentages are based on the number of CTR diaries retrieved by injection by subgroup in the population.

Table 11: CTRs by Maximum Severity – Initial Treatment (V1/V1b) – Safety Population

CTR	Severity	Needle	Cannula	Total
Number of subjects		116	117	233
Number of CTR diaries retrieved			110	113
At least 1 CTR	None	12 (10.9%)	30 (26.5%)	42 (18.8%)
	Mild	50 (45.5%)	64 (56.6%)	114 (51.1%)
	Moderate	39 (35.5%)	18 (15.9%)	57 (25.6%)
	Severe	9 (8.2%)	1 0.9%)	10 (4.5%)
Redness	None	56 (50.9%)	87 (77.0%)	143 (64.1%)
	Mild	41 (37.3%)	23 (20.4%)	64 (28.7%)
	Moderate	10 (9.1%)	3 (2.7%)	13 (5.8%)
	Severe	3 (2.7%)	0	3 (1.3%)
Pain	None	89 (80.9%)	92 (81.4%)	181 (81.2%)
	Mild	19 (17.3%)	20 (17.7%)	39 (17.5%)
	Moderate	2 (1.8%)	1 (0.9%)	3 (1.3%)
	Severe	0	0	0

CTR	Severity	Needle	Cannula	Total
Tenderness	None	50 (45.5%)	45 (39.8%)	95 (42.6%)
	Mild	54 (49.1%)	59 (52.2%)	113 (50.7%)
	Moderate	6 (5.5%)	9 (8.0%)	15 (6.7%)
	Severe	0	0	0
Firmness	None	59 (53.6%)	65 (57.5%)	124 (55.6%)
	Mild	36 (32.7%)	44 (38.9%)	80 (35.9%)
	Moderate	14 (12.7%)	4 (3.5%)	18 (8.1%)
	Severe	1 (0.9%)	0	1 (0.4%)
Swelling	None	37 (33.6%)	59 (52.2%)	96 (43.0%)
	Mild	48 (43.6%)	45 (39.8%)	93 (41.7%)
	Moderate	22 (20.0%)	9 (8.0%)	31 (13.9%)
	Severe	3 (2.7%)	0	3 (1.3%)
Lumps/Bumps	None	50 (45.5%)	63 (55.8%)	113 (50.7%)
	Mild	40 (36.4%)	43 (38.1%)	83 (37.2%)
	Moderate	18 (16.4%)	6 (5.3%)	24 (10.8%)
	Severe	2 (1.8%)	1 (0.9%)	3 (1.3%)
Bruising	None	31 (28.2%)	70 (61.9%)	101 (45.3%)
	Mild	45 (40.9%)	37 (32.7%)	82 (36.8%)
	Moderate	28 (25.5%)	6 (5.3%)	34 (15.2%)
	Severe	6 (5.5%)	0	6 (2.7%)
Itching	None	95 (86.4%)	103 (91.2%)	198 (88.8%)
	Mild	14 (12.7%)	9 (8.0%)	23 (10.3%)
	Moderate	1 (0.9%)	1 (0.9%)	2 (0.9%)
	Severe	0	0	0
Discoloration	None	62 (56.4%)	81 (71.7%)	143 (64.1%)
	Mild	31 (28.2%)	29 (25.7%)	60 (26.9%)
	Moderate	14 (12.7%)	3 (2.7%)	17 (7.6%)
	Severe	3 (2.7%)	0	3 (1.3%)

Abbreviation: CTR = Common Treatment Response. All percentages are based on the number of subjects with the specific CTR by injection by subgroup in the population.
Maximum severity (Severe>Moderate>Mild) reported by the subject for the particular CTR in the diary for at least one day.

Table 12: CTRs by Total Duration – Initial Treatment (V1/V1b)– Safety Population

Total Duration (days)							
CTR after initial injection	**Group**	**Subjects Experiencing the CTR**	**1-3**	**4-7**	**8-14**	**15-30**	**Last Day Diary**
Any CTR	Needle	98 (89.1%)	81 (73.6%)	67 (60.9%)	46 (41.8%)	43 (39.1%)	13 (11.8%)
	Cannula	83 (73.5%)	70 (61.9%)	42 (37.2%)	22 (19.5%)	23 (20.4%)	14 (12.4%)
	Total	181 (81.2%)	151 (67.7%)	109 (48.9%)	68 (30.5%)	66 (29.6%)	27 (12.1%)
Redness	Needle	54 (49.1%)	35 (31.8%)	13 (11.8%)	2 (1.8%)	4 (3.6%)	2 (1.8%)
	Cannula	26 (23.0%)	19 (16.8%)	3 (2.7%)	1 (0.9%)	3 (2.7%)	0
	Total	80 (35.9%)	54 (24.2%)	16 (7.2%)	3 (1.3%)	7 (3.1%)	2 (0.9%)
Pain	Needle	21 (19.1%)	15 (13.6%)	4 (3.6%)	2 (1.8%)	0	0
	Cannula	21 (18.6%)	18 (15.9%)	1 (0.9%)	1 (0.9%)	1 (0.9%)	0
	Total	42 (18.8%)	33 (14.8%)	5 (2.2%)	3 (1.3%)	1 (0.4%)	0
Tenderness	Needle	60 (54.5%)	29 (26.4%)	21 (19.1%)	7 (6.4%)	3 (2.7%)	0
	Cannula	68 (60.2%)	40 (35.4%)	14 (12.4%)	7 (6.2%)	7 (6.2%)	2 (1.8%)
	Total	128 (57.4%)	69 (30.9%)	35 (15.7%)	14 (6.3%)	10 (4.5%)	2 (0.9%)
Firmness	Needle	51 (46.4%)	19 (17.3%)	15 (13.6%)	8 (7.3%)	9 (8.2%)	0
	Cannula	48 (42.5%)	29 (25.7%)	12 (10.6%)	4 (3.5%)	3 (2.7%)	2 (1.8%)
	Total	99 (44.4%)	48 (21.5%)	27 (12.1%)	12 (5.4%)	12 (5.4%)	2 (0.9%)
Swelling	Needle	73 (66.4%)	26 (23.6%)	17 (15.5%)	17 (15.5%)	13 (11.8%)	4 (3.6%)
	Cannula	54 (47.8%)	29 (25.7%)	12 (10.6%)	7 (6.2%)	6 (5.3%)	3 (2.7%)
	Total	127 (57.0%)	55 (24.7%)	29 (13.0%)	24 (10.8%)	19 (8.5%)	7 (3.1%)
Lumps/ Bumps	Needle	60 (54.5%)	23 (20.9%)	14 (12.7%)	12 (10.9%)	11 (10.0%)	5 (4.5%)
	Cannula	50 (44.2%)	21 (18.6%)	10 (8.8%)	6 (5.3%)	13 (11.5%)	7 (6.2%)
	Total	110 (49.3%)	44 (19.7%)	24 (10.8%)	18 (8.1%)	24 (10.8%)	12 (5.4%)
Bruising	Needle	79 (71.8%)	6 (5.5%)	32 (29.1%)	22 (20.0%)	19 (17.3%)	2 (1.8%)
	Cannula	43 (38.1%)	17 (15.0%)	12 (10.6%)	11 (9.7%)	3 (2.7%)	2 (1.8%)
	Total	122 (54.7%)	23 (10.3%)	44 (19.7%)	33 (14.8%)	22 (9.9%)	4 (1.8%)
Itching	Needle	15 (13.6%)	9 (8.2%)	4 (3.6%)	1 (0.9%)	1 (0.9%)	0
	Cannula	10 (8.8%)	7 (6.2%)	2 (1.8%)	0	1 (0.9%)	0
	Total	25 (11.2%)	16 (7.2%)	6 (2.7%)	1 (0.4%)	2 (0.9%)	0
Discoloration	Needle	48 (43.6%)	14 (12.7%)	12 (10.9%)	10 (9.1%)	12 (10.9%)	4 (3.6%)
	Cannula	32 (28.3%)	14 (12.4%)	8 (7.1%)	4 (3.5%)	6 (5.3%)	3 (2.7%)
	Total	80 (35.9%)	28 (12.6%)	20 (9.0%)	14 (6.3%)	18 (8.1%)	7 (3.1%)

Abbreviation: CTR = Common Treatment Response.
All percentages are based on the number of CTR diaries retrieved by injection by group in the population.
116 subjects were treated with a needle and 110 CTR diaries were retrieved. 117 subjects were treated with a cannula and 113 CTR diaries were retrieved.
Total duration is defined as the number of days +1 between the first and last occurrence of the CTR in the diary, no matter if there was a gap between the several occurrences.

