SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Injectable Dermal Filler

Device Trade Name: RHA®4 and RHA® Dynamic Volume

Device Procode: LMH (Implant, Dermal, For Aesthetic Use)

Applicant's Name and Address: TEOXANE S.A.
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Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P170002/S048

Date of FDA Notice of Approval: September 18, 2025

RHA®4 was approved on October 19, 2017 under the original PMA P170002 and RHA® Dynamic Volume (formerly RHA®4 Mepi) was approved on October 13, 2023 under panel-track supplement P170002/S026. Both were approved for injection into the deep dermis to superficial subcutaneous tissue for the correction of moderate to severe dynamic facial wrinkles and folds, such as nasolabial folds (NLFs), in adults aged 22 years or older. The SSEDs to support the indication of RHA®4 and RHA®4 Dynamic Volume for the correction of moderate to severe dynamic facial wrinkles and folds, such as nasolabial folds (NLFs) are available on the CDRH website and are incorporated by reference here.

The current supplement was submitted to expand the indication of RHA®4 and RHA® Dynamic Volume for injection into the subcutaneous to supraperiosteal layers for cheeks augmentation and/or correction of age-related midface contour deficiencies, in adults aged 22 years or older.

II. INDICATIONS FOR USE

RHA4® is indicated for injection into the deep dermis to superficial subcutaneous tissue for the correction of moderate to severe dynamic facial wrinkles and folds, such as nasolabial folds (NLF), in adults aged 22 years or older.

RHA®4 is indicated for injection into the subcutaneous to supraperiosteal layers for cheeks augmentation and/or correction of age-related midface contour deficiencies, in adults aged 22 years or older.

RHA® Dynamic Volume is indicated for injection into the deep dermis to superficial subcutaneous tissue for the correction of moderate to severe dynamic facial wrinkles and folds, such as nasolabial folds (NLF), in adults aged 22 years or older.

RHA® Dynamic Volume is indicated for injection into the subcutaneous to supraperiosteal layers for cheeks augmentation and/or correction of age-related midface contour deficiencies, in adults aged 22 years or older.

III. CONTRAINDICATIONS

- RHA®4 and RHA® Dynamic Volume are contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.
- RHA®4 and RHA® Dynamic Volume contain trace amounts of gram-positive bacterial proteins and is contraindicated for patients with a history of allergies to such material.
- RHA®4 and RHA® Dynamic Volume should not be used in patients with previous hypersensitivity to local anesthetics of the amide type, such as lidocaine or mepivacaine.
- RHA®4 and RHA® Dynamic Volume should not be used in patients with bleeding disorders.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the RHA®4 and RHA® Dynamic Volume labeling.

V. DEVICE DESCRIPTION

RHA®4 and RHA® Dynamic Volume are viscoelastic, sterile, non-pyrogenic, clear, colorless, and biodegradable gel implants. They are produced with sodium hyaluronate (NaHA) with a concentration of 23 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®4 contains 0.3% lidocaine hydrochloride monohydrate to reduce pain on injection.
RHA® Dynamic Volume contains 0.3% mepivacaine hydrochloride to reduce pain on injection.

RHA®4 and RHA® Dynamic Volume are supplied in individual blisters containing a 1.2 ml treatment syringe with two 27G ½ inch hypodermic needles.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for cheek augmentation and correction of age-related midface contour deficiencies: surgical implants, autologous fat injections, face-lift surgery, approved soft tissue filler for this indication. 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®4 has been sold in the United States since 2020 and RHA®4 Mepi for the approved indication when injected into the dynamic facial wrinkles and folds will be launched late 2025. RHA®4 has been commercially available in the European Union and registered in more than 45 countries around the world since 2015. It has been approved for a wide range of indications including for midface volume deficiency. Neither RHA®4 or RHA®4 Mepi has been removed from the marketplace for any reasons related to safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Common treatment responses which can occur with the use of RHA®4, RHA® Dynamic Volume and other dermal fillers, 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 nasolabial folds and other locations of the face, as part of the post-marketing surveillance on the use of RHA®4 in and outside the United States. The following adverse events were reported on the use of RHA®4 worldwide with a prevalence equal or superior to one occurrence for 100,000 syringes: skin edema, skin swelling, injection site mass (inflammatory or non-inflammatory), skin induration, injection site inflammation, pain, erythema, granuloma, vascular complications, ecchymosis, skin infection and tenderness.