The incidence rate of any CTR tended to be higher when injected with a needle (89%) than when injected with a cannula (73%). The CTR incidence

rates by duration were similar between needle and cannula following initial treatment.

The TI reviewed all CTRs to ensure they were elevated as appropriate to the status of an AE. CTRs were not considered AEs unless the duration and/or severity were in excess of that typically observed following injection of a dermal filler and were clinically significant as determined by the TI. However, CTRs that were noted on the last day of the CTR diary were recorded automatically as AEs regardless of their severity (30-day rule). Overall, for CTRs that were automatically elevated to the level of an AE after 30 days, the TI determined that all the AEs were of "mild" intensity.

b) Adverse Device Effects that occurred in the PMA clinical study

All Adverse Device Effects (Table 13) were the types and frequency of adverse events that are typically experienced following the injection of a dermal filler into the infraorbital hollows.
From Visit 1/1b to Visit 8 (i.e., not including retreatment injections), 57 ADEs were reported (Table 13):

- 19.0% (22/116) subjects (28 events) in the needle group
- 15.4% (18/117) subjects (29 events) in the cannula group

Overall, most ADEs were obtained from the diary. Of the 57 ADEs reported from 40 subjects (17.2%, 40/233) after initial treatment:

- 8.6% (40/233) of subjects experienced ADEs that were CTRs automatically elevated to AEs because they were present on the last day of the diary.
- 3.4% (8/233) of subjects experienced ADEs that were automatically elevated to AEs because they were reported as "Other" in the diary.
- 3.4% (8/233) of subjects experienced ADEs that were identified by the TI during a visit.
- 2.1% (5/233) of subjects experienced ADEs that were reported from a pre-identified list of AEs in the subject diary but were not a CTR. Out of these 5 ADEs (in 5 subjects), none were related to visual disturbances (3 events of headache, 1 event of atypical migraine and 1 event of swelling in infraorbital area on the right side). All were mild except 1 event of headache reported as moderate.

Table 13: Adverse Events Profile Overview (Initial, Touch-Up) Visit 1/1b to Visit 8 – Safety Population

From V1 to V7	Needle (N=116)		Cannula (N=117)		Total (N=233)	
	Number of events	Number of subjects (%)	Number of events	Number of subjects (%)	Number of events	Number of subjects (%)
Overall						
Number of subjects		116		117		233
All AEs	34	26 (22.4%) [15.8-30.8%]	58	36 (30.8%) [23.1-39.6%]	92	62 (26.6%) [21.3-32.6%]
AESIs	0	0	4	3 (2.6%) [0.9-7.3%]	4	3 (1.3%) [0.4-3.7%]
ADEs	28	22 (19.0%) [12.9-27.0%]	29	18 (15.4%) [10.0-23.0%]	57	40 (17.2%) [12.9-22.5%]
UADEs	0	0	0	0	0	0
Serious AEs	0	0	1	1 (0.9%) [0.2-4.7%]	1	1 (0.4%) [0.1-2.4%]
Device-related Serious AEs	0	0	0	0	0	0

Abbreviations: ADE = adverse device effect; AE = adverse event; AESI = adverse event of special interest; N = number of subjects; SAE = serious adverse event; SAFT = safety (population); UADE = unanticipated adverse device effect

Notes: Number (%) of subjects with at least 1 AE in the category. All percentages are based on the number of subjects by group in the population. An AESI is any new vision disturbances including, but not limited to, any loss of vision, blurriness, double vision, pain in or around the eye, blindness, blind spot or shadow in the visual field, trouble moving eyes, ocular hypotonia, ptosis, etc. that occurs after any administration of the filler. A related AE is an AE that was judged by the investigator to be Possibly Related or Probably Related or Causal relationship to study device or study procedure. AEs with a missing relationship were counted as Related. A device-related SAE is a related AE also considered serious.

The type and rates of ADEs were also comparable between the needle and cannula groups as shown by Table 14.

Similar safety profiles were observed between the needle and cannula groups: a total of 19.0% (22/117) and 15.4% (18/117) subjects in needle and cannula groups respectively, experienced at least 1 ADE between Visit 1/1b and Visit 8.

The most common events were:

- Injection site discoloration experienced by 5.2% (12/233) of subjects (14 events)
- Injection site mass, experienced by 3.9% (9/233) of subjects (10 events)
- Injection site swelling, experienced by 3.9% (9/233) of subjects (9 events)

There were no noticeable differences of the frequencies of ADEs between the needle and cannula groups.

Table 14: ADEs sorted by SOC and PT (Visit 1/1b to Visit 8 – Initial Treatment to 52 Weeks Follow-Up Excluding Retreatment – Pooled) – Safety Population

From V1/V1b to V8	Needle (N=116)		Cannula (N=117)		Total (N=233)	
SOC PT	Number of events	Number of subjects	Number of events	Number of subjects	Number of events	Number of subjects
Any ADE	**28**	**22 (19.0%)**	**29**	**18 (15.4%)**	**57**	**40 (17.2%)**
General Disorders and Admin. Site Conditions	**24**	**19 (16.4%)**	**24**	**15 (12.8%)**	**48**	**34 (14.6%)**
Injection Site Discolouration	5	5 (4.3%)	9	7 (6.0%)	14	12 (5.2%)
Injection Site Mass	5	4 (3.4%)	5	5 (4.3%)	10	9 (3.9%)
Injection Site Swelling	5	5 (4.3%)	4	4 (3.4%)	9	9 (3.9%)
Injection Site Bruising	3	3 (2.6%)	1	1 (0.9%)	4	4 (1.7%)
Injection Site Oedema	2	2 (1.7%)	0	0	2	2 (0.9%)
Injection Site Pain	0	0	2	2 (1.7%)	2	2 (0.9%)
Injection Site Reaction	1	1 (0.9%)	1	1 (0.9%)	2	2 (0.9%)
Injection Site Erythema	1	1 (0.9%)	0	0	1	1 (0.4%)
Injection Site Haemorrhage	0	0	1	1 (0.9%)	1	1 (0.4%)
Injection Site Induration	0	0	1	1 (0.9%)	1	1 (0.4%)
Injection Site Scab	1	1 (0.9%)	0	0	1	1 (0.4%)
Injection Site Urticaria	1	1 (0.9%)	0	0	1	1 (0.4%)
Nervous System Disorders	**3**	**3 (2.6%)**	**2**	**2 (1.7%)**	**5**	**5 (2.1%)**
Headache	3	3 (2.6%)	1	1 (0.9%)	4	4 (1.7%)
Atypical Migraine	0	0	1	1 (0.9%)	1	1 (0.4%)
Eye Disorders	**0**	**0**	**2**	**1 (0.9%)**	**2**	**1 (0.4%)**
Abnormal Sensation In Eye	1	1 (0.9%)	0	0	1	1 (0.4%)
Asthenopia	1	1 (0.9%)	0	0	1	1 (0.4%)
Injury, Poisoning And Procedural Complications	**0**	**0**	**1**	**1 (0.9%)**	**1**	**1 (0.4%)**
Contusion	0	0	1	1 (0.9%)	1	1 (0.4%)
Skin And Subcutaneous Tissue Disorders	**1**	**1 (0.9%)**	**0**	**0**	**1**	**1 (0.4%)**
Erythema	1	1 (0.9%)	0	0	1	1 (0.4%)

Abbreviations: ADE = adverse device effect; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; PT = preferred term; SAFT = safety (population); SOC = system organ class; V = visit

All percentages were based on the number of subjects by group in the population. ADEs were coded using MedDRA version 24.0. AEs are displayed by descending subject frequency of SOC, then descending subject frequency of PT within SOC in the Total column, then alphabetically.

The majority (93.0%, 53/57) of ADEs were mild and the remaining were moderate (7.0%, 4/57) (Table 15). There were no severe ADEs. The rates were similar between the needle and cannula groups: 28 ADEs reported in the needle subgroup by 22/116 subjects [19.0%]; 29 ADEs reported in the cannula subgroup by 18/117 subjects [15.4%]). There were no severe ADEs reported.

Of the 57 events reported between Visit 1/1b and Visit 8, 24.6% (14/57) of ADEs lasted 1 to 3 days, 50.9% (29/57) ADEs lasted less than 14 days and 71.9% (41/57) were resolved in 30 days. ADEs tended to resolve faster in the needle subgroup with 67.9% (19/28) that lasted less than 14 days against 34.5% (10/29) in the cannula subgroup that lasted less than 14 days. The mean (SD) duration of ADEs was 34.1 (55.38) days for all the subjects treated, with 38.9 (41.15) days in the cannula subgroup, and 29.0 (67.47) days in the needle subgroup.
A small proportion of ADEs lasted more than 90 days (5/57, 8.8%) with a similar proportion in the needle (2/28, 7.1%) and cannula (3/29, 10.3%) subgroups. Two (2) events in the needle subgroup and 3 events in the cannula subgroup, recorded for 5 subjects, lasted more than 90 days. Of these 5 ADEs, the longest duration was 264 days, recorded for a persistent edema of mild severity that resolved without sequelae. This was followed by an event lasting 261 days, a worsening of left eye festoon of mild severity, which also resolved without sequelae. Three additional ADEs had durations ranging from 97 to 155 days: "bilateral periorbital puffiness" (155 days), "Tyndall effect" (148 days), and "left lateral IOH region visible filler product" (97 days), all of mild severity and which resolved without sequelae.

Almost all ADEs resolved by exit, except 3 ongoing events related to 2 subjects lost-to-follow-up (1 subject with mild Tyndall effect and mild swelling of the lower left eyelid was last seen 71 days after ADE was identified and 1 subject with moderate bruising on the left cheek was last seen 13 days after ADE was identified)

Table 15: ADEs Sorted by Severity (Visit 1/1b to Visit 8 – Initial Treatment to 52 Weeks Follow-Up Excluding Retreatment – Pooled) – Safety Population

From V1/1b to V8	Needle (N=116)		Cannula (N=117)		Total (N=233)	
Severity	Number of events	Number of subjects	Number of events	Number of events	Number of subjects	Number of events
Any ADE	**28**	**22 (19.0%)**	**29**	**18 (15.4%)**	**57**	**40 (17.2%)**
Mild	26	21 (18.1%)	27	16 (13.7%)	53	37 (15.9%)
Moderate	2	2 (1.7%)	2	2 (1.7%)	4	4 (1.7%)
Severe	0	0	0	0	0	0

Abbreviations: ADE = adverse device effect.
All percentages are based on the number of subjects by group in the Safety population.
ADEs with a missing severity were counted as Severe.

Table 16: ADEs Sorted by Duration (Visit 1/1b to Visit 8 – Initial Treatment to 52 Weeks Follow-Up Excluding Retreatment – Pooled) – Safety Population

From Visit 1/1b to Visit 8		Needle (N=116)		Cannula (N=117)		Total (N=233)	
Duration of ADE Characteristics (days)	Duration of AE (days)	Number of events	Number of subjects	Number of events	Number of subjects	Number of events	Number of Subjects
Any ADE		**28**	**22 (19.0%)**	**29**	**18 (15.4%)**	**57**	**40 (17.2%)**
	1-3	8	7 (6.0%)	6	5 (4.3%)	14	12 (5.2%)
	4-7	11	8 (6.9%)	1	1 (0.9%)	12	9 (3.9%)
	8-14	0	0	3	3 (2.6%)	3	3 (1.3%)
	15 - 30	4	4 (3.4%)	8	5 (4.3%)	12	9 (3.9%)
	31 - 90	3	3 (2.6%)	8	5 (4.3%)	11	8 (3.4%)
	>90	2	2 (1.7%)	3	3 (2.6%)	5	5 (2.1%)
N (missing)		28 (0)		29 (0)		57 (0)	
Mean (SD)		29.0 (67.47)		38.9 (41.5)		34.1 (55.38)	
95% CI Mean		2.8 - 55.2		23.3 - 54.6		19.4 - 48.7	
Min to Max		1 to 264		1 to 155		1 to 264	

Abbreviations: ADE = adverse device effect. CI = Confidence Interval; Max = Maximum; Min = Minimum; SD = Standard Deviation.
All percentages are based on the number of subjects by group in the Safety population.
For ongoing ADEs, missing end date is assigned to date of last contact to derive current duration of the event.
At time of this analysis, 1 ADE was ongoing in category 8 - 14 days, 2 ADEs were ongoing in category 31 - 90 days.

c) Tyndall Effect

Overall, the Tyndall effect was observed in seven (7) subjects: 2 in the needle subgroup and 5 in the cannula subgroup. All effects were assessed as mild. For 1 subject who was lost to follow-up, the outcome is unknown (assigned to cannula subgroup, initially in the No-Treatment control group and did not return after the 2-week visit following injection). For all other 6 subjects, the effect resolved without sequela.

d) Adverse Events of Special Interests (AESI)

Altogether, four (4) events of visual disturbances (visual acuity reduced, headache, blurred vision, and atypical migraine) in 3 subjects were reported as Adverse Events of Special Interests (AESI), all randomly assigned to the cannula subgroup, at 2 different investigational sites. All AESIs were not related to the study devices, though the atypical migraine was possibly related to study device and unrelated to study procedure. All AESIs were mild and resolved without sequalae.

There were two Serious Adverse Events (SAE) that were not device or procedure related. There were no Unanticipated Adverse Device Effects

(UADE). There were no deaths, and no subjects prematurely withdrew due to an ADE.

e) Pain at injection

Injection pain during injection (initial and retreatment) was measured using a 10cm (100mm) Visual Analog Scale (VAS), and is presented in millimeters (i.e., 100 points within the 10cm VAS). Injection pain was assessed immediately, 5, 15, and 30 minutes after filler injection.

The average level of pain noted during initial injections was similar between treatment groups, with 2.2 ± 7.95 and 1.2 ± 4.52 in the needle and the cannula subgroups, respectively. Injection site pain was reduced to 0.2 ± 0.76 mm and 0.8 ± 3.52 mm in the needle and the cannula subgroups, respectively by 5 minutes post-injection. Pain at time of injection was clinically negligible on the 0-100 scale, and it continued to decrease at 5, 15 and 30 minutes following injection. There were no observable differences of reported pain between the needle and cannula subgroups.

Similar findings were observed following retreatment injections.

The majority of subjects did not receive pre-injection anesthesia (overall 30.5% (71/233) subjects received anesthetics) confirming that the low pain scores accurately reflect the device's pain profile.

2. Effectiveness Results

The analysis of effectiveness was based on 183 subjects who received treatment with RHA Redensity® Eye Lido and 65 subjects who were initially assigned in the No-Treatment control group 12 weeks after initial treatment. Subjects in the No-Treatment group crossed-over to receive treatment after the primary endpoint and their data were pooled for effectiveness endpoints throughout the duration of the study. Key effectiveness outcomes are presented in Table 17 to Table 21.