Additionally, other less frequent adverse reactions have also been reported, including implant migration, allergic reaction, skin discoloration/Tyndall effect, abscess, overcorrection, pruritus, anaphylactic reaction, skin necrosis, urticaria, blister, scab, angioedema, chapped lips, dermatitis, dry skin, fibrosis, herpes breakout, numbness, pustules, telangiectasia and visual impairment.

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 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, and skin necrosis

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, 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®4 and RHA® Dynamic Volume

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®4 Mepivacaine for RHA® Dynamic Volume	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 (RHA® Dynamic Volume)	To ensure gel meets specifications	Passed

B. Biocompatibility Studies

Table 2: Summary of biocompatibility studies for RHA®4 and RHA® Dynamic Volume

Test	Method	ISO Standard or USP	Results
Cytotoxicity	In vitro mammalian cell culture test	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®4 was non-irritant at 26 days. RHA® Dynamic Volume was non-irritant at 20 days.
Pyrogenicity	Rabbit pyrogen study	USP 36 NF 31	Non-pyrogenic.
Genotoxicity	Ames test (bacterial reverse mutation study)	ISO 10993-3	Non-mutagenic.
Genotoxicity	Mouse lymphoma assay	ISO 10993-3	Non- mutagenic.
Genotoxicity	Mouse peripheral blood micronucleus test (for RHA®4 only)	ISO 10993-3	Non-genotoxic.
Acute systemic toxicity	Mice intraperitoneal study	ISO 10993-11	No evidence of acute systemic toxicity.
Sub-acute and subchronic systemic toxicity	Intradermal injection in Sprague-Dawley rats (for RHA®4 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® and RHA® Dynamic Volume products.

C. Stability studies

Stability data have been collected on three batches per product (RHA®4 and RHA® Dynamic Volume) through a 24-month stability study conducted at 25°C ± 2°C and 60% ± 5% relative humidity (ICH long term storage conditions). As part of stability testing, products were characterized via microbiological, physical, and chemical specifications parameters, including lidocaine hydrochloride monohydrate content for RHA®4 and mepivacaine hydrochloride content for RHA® Dynamic Volume, 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®4 and RHA® Dynamic Volume dermal fillers have a 24-month shelf life with recommended storage conditions up to 25°C (77°F).

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed one clinical study to establish a reasonable assurance of safety and effectiveness when injecting RHA®4 into the subcutaneous to supraperiosteal layers for cheek augmentation and/or correction of age-related midface contour deficiencies in adults aged 22 years or over in the U.S. under IDE # G210086. Data from this clinical study was the basis for the PMA approval decision. Those data were leveraged for RHA® Dynamic Volume as they are identical products with a different anesthetic agent. Clinical study IDE G190118 had demonstrated the non-inferiority of mepivacaine to lidocaine in the device. A summary of the clinical study with RHA®4 is presented below.

Please note: RHA® Dynamic Volume is strictly identical to RHA®4 except for the small amount of anesthetic medicine: RHA® Dynamic Volume contains mepivacaine and RHA®4 contains lidocaine. Both anesthetics agents are of the same family with the same mechanisms of effect. Details about the supporting clinical data of the equivalency of both products were documented under SSED of panel-track supplement P170002/S026. RHA® Dynamic Volume and RHA®4 have the same indication. The long-term safety and effectiveness of RHA® Dynamic Volume were evaluated in a clinical study (presented hereafter) using RHA®4 over 52 weeks after initial or touch-up treatments and for 12 weeks following retreatment.

A. Study Design

Subjects were treated between October 29, 2021 and January 29, 2024. The database for this PMA reflected data collected through March 19, 2024 and included 201 treated subjects with 152 subjects who received injection with RHA®4 and 49 subjects with the control. There were 8 U.S. investigational sites.

The study was a controlled, randomized, blinded evaluator, between subject, multicenter, prospective non-inferiority clinical study to evaluate the safety and effectiveness of RHA®4 for cheek augmentation and/or midface contour deficiencies against a control. Subjects meeting inclusion/exclusion criteria were randomized 3:1 ratio into the treatment or control group (Juvederm® Voluma™ XC [Allergan]). The control was an FDA approved hyaluronic acid soft tissue filler with similar characteristics to RHA®4 and marketed for midface correction. The study duration was nearly 16 months and included repeat treatment.