The primary effectiveness endpoint was to assess the effectiveness (superiority) of RHA Redensity® Eye Lido versus the No-Treatment control for the correction of moderate to severe tissue volume deficiencies in the infraorbital regions at 12 weeks after the initial treatment. The effectiveness of RHA Redensity® Eye Lido was demonstrated if the responder rate for subjects treated with RHA Redensity® Eye Lido was statistically superior to the responder rate for subjects of the No-Treatment control group 12 weeks (Visit 5) after randomization as assessed by the Table 17 using the validated TIOHS.

To successfully achieve the primary endpoint, the lower bound of the 2-sided 95% Confidence Interval (CI) for the responder rate for RHA

Redensity® Eye Lido needed to be at least 70%, and the lower bound of the 2sided 95% CI for the difference in the responder rate between subjects treated with RHA® Redensity Eye Lido and those in the No-Treatment control group needed to be at least 50%. The responder rate at 12 weeks after treatment and the difference of responder rate between treatment and No-Treatment groups were used to establish superiority of treatment with RHA® Redensity Eye Lido. A subject was considered a TIOHS responder if he/she presented with a ≥1-grade improvement in each of the eyes as assessed by the BLE before initial treatment and 12 weeks after the initial treatment (Visit 5).

As shown in Table 17, the responder rate of subjects treated with RHA Redensity® Eye Lido was superior to that of subjects in the No-Treatment control group.

In RHA Redensity® Eye Lido group, 79.0% of subjects with a 95% confidence interval [72.2% - 84.5%] responded at week 12 and thus met the first criterion (lower bound ≥70%). The responder rate in the No-Treatment control group was 9.8% [3.9 – 22.2]. The difference in the responder rate between subjects treated with RHA Redensity® Eye Lido and the No-Treatment control group was 69.3% [58.7 - 79.8], which met the second criterion (lower bound ≥50%). This difference was statistically significant ($p<0.0001$) for ITT population, which demonstrates the effectiveness of RHA Redensity® Eye Lido.

Table 17: Summary of TIOHS Responder Rates by BLE at Visit 5 – Multiple Imputations (ITT populations)

Category	RHA Redensity® Eye Lido (N = 183)	No-Treatment (N = 65)
N (observed cases + imputed)	183 (173 + 10)	65 (52 + 13)
Responder [95% CI]	79.0% [72.2 - 84.5]	9.8% [3.9 - 22.2]
Not responder	21.0%	90.2%
p-value	< .0001	
Odds ratio RHA® Redensity Eye Lido vs No-Treatment [95% CI]	123.84 [21.46 - 714.78]	
Difference in responder rate (RHA Redensity Eye Lido–No-Treatment) [95% CI]	69.3% [58.7 - 79.8]	

N = number of subjects; TIOHS = Teoxane Infraorbital Hollows Scale

Note: A responder is defined as a subject with an absolute ≥1-grade improvement in each of the eyes compared to baseline on the TIOHS as assessed by BLE. For subjects lost-to-follow-up or not present at the primary endpoint visit for the TIOHS assessment, missing value is imputed using regression method within FCS for multiple imputation. Baseline is defined as the last non-missing measurement preceding the initial treatment for subjects assigned to RHA Redensity® Eye Lido and randomization date/time for subjects assigned to control groups. For achieving the superiority, observed p-value must be ≤0.025. The following 2 conditions must be met: 1) the lower bound of 2-sided 95% confidence interval for responder rate for RHA Redensity® Eye Lido is at least 70%; 2) the lower bound of 2-sided 95% confidence interval for the difference in the responder rate between subjects treated with RHA Redensity® Eye Lido and the No-Treatment control group is at least 50%. Percentages of responders and 95% CI for responders are based on the Wilson method in the article from The American Statistician, 2020, vol, 74, issue 2, 109-115. Due to the site effect on TIOHS responder rate, a logistic model was used with a p-value derived from the following model: logistic

regression model by treatment arm using baseline TIOHS grade score and site as covariates. 95% CI for odds ratio were obtained using Wald method. Baseline TIOHS grade score was defined as the maximum grade at baseline between both eyes. The odds that a subject responds in RHA Redensity® Eye Lido group are 123.8 times the odds that a subject responds in No-Treatment group. 95% CI for the difference in responder rate are obtained using the Wald method. All percentages are based upon the total number of subjects with non-missing data for the TIOHS at Visit 5 after imputation.

The co-primary endpoint was the change from Baseline in selected questions of the FACE-Q Appraisal of lower eyelids domain score (converted to a 0-100 scale – Rasch conversion) at 12 weeks. The effectiveness of RHA Redensity® Eye Lido was demonstrated if the modified FACE-Q Appearance of lower eyelids change from Baseline score for subjects treated with RHA Redensity® Eye Lido was statistically superior (by at least 12 points) to the subjects of the No-Treatment control group 12 weeks (Visit 5) after randomization.

To successfully achieve the co-primary endpoint, the mean change from Baseline of the modified FACE-Q *Appraisal of lower eyelids* raw score for RHA Redensity® Lido needed to be ≥ 3 and the difference between the modified FACE-Q *Appraisal of lower eyelids* change from Baseline for subjects treated with RHA Redensity® Eye Lido and the No-Treatment control group needed to be ≥12.

The results of the co-primary endpoint are summarized in Table 18. The modified FACE-Q *Appraisal of lower eyelids* raw score in the RHA Redensity® Eye Lido group mean change from baseline at Visit 5 was 4.8 [4.2-5.3], thereby achieving a lower bound 95% CI score that was greater than 3. The difference of the Rasch converted score between the RHA Redensity® Eye Lido treated group and the No-Treatment control group in mean change from Baseline of the modified FACE-Q was 38.8 [32.1 - 45.6], thereby achieving a lower bound for the difference that was greater than 12.

Table 18: Modified FACE-Q Change from Baseline at Visit 5: ANCOVA – Multiple Imputations (ITT)

Category	RHA Redensity® Eye Lido N = 183	No-Treatment N = 65
Rasch converted score at Baseline		
n (observed cases + imputed)	183 (173 + 10)	65 (52 + 13)
Mean (SD)	27.1 (19.78)	32.1 (25.03)
95% CI Mean	24.2 - 29.9	25.9 - 38.3
Min to Max	0 to 73	0 to 100
Rasch converted score at Visit 5 [(a)]		
n (observed cases + imputed)	183 (173 + 10)	65 (52 + 13)
Mean (SD)	64.6 (22.33)	28.0 (22.00)
95% CI Mean	61.3 - 67.8	22.5 - 33.4
Min to Max	0 to 100	0 to 80
Change from Baseline (SD)	37.5 (27.04)	-4.1 (17.48)

Category	RHA Redensity® Eye Lido N = 183	No-Treatment N = 65
95% CI Change from Baseline	33.6 - 41.5	-8.5 - 0.2
ANCOVA model at Visit 5 based on Rasch converted score		
H0: LS mean RHA Redensity® Eye Lido = LS mean No-Treatment 1-sided p-value	< .0001	
Estimate of difference in LS means	38.8	
95% CI for difference in LS means	[32.1 to 45.6]	

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; FCS = fully conditional specification; ITT = intent-to-treat; LS = least squares; N = number of subjects; n = number of observations; SD = standard deviation

Note: To successfully achieve the co-primary endpoint, the following conditions must be met: 1) the lower bound of 2-sided 95% confidence interval for the change from Baseline of the modified FACE-Q "Appraisal of lower eyelids" raw score for RHA Redensity® Eye Lido is at least 3; 2) the lower bound of 2-sided 95% confidence interval for the difference in mean change from Baseline of the modified FACE-Q between RHA Redensity® Eye Lido treated group and the No-Treatment control group is at least 12. When less than 50% of the scale's items are missing, the mean of the completed items was used to calculate the raw score, rounded to the nearest integer. Modified 4-item FACE-Q "Appraisal of lower eyelids" is used. As ANCOVA assumptions of normality are met, p-value is derived from the following model: ANCOVA by treatment arm using baseline modified FACE-Q score and site as covariates. Baseline is defined as the last non-missing measurement preceding the initial treatment for subjects assigned to RHA Redensity® Eye Lido and randomization date/time for subjects assigned to control groups.