1. 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 1 a reliable method of contraception throughout the study:
- Had midface volume loss of grades 2 to 3 on the Teoxane Midface Volume Deficiency Scale (TMVDS) (ranging from 0 = absent to 4 = very severe). The blinded live evaluation (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.
- Had cheeks of the same TMVDS grade on the left and right side of the face (i.e., approximate bilateral symmetry).
- 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 <u>not</u> 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
- Had known susceptibility to keloid formation, hypertrophic scarring, or clinically significant skin pigmentation disorders as judged by the TI
- Had a history of severe chronic systemic diseases, including but not limited to, poorly controlled diabetes mellitus (all types), congestive heart failure, severe liver disease, severe kidney disease, and others that are likely to interfere with the measured parameters or to put the subjects to an undue risk 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 an active inflammation, infection, cancerous or precancerous lesion, or unhealed wound on the midface, or has undergone radiation treatment in the area to be treated
- Had any significant concomitant skin disease present within 6 months prior to Visit 1 (such as moderate to severe rosacea, acne vulgaris, actinic keratosis, or seborrheic keratosis) that

may interfere with study assessments and interpretation of study results or would require medical or surgical intervention on the cheek during the study

- Exhibited any physical attribute that may prevent assessment or treatment of the midface volume deficiency, such as excessive facial hair (men with a beard are required to shave before each study visit), traumatic or noticeable facial scars, tattoos, and/or excessive hyperpigmentation in the treatment areas, as judged by the TI
- Had midface volume deficit due to congenital defect, trauma, abnormalities in adipose tissue related to immune-mediated diseases such as generalized lipodystrophy (e.g., juvenile dermatomyositis), partial lipodystrophy (e.g., Barraquer-Simons syndrome), and inherited disease
- 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
- Had previously undergone or was planning to undergo prohibited treatment/procedures during certain time periods
- 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).
- Had unstable weight, as judged by the TI
- Had no teeth or misses significant portion of dentition that changes the face appearance; subjects with dentures sufficiently replacing missing natural teeth are allowed
- Currently received or had received oral or injectable corticosteroids, immunosuppressants or chemotherapy within 3 months before Visit 1. Inhaled and topical corticotherapy not including head or neck was permitted

2. Follow-up Schedule

At Visit 1, subjects were randomized to RHA®4 or control treatment group. They received injection in their midface region as defined by the protocol. The Treating Investigator (TI) determined the injection technique and depth of injection (subcutaneous and/or supraperiosteal). RHA®4 may be injected with a 27G ½" needle or 25G 2" cannula using a multilayering technique. The control

device was injected as per its IFU). The maximum volume of administration of RHA®4 was 3 mL per treatment session on each side, with a maximum of 6 mL at each treatment session. After 4 weeks, subjects may receive additional treatment with the same device as originally injected (RHA®4 or control) to achieve optimal correction if deemed necessary by the TI.

Following any injection (initial, touch up, retreatment), subjects were given a 30-Day diary to daily record common treatment responses (CTR) and any other adverse observations. They were instructed to record the severity of each CTR as mild, moderate, or severe.

All subjects were scheduled to return for follow-up examinations at 4, 8, 16, 24, 36, and 52 weeks after last treatment (initial or touch-up). The primary effectiveness endpoint (TMVDS) was evaluated at 8 weeks after last treatment. Subjects were followed for 52 weeks to evaluate the long-term safety, safety of retreatment and other secondary endpoints of RHA®4. Subjects were offered retreatment 52 weeks after last treatment. Retreatment was with RHA®4 irrespective of the assigned device at initial and touch-up treatment. Adverse events and complications were recorded at all visits.

The key timepoints are shown below in the tables summarizing safety and effectiveness.

Table 3: Treatment schedule and assessments

		Treatment (Tx) groups: RHA®4/ Control	**Safety Assessments**	**Effectiveness Assessments**
Initial treatment	V1	0 weeks Initial treatment	Visual assessments CTR diary AEs Pain VAS	BLE: TMVDS, NLF-WSRS, TIOHS TI: TMVDS Subject: Face-Q. TMNSQ
	V1a	3 days - Phone call	CTR diary AEs	N/A
	V1b	2 weeks	Visual assessments CTR diary AEs	N/A
Optional touch-up	V2	4 weeks Optional TU	Visual assessments CTR diary AEs Pain VAS if TU tx	TI: TMVDS, GAIS Subject: Face-Q, GAIS, Subject satisfaction, TMNSQ
If touch-up	V2a	3 days after TU – Phone call	CTR diary AEs	N/A
	V2b	2 weeks after TU	Visual assessments CTR diary AEs	N/A
	V2c	4 week after TU		TI: TMVDS, GAIS Subject: Face-Q, GAIS, Subject satisfaction, TMNSQ
	V3	8 weeks after last tx **Primary endpoint assessment**	Visual assessments AEs	BLE: TMVDS, NLF-WSRS, TIOHS, GAIS TI: TMVDS, GAIS Subject: Face-Q, GAIS, Subject satisfaction, TMNSQ
	V4	16 weeks after last tx		
	V5	24 weeks after last tx		
	V6	36 weeks after last tx		
Optional retreatment	V7	52 weeks after last tx – Exit or	Visual assessments CTR diary AEs	BLE: TMVDS, NLF-WSRS, TIOHS, GAIS TI: TMVDS, GAIS

		Treatment (Tx) groups: RHA®4/ Control	**Safety Assessments**	**Effectiveness Assessments**
		Optional retreatment with RHA® Dynamic Volume for both treatment groups	Pain VAS if retreatment	Subject: Face-Q, GAIS, Subject satisfaction, TMNSQ
If retreatment	V7a	+3 days after retreatment	CTR diary AEs	N/A
	V7b	2 weeks after retreatment	Visual assessments CTR diary AEs	N/A
	V7c	4 weeks after retreatment		BLE: TMVDS, NLF-WSRS, TIOHS, GAIS TI: TMVDS, GAIS Subject: Face-Q, GAIS, Subject satisfaction, TMNSQ
	V7d	12 weeks after retreatment - Exit	Visual assessments AEs	

Abbreviations: AE: Adverse Event; BLE: Blinded Live Evaluator; CTR: Common Treatment Response; FACE-Q: Satisfaction with cheeks questionnaire; GAIS: Global Aesthetic Improvement Scale; NLF-WSRS: Nasolabial Folds Wrinkle Severity Scale; TI: Treatment Investigator; TIOHS: Teoxane Infraorbital Hollows Scale TMNSQ: Teoxane Midface Naturalness Subject Questionnaire; TMVDS: Teoxane Midface Volume Deficit Scale; TU: Touch-up; Tx: Treatment; VAS: Visual Analog Scale

3. Clinical Endpoints

Safety was evaluated through a 30-Day patient Common Treatment Response (CTR) diary (after each injection), measures of injection site pain, visual assessments and AE assessments at each visit.

Subjects recorded the presence, duration, and severity of CTRs that may occur following the injection of a dermal filler, for the first 30 days after each treatment (initial, touch-up, and retreatment) in a patient diary: redness, pain, tenderness, firmness, swelling, lumps/bumps, bruising, itching, discoloration, and other. Subjects could fill out the description of the symptoms in the "other" category and it was automatically categorized as an AE. In addition, the CTR diary captured the occurrence of events associated with visual disturbances and possible symptoms of intravascular injection. Such events were automatically categorized as AEs and the subject was required to seek immediate medical assistance.

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. Additionally, CTRs that were present on the last day of diary entry, regardless of severity, were automatically recorded as AEs.

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.

Safety was also evaluated at each visit with visual assessment tests (before and 30 min post-injections, and at each study visit after the last treatment).

Pain at the injection site(s) was self-assessed by the subject using a 100 mm Visual Analog Scale (VAS), with the left end representing "no pain" and the right end representing "worst pain" during injection and 5, 15 and 30 minutes after injection.

Effectiveness was measured by assessing midface volume improvement based on the validated Teoxane Midface Volume Deficiency Scale (TMVDS[1]) (Table 4) from pre-injection midface volume treated with the RHA®4 compared to the improvement from pre-injection midface volume treated with the control device, as assessed by the BLE at 8 weeks after the last injection (initial or touch-up).