(a) For subjects lost-to-follow-up or not present at the primary endpoint visit for the FACE-Q assessment, missing value is imputed using regression method within FCS for multiple imputation.

Sensitivity analyses confirmed the robustness of the primary endpoint analysis.

In summary, results support the following claim:

The proportion of responders, showing ≥1-grade improvement on the TIOHS was 79.0% in the treatment group and 9.8% in the No-Treatment group, 12 weeks after injection. The results showed that treatment of the infraorbital region with RHA Redensity® Eye Lido was statistically superior to no treatment and clinically significant (p<0.0001). The mean change from Baseline of the raw score of the modified FACE-Q was 4.8 for subjects in the treatment group and -0.6 for subjects in the No-treatment group. And the difference from Baseline of the Rasch converted score was 37.5 in the treatment group and -4.1 in the No-treatment group. At 12 weeks after initial treatment, 80.9% of subjects treated with RHA Redensity® Eye Lido reported improvement in the appearance of their infraorbital region based on the study-specific FACE-Q questionnaire 'Appraisal of lower eyelid module', with a mean Rasch converted score increasing from 27.1 at Baseline to 64.6. The improvement in Rasch converted score at 12 weeks was statistically superior to no treatment (p<0.0001).

Teoxane validated TIOHS scale was used to assess any change in the severity of the infraorbital hollows following the treatment of the

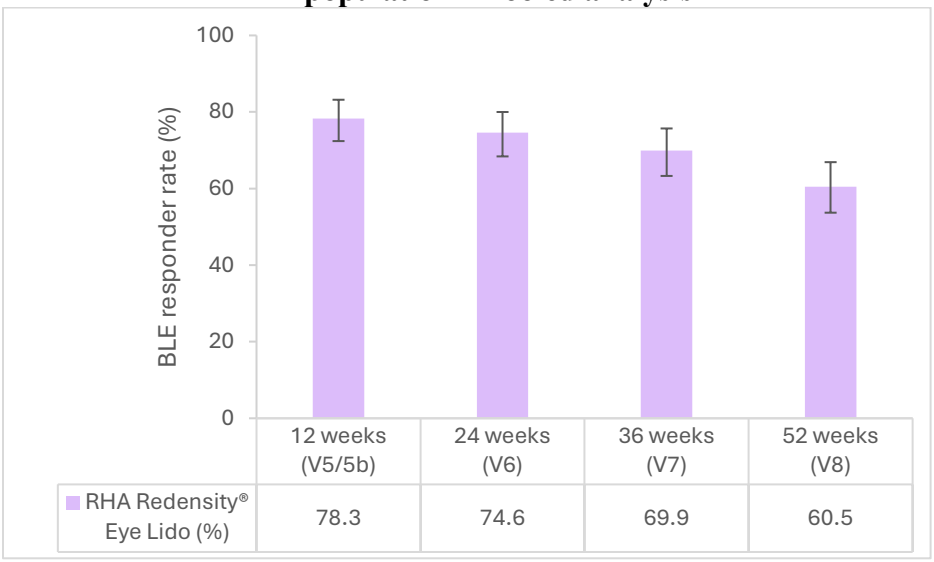
infraorbital region. TIOHS change from Baseline and the responder rate were also assessed by the BLE at each visit.

Table 19: TIOHS Responder Rate (BLE) – ITT Population (Pooled)

Visit	RHA Redensity® Eye Lido
Week 12	173/221 (78.3%)
Week 24	159/213 (74.6%)
Week 36	146/209 (69.9%)
Week 52	124/205 (60.5%)

For the pooled population (248 subjects), we observed an expected slow decrease of the responder rate (BLE assessment) with time throughout the course of the study (52 weeks after last treatment). Results showed that subjects injected with RHA Redensity® Eye Lido were able to sustain infraorbital correction over time, as the correction was still visible in more than 60% of subjects at 1-year post treatment (Figure 2). There were 31.7% of subjects who presented 2-grades improvement 12 weeks after Baseline and 5.9% with 3-grades improvement.

Figure 2: TIOHS Rate of Responders (≥1-Grade Difference from Baseline), as Assessed by the Blinded Live Evaluator, through the Follow-Up Period (V5/V5b to V8) – ITT population – Pooled analysis



The responder rate by number of grades (Table 20) showed that for the pooled population, 78.3% (173/221) of subjects had 1-grade improvement, 31.7% (70/221) of subjects had 2-grades improvements and 5.9% (13/221) had 3-grades improvements on both eyes at 12 weeks after initial treatment. And 52 weeks after treatment, 60.5% (124/205) of subjects maintained 1-grade improvement and 20.5% (42/205) maintained 2-grades improvement on both eyes. None had 3-grades improvement on both eyes.

Table 20: TIOHS Responder Rate by Number of Grade (BLE) at 12 Weeks – ITT Population

Visit	Category	RHA Redensity® Eye Lido (N = 221 V5; N=205 V8)
Visit 5/5b (12 weeks after Initial treatment)	≥1-grade improvement from baseline for at least one eye	185 (83.7%)
	≥2-grade improvement from baseline for at least one eye	90 (40.7%)
	≥3-grade improvement from baseline for at least one eye	18 (8.1%)
	≥1-grade improvement from baseline for both eyes	173 (78.3%)
	≥2-grade improvement from baseline for both eyes	70 (31.7%)
	≥3-grade improvement from baseline for both eyes	13 (5.9%)
Visit 8 (52 weeks after initial treatment)	≥1-grade improvement from baseline for at least one eye	142 (69.3%)
	≥2-grade improvement from baseline for at least one eye	61 (29.8%)
	≥3-grade improvement from baseline for at least one eye	1 (0.5%)
	≥1-grade improvement from baseline for both eyes	124 (60.5%)
	≥2-grade improvement from baseline for both eyes	42 (20.5%)
	≥3-grade improvement from baseline for both eyes	0

The GAI score assessed after RHA Redensity® Eye Lido injection into the infraorbital hollows (Table 21) were reported as improved or much improved for at least 92.8% (205/221) of subjects as assessed by the BLE, 96.4% (212/220) of subjects as assessed by the TI and 89.1% (197/221) of the subjects as assessed by the subjects at 12 weeks after Baseline. The GAI score remained high 52 weeks after Baseline with 74.1% responders when assessed by the BLE, 75.1% responders when assessed by the TI and 65.9% responders when assessed by the subject.