Table 4: Teoxane Midface Volume Deficiency Scale (TMVDS)

Category	Grade	Description
Absent	0	**- Full or round face.** - No visible signs of volume deficit noted in the overall midface.
Mild	1	**- Presence of slight flattening of the anteromedial cheek or very minor contour deficit in the lateral malar area.** - Presence of mild infra-orbital hollows and/or mild nasolabial folds.
Moderate	2	**- Presence of moderate flattening of the anteromedial cheek and/or moderate hollowing in the lateral malar area.** - Descent of the facial fat pads creating moderate nasolabial folds and mild to moderate infra orbital hollows. - Mild pre-jowl sulcus and/or mild to moderate naso-jugal folds extending beyond the mid pupil.
Severe	3	**- Significant flattening of the anteromedial cheek and/or severe submalar hollowing.** - Obvious descent of the facial fat pads creating bony prominence of the zygoma. - Moderate to severe infra-orbital hollowing and nasolabial folds. - May have moderate presence of pre-jowl sulcus and jowls.
Very Severe	4	**- Very severe facial wasting.** - Obvious descent of the facial fat pads creating very deep, heavy / nasolabial folds and jowls. - Very severe infra orbital hollowing and deep naso-jugal folds. - Prominence of bony landmarks, visibility of facial musculature, and/or moderate to severe pre-jowl sulcus.

The primary effectiveness endpoint was the difference in the Teoxane Midface Volume Deficiency Scale (TMVDS) change from Baseline to 8 weeks after last injection (initial or touch-up) between subjects treated with RHA®4 and those treated with the control. Assessment of the subject's midface volume was based on the validated Teoxane Midface Volume Deficiency Scale (TMVDS) as rated by the Blinded Live Evaluator. The proportion of responders with a ≥1-grade point improvement on the TMVDS at 8 weeks after last injection (initial or touch-up) when compared to pretreatment (Baseline) was calculated. A change in the TMVDS ≥1 grade compared to pretreatment would be considered clinically meaningful.

Secondary effectiveness endpoints throughout the course of the study included: change from Baseline and responder rate of TMVDS score as rated by the BLE and TI (responder is a change of ≥ 1-grade

1 The development and validation of the TMVDS has been published in the *Journal Dermatologic Surgery*, by Bury et al., in July 2025 (Creation and validation of a photonumeric scale for assessment of midface volume deficit).

on the TMVDS); Global Aesthetic Improvement (GAI) as assessed by the BLE, TI and subject; Change from Baseline and responder rate of TMVDS score as rated by the Independent Photographic Reviewer (IPR) at 8 weeks after last treatment; Change from Baseline and responder rate of the severity of the nasolabial folds as assessed by the BLE using the validated Teoxane Nasolabial Fold Wrinkle Severity Rating Scale (NLF-WSRS); Change from Baseline and responder rate of the severity of the infraorbital hollows as assessed by the BLE using the validated Teoxane Infra-Orbital Hollows Scale (TIOHS); Impact and effectiveness of study treatment from the subjects' perspective, as assessed by the *Satisfaction with cheeks* domain of the validated FACE-Q© patient-reported outcome measurement at rest and when smiling, by the subject satisfaction questionnaire and the naturalness of the cheek subject questionnaire;

With regard to success/failure criteria, the effectiveness of RHA®4 would be demonstrated if the TMVDS change from Baseline for subjects treated with RHA®4 was statistically non-inferior to the change from Baseline for subjects treated with the control with a non-inferiority margin of ≥0.5, and the proportion of responders among subjects treated with the control is ≥70%.

To demonstrate the TMVDS (BLE) change from Baseline at Visit 3 (week 8) after last treatment of RHA®4 was non-inferior to that of Control, the following hypotheses for the difference in means was tested:

H_0: d_{RHA4}-$d_{Control} \geq 0.5$
H_1: d_{RHA4}-$d_{Control} < 0.5$

If the upper bound of the two-sided 95% confidence interval (CI) of the difference of RHA®4 Minus Control was <0.5, then the non-inferiority was demonstrated (with 0.5 as the non-inferiority margin).

B. Accountability of PMA Cohort

At the time of database lock, a total of 257 subjects were screened. 56 subjects did not meet the inclusion/exclusion criteria resulting in 201 enrolled subjects. Out of these enrolled subjects:

- 201 subjects (100%) were assigned to the Safety Population
- 201 subjects (100%) to the ITT population
- 173 subjects (86.1%) to the PP population (21 subjects (13.8%) in RHA®4 group and 7 subjects (14.3%) in control group: 13 subjects missed visit 2 (to allow for touch-up) or visit 3 (primary endpoint); 12 subjects had deviation of effectiveness assessment impacting the primary endpoint; 8 subjects had their primary endpoint visit out-of-window, 2 subjects had a deviation related to the administration of the device and 1 subject was related to an exclusion criteria).

Table 5: Subject Accountability and Disposition

	RHA®4	Control
Screened	257	
Enrolled	201	
Safety population	152	49
ITT population	152	49
PP population	131	42
Number of subjects who completed the study	126 (82.9%)	43 (87.8%)
Number of subjects at primary endpoint visit (V3)	137 (90.1%)	45 (91.8%)
Number of subjects at V7	128 (84.2%)	44 (89.8%)
Number of subjects who received repeat treatment at V7	77 (50.7%)	29 (59.2%)
Number of subjects withdrawn from study	26 (17.1%)	6 (12.2%)
Reason for discontinuation		
A subject or legal representative withdrawal	18 (11.8%)	1 (2.0%)
Lost to follow-up	6 (3.9%)	3 (6.1%)
Sponsor decision	1 (0.7%)	1 (2.0%)
Other	1 (0.7%)	1 (2.0%)

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

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are 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®4 implant for midface volume deficiency. Subjects had a mean age of approximately 55 years, and most subjects were female (approximately 89.6% (180/201) of study subjects).
The majority of subjects were white (87.0% - 174/201), with 12.5% (25/201) of subjects identifying as Black or African American. 19.9% (40/201) 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 to VI, with approximately 71.1% (143/201) and 28.9% (58/201) of subjects had skin types I-III and IV-VI, respectively (and 14% (28/201) of subjects having skin types V/VI) (with 9.0% (18/201) of type V and 5.0% (10/201) of type VI).

Table 6: Demographic Characteristics at Baseline

Demographic Variable	RHA®4 *N=152*	Control *N=49*	Total *N=201*
Age (years)			
N (missing)	152 (0)	49 (0)	201 (0)
Mean ± SD	55.4 ± 9.97	55.6 ± 7.85	55.5 ± 9.48
Min, Max	24, 79	34, 68	24, 79
Gender			

Demographic Variable	RHA®4 *N=152*	Control *N=49*	Total *N=201*
N (missing)	152 (0)	49 (0)	201 (0)
Male	18 (11.8%)	3 (6.1%)	21 (10.4%)
Female	134 (88.2%)	46 (93.9%)	180 (89.6%)
Race[a]			
N (missing)	152 (0)	48 (1)	200 (1)
American Indian or Alaska Native	0 (0.0%)	1 (2.1%)	1 (0.5%)
Asian	3 (2.0%)	0 (0.0%)	3 (1.5%)
Black or African American	19 (12.5%)	6 (12.5%)	25 (12.5%)
White	132 (86.8%)	42 (87.5%)	174 (87.0%)
Ethnicity			
N (missing)	152 (0)	49 (0)	201 (0)
Hispanic or Latino	31 (20.4%)	9 (18.4%)	40 (19.9%)
Not-Hispanic or Latino	120 (78.9%)	39 (79.6%)	159 (79.1%)
Not available	1 (0.7%)	1 (2.0%)	2 (1.0%)
Fitzpatrick Skin Type			
N	152 (0)	49 (0)	201 (0)
I-III	**107 (70.4%)**	**36 (73.5%)**	**143 (71.1%)**
I	5 (3.3%)	0 (0.0%)	5 (2.5%)
II	40 (26.3%)	15 (30.6%)	55 (27.4%)
III	62 (40.8%)	21 (42.9%)	83 (41.3%)
IV-VI	**45 (29.6%)**	**13 (26.5%)**	**58 (28.9%)**
IV	23 (15.1%)	7 (14.3%)	30 (14.9%)
V	14 (9.2%)	4 (8.2%)	18 (9.0%)
VI	8 (5.3%)	2 (4.1%)	10 (5.0%)

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. A subject could be counted in several categories.

Extent of exposure

The number of treatment sessions is described in Table 7 below. All subjects who received retreatment were injected with RHA®4 only irrespective of their initial group assignment.