Table 21: GAIS as Assessed by BLE, TI and Subject – ITT Population

		RHA Redensity® Eye Lido
GAI (BLE)		
V5/V5b (W12)	N	221
	GAIS responder	205 (92.8%)
V8 (W52)	N	205
	GAIS responder	152 (74.1%)
GAI (TI)		
V5/V5b (W12)	N	220
	GAIS responder	212 (96.4%)
V8 (W52)	N	205
	GAIS responder	154 (75.1%)
GAI (Subject)		
V5/V5b (W12)	N	221
	GAIS responder	197 (89.1%)
V8 (W52)	N	205
	GAIS responder	135 (65.9%)

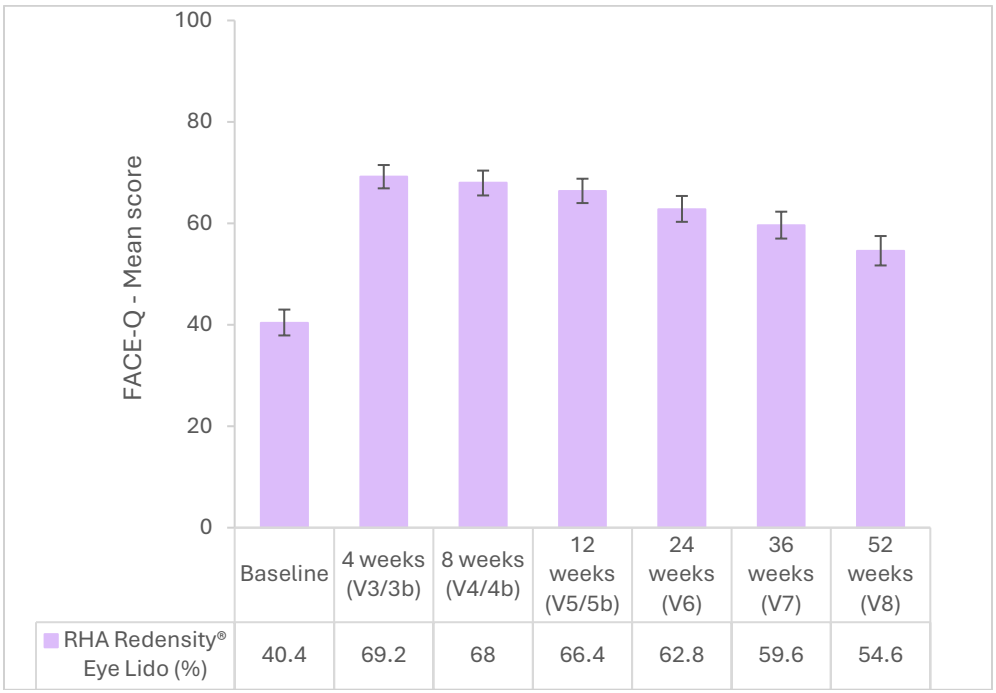
Responder: improved or much improved on GAI scale (much worse, worse, no change, improved, much improved)

Impact and effectiveness of study treatment procedures, from the subjects' perspective, was assessed at every in-clinic study visit (before and after

treatment with a study device, if applicable), using the *Appraisal of lower eyelids* domain of the validated FACE-Q© patient-reported outcome measurement questionnaire.

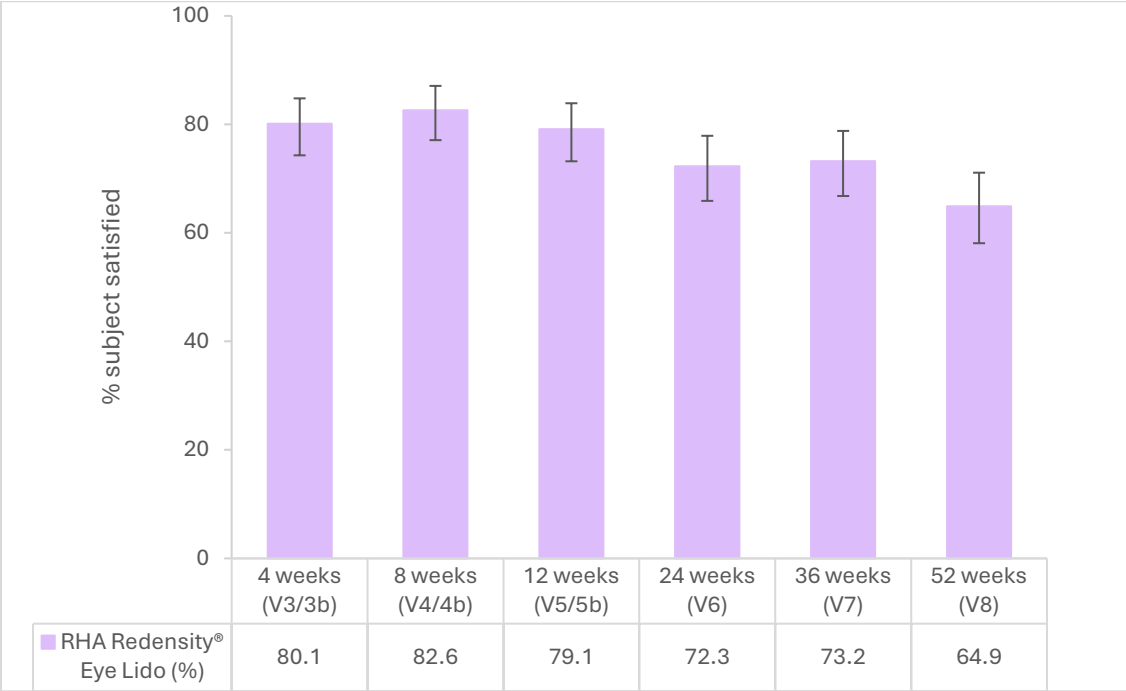
At all timepoints, the scores of all subjects who received treatment in their infraorbital hollows with RHA® Redensity Eye Lido were higher than pre-injection scores, indicating subject-perceived improvement in the appearance of their lower eyelids. The mean Rasch converted score improved from 40 to more than 66 at 12 weeks and stayed high to more than 54 at 52 weeks (Figure 3). This shows that the satisfaction of the appearance of the infraorbital region was achieved and maintained following treatment with RHA® Redensity Eye Lido.

Figure 3: FACE-Q – Appraisal of Lower Eyelids – ITT Population



For subjects who received treatment with RHA Redensity® Eye Lido in their infraorbital regions, the responder rates based on subject satisfaction was more than 79% (174/220) at 12 weeks after treatment and remained high at 64.9% (133/205) at 52 weeks after treatment. Subject reported a high degree of satisfaction with the treatment across all timepoints.

Figure 4: Subject Satisfaction (Satisfied or Very Satisfied) V3/V3b to V8 (Pooled) – ITT Population



	4 weeks (V3/3b)	8 weeks (V4/4b)	12 weeks (V5/5b)	24 weeks (V6)	36 weeks (V7)	52 weeks (V8)
RHA Redensity® Eye Lido (%)	80.1	82.6	79.1	72.3	73.2	64.9

Subject assessment about the effectiveness of the treatment was also assessed using Teoxane Periorbital Subject Assessment Questionnaire (PSAQ). There was a reduction in the perception of looking old and tired at 12 weeks and 52 weeks after initial treatment with RHA Redensity® Eye Lido compared to Baseline. Improvements were observed for all the statements throughout the study duration.

3. Subgroup Analyses

The following baseline characteristics were evaluated for potential associated with safety and effectiveness outcomes: Fitzpatrick Skin Type (FST), age, sex, ethnicity, administration method, volume injected, site, injection depth and injection technique. Subgroup analyses were performed to determine their potential impact on the change of the responder rate on the TIOHS at 12 weeks after injection as well as the incidence rate of CTRs and ADEs.

The study was not specifically powered for any of the subgroup analyses.

a) Safety: CTRs

CTRs were stratified by Fitzpatrick Skin Type (FST). All FST were appropriately represented with 65%, 35% and 10% of subjects with FST I-III, IV-VI and V/VI, respectively.

Out of 150 subjects who received the initial injection at Visit 1/1b in the FST I-III subgroup, 141 CTR diaries were retrieved, and 128 subjects (128/141, 90.8%) reported at least 1 CTR. Out of 83 subjects in the FST IV-VI subgroup, 82 CTR diaries were retrieved, and 53 subjects (53/82, 64.6%) reported at least 1 CTR. Out of 24 subjects in the FST V/VI subgroup, 24 CTR diaries were retrieved, and 18 subjects (18/24, 75.0%) reported at least 1 CTR.

Swelling was the most frequent CTR for subjects with FST I-III and it was tenderness for subjects with FST IV-VI and V/VI.