Table 7: Number of treatment session – Safety population

Treatment	RHA®4 (N=152)	Control (N=49)	Total (N=202)
Initial treatment	152 (100%)	49 (100%)	201 (100%)
Touch-up treatment	96 (63.2%)	41 (83.7%)	137 (68.2%)
Retreatment	77 (50.7%)	29 (59.2%)	106 (52.7%)
Number of subjects receiving 1 treatment (i.e., only initial treatment)	36 (23.7%)	4 (8.2%)	40 (19.9%)
Number of subjects receiving all 3 injections (initial, touch-up and retreatment)	57 (37.5%)	25 (51.0%)	82 (40.6%)

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

A smaller proportion of subjects (63.2%) in the RHA®4 group required a touch-up when compared to the subjects in the Control group (83.7%). Similarly, a smaller proportion of subjects received 3 injections (initial treatment, touch-up and retreatment) in the RHA®4 group than in the Control group (37.5% vs 51.0%).

The maximum volume allowed was 6.0 mL per injection session, with a maximum of 3.0 mL per cheek per session.
The average volume injected for initial treatment was similar between treatment groups with volumes of 2.87±1.13 mL and 2.50±0.98 mL in the RHA®4 and Control groups, respectively. Similar volumes were injected at initial treatment for left and right cheeks, in both treatment groups. Injection volumes used for touch-up treatment in both cheeks were similar in both treatment groups, with 1.33±0.38 mL and 1.21±0.69 mL in the RHA®4 and Control groups, respectively.
Volumes injected to achieve optimal cosmetic results were comparable in both treatment groups: a total volume of 3.70±1.56 mL and 3.51±1.37 mL was used in the RHA®4 and Control groups, respectively. Volume injected at retreatment (with RHA®4 only) at the end of the study was slightly higher in subjects initially assigned to receive the control device, with 2.10±0.81 mL compared to 1.74±0.98 mL in subjects initially assigned to receive RHA®4. No meaningful difference was observed between volumes injected in the left and right cheek.

The majority of treatments used the cannula only or combined with the needle at initial, touch-up and retreatment. Cannula only was more often used with RHA®4 than with the control: 53.9% (82/152) and 34.7% (17/49) at initial treatment respectively. A similar difference was also observed at touch-up treatment (RHA®4 only was used at retreatment). The rate of using only the needle was highest for touch-up treatment: 37.5% (36/152) and 41.5% (17/49) for RHA®4 and the control respectively as shown in Table 8. RHA®4 and the control were mainly injected using the multilayering technique (i.e. combination of subcutaneous and supraperiosteal depths of injection) at initial treatment: 75.0% (114/152) and 73.5% (36/459) respectively.

Table 8: Method of injection and injection depth – Safety population

Treatment	RHA®4 (N=152)	Control (N=49)	Total (N=202)
Initial treatment			
Needle only	19 (12.5%)	7 (14.3%)	26 (12.9%)
Cannula only	82 (53.9%)	17 (34.7%)	99 (49.3%)
Needle + Cannula	51 (33.6%)	25 (51.0%)	76 (37.8%)
Subcutaneous	32 (21.1%)	1 (2.0%)	33 (16.4%)
Supraperiosteal	6 (3.9%)	12 (24.5%)	18 (9.0%)
Both	114 (75.0%)	36 (73.5%)	150 (74.6%)
Touch-up treatment			
Needle only	36 (37.5%)	17 (41.5%)	53 (38.7%)
Cannula only	39 (40.6%)	10 (24.4%)	49 (35.8%)
Needle + Cannula	21 (21.9%)	14 (34.1%)	35 (25.5%)
Subcutaneous	15 (15.6%)	7 (17.1%)	22 (16.1%)
Supraperiosteal	19 (19.8%)	14 (34.1%)	33 (24.1%)
Both	62 (64.6%)	20 (48.8%)	82 (59.9%)
Retreatment			
Needle only	15 (19.5%)	8 (27.6%)	23 (21.7%)
Cannula only	48 (62.3%)	15 (51.7%)	63 (59.4%)
Needle + Cannula	14 (18.2%)	6 (20.7%)	20 (18.9%)

Treatment	RHA®4 (N=152)	Control (N=49)	Total (N=202)
Subcutaneous	28 (36.4%)	11 (37.9%)	39 (36.8%)
Supraperiosteal	14 (18.2%)	4 (13.8%)	18 (17.0%)
Both	35 (45.5%)	14 (48.3%)	49 (46.2%)

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the cohort of 201 subjects available for up to 52 weeks evaluation after initial or touch-up treatment. The common treatment responses for this study are presented below in Table 9 to Table 11. Adverse device effects are reported in Table 12 to Table 16.