Overall, there was a higher percentage of CTR response in the Fitzpatrick I-III skin type subgroup (90.8%, 128/141) than in the subgroups with FST IV-VI (64.6%, 53/82) or FST V/VI (75.0%, 18/24). However, no statistical analysis was conducted to evaluate these differences and therefore no definite conclusions can be drawn from the observations.

The higher incidence rate of CTRs in the needle group than in the cannula group tended to be more pronounced for subjects with FST IV-VI and V/VI, however, no conclusion can be drawn because of the disproportionally smaller number of subjects of FST V/VI.

CTR incidence rate was stratified by injection depth and injection technique. Due to the disproportionate number of subjects in some categories, no trend or conclusion could be drawn.

When stratified by injection volume, the CTR incidence rate tended to be lower with lower volumes injected: with ≤1 mL, 66.7% (44/66); with >1 mL to ≤1.5 mL, 81.8% (27/33); and with ≥1.5 mL to ≤2 mL, 88.7%, (10/12).

b) Safety: ADEs

All Fitzpatrick Skin Types (FST) were appropriately represented. Proportion of subjects being FST I-III vs IV-VI and FST IV/VI were similar between needle and cannula subgroups:

- FST I-III: 67.2% (78/116) and 61.5% (72/117) of subjects in the needle and cannula groups, respectively
- FST IV-VI: 32.8% (38/116) and 38.5% (45/117) of subjects in the needle and cannula groups, respectively
- FST V/VI: 8.6% (10/116) and 12.0% (14/117) of subjects in the needle and cannula groups, respectively

The ADE profile of subjects injected with RHA Redensity® Eye Lido was not impacted by the Fitzpatrick Skin Type. The proportion of subjects who experienced at least 1 ADE was similar for all Fitzpatrick Skin Types:

- 17.3% (26/150) subjects with FST I-III
- 16.9% (14/83) subjects with FST IV-VI
- 12.5% (3/24) subjects with FST V/VI

Within the FST IV-VI subgroup, there was a difference in ADE rate between the needle and cannula subgroups, 26.3% of subjects (10/38) and 8.9% of subjects (4/45), respectively. This trend was reversed in the FST I-III subgroup and the FST V/VI: the ADE rate was lower in the needle subgroup than in cannula subgroup: FST I-III: 15.4% (2/78) subjects (needle) versus 19.4% (14/72) subjects (cannula) and FST V/VI: 10.0% (1/10) subjects (needle) versus 14.3% (2/14) subjects (cannula). No formal conclusion can be made in regard to the relationship of the administration methods and the FST subgroups as this would require further investigation and analysis.

Table 22: ADE Profile Overview by Fitzpatrick Skin Type (Visit 1/1b to Visit 8 – Initial Treatment to 52 Weeks Follow-Up Excluding Retreatment – Pooled) – Safety Population

FST	From V1/1b to V8	Needle (N= 116)		Cannula (N= 117)		Total (N= 233)	
		Number of events	Number of subjects	Number of events	Number of subjects	Number of events	Number of subjects
I-III	Number of subjects		78		72		150
	Any ADE	17	12 (15.4%)	22	14 (19.4%)	39	26 (17.3%)
IV-VI	Number of subjects		38		45		83
	Any ADE	11	10 (26.3%)	7	4 (8.9%)	18	14 (16.9%)
V/VI	Number of subjects		10		14		24
	Any ADE	1	1 (10.0%)	4	2 (14.3%)	5	3 (12.5%)

Abbreviations: ADE = adverse device effect. N = number of subjects; SAFT = safety (population)

Notes: All percentages are based on the number of subjects by treatment group and Fitzpatrick skin type in the Safety population. Events occurring between Visit 1 and Visit 8 for subjects initially assigned to RHA® Redensity Eye Lido and events occurring between Visit 1b and Visit 8 for subjects initially assigned to No-Treatment are considered.

All ethnicities were appropriately represented, with 25.3% (59/233) and 72.5% (169/233) of subjects being Hispanic and Non-Hispanic or Latino, respectively.

ADEs were not correlated with ethnicity: 13.6% (8/59) of Hispanics or Latino subjects and 18.3% (31/169) of Not Hispanics or Latino subjects experienced at least 1 ADE. There were no observable differences of rate of ADEs between the needle and cannula subgroups.

Sex was appropriately represented, with 12.0% (28/233) and 88.0% (205/233) of male and female subjects, respectively.
ADEs were not correlated with sex: 10.7% (3/28) of male subjects and 18.0% (37/205) of female subjects experienced at least 1 ADE. There was no observable difference between the needle and cannula subgroups for female. For male subjects, the higher incidence rate of ADEs when injected

with a needle than when injected with a cannula (18.8% (3/16) versus 0% (0/12) respectively) cannot lead to conclusion due to the small number of male subjects.

The median age was 51 years old with 51.5% (120/233) of subjects aged 22 to 51 years old and 48.5% (113/233) of subjects older than 51 years old.
ADEs were not correlated with age: 15.0% (18/120) of younger subjects and 19.5% (22/113) of older subjects experienced at least 1 ADE. There were no observable differences of rate of ADEs between the needle and cannula subgroups.

The proportion of subjects injected with ≤1 mL was 29.6% (69/233), there were 15.0% (35/233) of subjects injected with >1mL and ≤1.5 mL and the majority of subjects 55.3% (129/233) was injected with ≥1.5 mL of RHA Redensity® Eye Lido.
ADE rates by injection volume subgroup appear to be somewhat positively correlated with higher injection volumes however, no formal analysis was conducted.

- Injection volume ≤1 mL: 10.1% of subjects (7/69) experienced an ADE
- Injection volume >1 mL to ≤1.5 mL: 5.7% of subjects (2/35) experienced an ADE
- Injection volume >1.5 mL to ≤2 mL: 24.0% of subjects (31/129) experienced an ADE

There were no observable differences of rates of ADEs between the needle and cannula subgroups.

Few subjects were injected into the sub-dermis with only 15.0% (35/233) and the majority of subjects were injected into the supraperiosteum 51.1% (119/233) and the remaining into both depth planes, 33.9% (79/233).

Only 5.7% (2/35) of subjects injected in the sub-dermis experienced at least 1 ADE against 21.0% (25/119) and 16.5% (13/79) for subjects injected into the supraperiosteum or both layers of injection, respectively. No conclusion can be drawn due to the disproportionally small number of subjects injected only into the sub-dermis and nearly all of them were injected with the cannula. In addition, the treatment of tissue volume deficiencies in the infraorbital regions may be achieved with several approaches combining injection depth, volume and technique depending on the subject's anatomy. The injection depth was at the discretion of the TI to achieve optimum correction. The rate of ADEs was similar between the needle and cannula subgroups for each injection depth:

- Subjects injected in the sub-dermis only: 0% (0/2) subjects in needle subgroup and 6.1% (2/33) subjects in cannula subgroup experienced at least 1 ADE;

- Subjects injected in the supraperiosteum only: 20.6% (20/97) subjects in needle subgroup and 22.7% (5/22) subjects in cannula subgroup experienced at least 1 ADE;
- Subjects injected in the sub-dermis and the supraperiosteum layers: 11.8% (2/17) subjects in needle subgroup and 17.7% (11/62) subjects in cannula subgroup experienced at least 1 ADE;

The analysis of ADEs per the injection depth does not provide meaningful conclusions.

Different injections techniques may have been used to inject in the infraorbital regions: anterograde linear threading, retrograde linear threading, multi punctures technique or other. The technique was also often associated with the method of injection: for example, multipuncture technique was only used with the needle 82.8% (96/116) while retrograde linear threading was mostly used with cannula 77.8% (91/117) than with needle 3.4% (4/116). Therefore, the incidence rates of ADEs per injection technique did not provide any meaningful conclusion due to the disproportionate use of some injection techniques and very low numbers in others.

c) Effectiveness at primary endpoint

No apparent impact of Fitzpatrick Skin Type, ethnicity, sex and age on the responder rate at 12 weeks after treatment was observed; however, the study was not powered to detect subgroup differences. The responder rate tended to increase for subgroups based on increasing injection volume with 69.8% for volumes ≤1 mL and 89.3% in subjects treated with >1 mL and ≤1.5 mL and 81.3% in subjects treated with >1.5 mL. However, no conclusion could be drawn. The responder rate was also slightly higher at 12 weeks after treatment for subjects injected with a needle (82.4%) than for subjects injected with a cannula (75.6%).

4. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

XI. FINANCIAL DISCLOSURE

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study G200191 included 11 investigators. Nine of the clinical investigators had no disclosable financial

interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). Two of the clinical investigators had some financial interests with the US distributor of the products. They did not affect the reliability of the data submitted as steps were taken to minimize potential bias. The information provided does not raise any questions about the reliability of the data.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the General and Plastic Surgery Devices Advisory Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSION DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

Study results demonstrated that RHA Redensity® Eye Lido was superior to No-Treatment control 12 weeks after initial treatment for the correction of moderate to severe tissue volume deficiencies in the infraorbital hollows in adults aged 22 years or older. Also, the proportion of responders at 12 weeks in the RHA Redensity® Eye Lido group (79.0%) and the difference of the responder rate between the treatment and No-Treatment groups (58.7%) were above the thresholds (≥70% and ≥50%, respectively) to confirm superiority.

Additionally, the change from Baseline of the modified FACE-Q *Appraisal of lower eyelids* was statistically superior in the RHA Redensity® Eye Lido group. The mean change from baseline at 12 weeks based of the Rasch converted score 37.5 in the RHA Redensity® Eye Lido group indicating an improvement vs -4.1 in the No-Treatment group indicating a lack of improvement or worsening. The lower bound of the 95% CI of the mean change from Baseline of the raw score at 12 weeks in the RHA Redensity® Eye Lido group was above the prespecified threshold of ≥3. The lower bound of the 95% CI for the difference in mean change from baseline in the converted Rasch score between the RHA Redensity® Eye Lido group and the no-treatment group also exceeded the prespecified threshold of ≥12.

The treatment of the infraorbital regions with RHA Redensity® Eye Lido demonstrated a substantial improvement in the percentage of subjects achieving at least a 2 or 3 grade improvement from Baseline for both eyes at 12 weeks with 32.9% and 5.8% of subjects in the treatment group achieving these improvements, compared to 0% in the No-Treatment control group. These findings are based on observed point estimates, and no statistical conclusions can be drawn.

The response rates were consistent across various subgroups, including FSTs, age, sex, injection volume, method of administration, and ethnicity. Overall, RHA

Redensity® Eye Lido demonstrated marked effectiveness and long-term performance in improving the appearance of the periorbital region at 12 weeks (78.3%, 173/221) and up to 52 weeks (60.5%, 124/205) after treatment.

In the analysis of the pooled population of RHA Redensity® Eye Lido throughout the 52 weeks follow-up of the study, RHA Redensity® Eye Lido injected into the infraorbital region provided high levels of aesthetic improvement. GAI responder rates were high, as assessed by the BLE, the TI, and the subjects and showed a small decrease over time, indicating an expected loss of treatment effect with time. GAI responders were more than 89% at 12 weeks and more than 65% at 52 weeks for BLE, TI and subjects.

Subject satisfaction was also very high at 12 weeks (>79%) and nearly 65% of subjects remained satisfied or very satisfied 52 weeks after treatment.

Validated subject-reported outcome measure FACE-Q of *Appraisal of Lower Eyelids* evaluated subject satisfaction with the area under their eyes. At Baseline, responses to the questionnaire indicated that most subjects were very dissatisfied or dissatisfied with their appearance. Assessments improved after initial injection and remained improved at 12 and 52 weeks after injection with the Rasch converted score improvements from 40.4 at Baseline, more than 60 at 12 weeks and a slight decrease to 54.6 at 52 weeks.

The subject assessments using the PSAQ showed notable improvements in the appearance of the infraorbital region following RHA Redensity® Eye Lido treatment. Key indicators such as looking less tired and old, and having smoother, more natural, and radiant skin, all results showed marked improvements at 12 weeks post-treatment. By 52 weeks after initial treatment, these improvements were largely sustained, demonstrating the long-term performance of the treatment over the long-term.

The RHA Redensity® Eye Lido treatment demonstrated significant effectiveness and long-term performance in improving the appearance of the infraorbital region.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in clinical studies conducted to support PMA approval as described above.

Study treatment with RHA Redensity® Eye Lido formulation appeared to be safe and well tolerated when injected into the infraorbital region. There were no reports of deaths, Serious Adverse Events that were treatment related or Unexpected Adverse Device Effects in the study.

Adverse Device Effects rates were not negatively correlated with higher Fitzpatrick skin type or with ethnicity, age groups, volume injected, injection depth or administration method.

All Adverse Device Effects were types of events that are typically experienced following the injection of a dermal filler, the onset of all events was temporally associated with a recent injection of a study device, and all events were mild or moderate in intensity (no severe Adverse Device Effects were reported). There were no late onset Adverse Device Effects, and no events were deemed to be a granuloma. More than 50% of the Adverse Device Effects were resolved in 14 days. Most ADEs were mild (93.0%, 53/57) with only 4 subjects experienced moderate ADEs. There were no severe ADEs. The rate of ADEs when injected with a needle or a cannula was similar. Altogether, 4 AESIs were reported in 1.3% (3/233) of subjects between Visit 1/1b and Visit 8. All were mild, with 1 AESI (atypical migraine) considered to be possibly related to the study device and unrelated to the study procedure; all others were not related to the device or procedure. All AESIs resolved without sequalae. 2.8% (7/248) of subjects experienced a Tyndall effect and they were all mild and resolved without sequalae.

C. Benefit-Risk Determination

1. Benefit-Risk assessment

The probable benefits of the device are also based on data collected in the clinical study conducted to support PMA approval as described above.

The study was randomized, double blinded, between subject, multicenter and prospective, utilizing a validated scale (TIOHS) assessed by Blinded Live Evaluators to determine the primary effectiveness endpoint. Superiority of RHA Redensity® Eye Lido was confirmed versus the No-Treatment control.

The probable risks of the device are also based on the data collected in a clinical study conducted to support PMA approval as described above. Adverse Device Effects were all typical and expected in association with injection of a dermal filler and did not occur at rates different from those expected. Subjects reported high levels of satisfaction with their results, as assessed by multiple evaluation tools. Based on the safety and effectiveness conclusions drawn from the pivotal clinical study, it is reasonable to conclude that the benefits of the use of RHA Redensity® Eye Lido outweigh the risks when used in accordance with the Instructions For Use. Similarly, the benefits of the use of RHA Redensity® Eye outweigh the risks when used in accordance with the Instructions For Use.

2. Patient Perspective

Patient perspectives considered during the review included:

- Global Aesthetic Improvement (GAI) as assessed by the subject

- Impact and effectiveness of study treatment from the subjects' perspective as assessed by the *Appraisal of lower eyelids* domain of the validated FACE-Q© patient-reported outcome measurement
- Subject satisfaction survey
- Teoxane Periorbital Subject Assessment Questionnaire (PSAQ)

In conclusion, given the available information above, the data support the use of RHA Redensity® Eye Lido and RHA® Redensity Eye for injection into the sub-dermis and supraperiosteum layers for the correction of volume deficiencies in the infraorbital regions in adults aged 22 years or over the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of these devices when used in accordance with the indications for use. The benefits and risks of dermal fillers are sufficiently well understood for patients to make informed decisions about their use.

XIV. CDRH DECISION

CDRH issued an approval order on May 12, 2026.

The applicant's manufacturing facility was inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820), which was in effect at the time of the inspection. As of February 2, 2026, the revised part 820, referred to as the Quality Management System Regulation (QMSR), is effective.

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.