Safety of the RHA®4 implant when injected into the midface 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.

Common Treatment Responses after initial treatment

CTR data for initial treatment are presented in Table 9. CTRs for touch-up and repeat treatment were of the same proportions.

Out of 201 subjects, 187 subjects returned their diaries, with 141/152 in the RHA®4 group and 46/49 in the control group. Out of those subjects, 92.0% (172/187) experienced at least 1 CTR: 90.8% (128/141) of subjects in the RHA®4 group and 95.7% (44/46) of subjects in the control group (each subject may have reported more than 1 CTR).

After initial treatment, CTRs incidence rate was similar between treatment groups. The most common CTRs were tenderness (experienced by 81.3% (152/187) of subjects overall), firmness (75.9% (142/187) of subjects overall), swelling (67.4% (126/187) of subjects overall), and lumps/bumps (53.5% (100/187) of subjects overall).

For the RHA®4 group, within the diaries having at least 1 CTR, 94.5% (121/128) of the diaries contained only CTRs of mild or moderate severity, while 5.5% (7/128) of the diaries contained at least 1 CTR of severe severity. This proportion was similar in both treatment groups: 5.5% (7/128) in RHA®4 group and 6.8% (3/44) in the control group.

The most frequent severe CTR reported was firmness (4 in RHA®4 and 2 in control group) and lumps/bumps (4 in RHA®4 and 1 in control group). Those are consistent and anticipated from previous similar studies following an injection into the cheeks.

The duration of CTR incidence was similar between study groups. In the RHA®4 group, 59.6% (84/128) of subjects experienced a CTR up to 7 days and 29.1% (41/128) up to 30 days. In the

control group, 54.3% (25/44) of subjects experienced a CTR up to 7 days and 30.4% (14/44) up to 30 days.
By the end of the diary, nearly all CTRs had resolved. On the last day of the diary, 12.8% (18/128) of subjects in the RHA®4 group were experiencing a CTR with 8.7% (4/44) of subjects in the control group. The most frequent CTRs were lumps/bumps and firmness.

Table 9: CTRs incidence rate – initial treatment – Safety population

CTR	RHA®4	Control	Total
Number of subjects	152	49	201
Number of CTR diaries returned	141	46	187
≥1 CTR	128 (90.8%)	44 (95.7%)	172 (92.0%)
Redness	61 (43.3%)	17 (37.0%)	78 (41.7%)
Pain	70 (49.6%)	20 (43.5%)	90 (48.1%)
Tenderness	113 (80.1%)	39 (84.8%)	152 (81.3%)
Firmness	108 (76.6%)	34 (73.9%)	142 (75.9%)
Swelling	98 (69.5%)	28 (60.9%)	126 (67.4%)
Lumps/Bumps	77 (54.6%)	23 (50.0%)	100 (53.5%)
Bruising	74 (52.5%)	16 (34.8%)	90 (48.1%)
Itching	17 (12.1%)	2 (4.3%)	19 (10.2%)
Discoloration	32 (22.7%)	6 (13.0%)	38 (20.3%)

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

Table 10: CTRs by maximum severity – initial treatment – Safety population

CTR	Severity	RHA®4	Control	Total
Number of subjects		152	49	201
Number of CTR diaries returned		141	46	187
≥1 CTR		128 (90.8%)	44 (95.7%)	172 (92.0%)
At least 1 CTR	Mild	69 (53.9%)	26 (59.1%)	95 (55.2%)
	Moderate	52 (40.6%)	15 (34.1%)	67 (39.0%)
	Severe	7 (5.5%)	3 (6.8%)	10 (5.8%)
Redness	Mild	51 (83.6%)	13 (76.5%)	64 (82.1%)
	Moderate	10 (16.4%)	3 (17.6%)	13 (16.7%)
	Severe	0	1 (5.9%)	1 (1.3%)
Pain	Mild	55 (78.6%)	18 (90.0%)	73 (81.1%)
	Moderate	15 (21.4%)	2 (10.0%)	17 (18.9%)
	Severe	0	0	0
Tenderness	Mild	86 (76.1%)	33 (84.6%)	119 (78.3%)
	Moderate	26 (23.0%)	5 (12.8%)	31 (20.4%)
	Severe	1 (0.9%)	1 (2.6%)	2 (1.3%)

CTR	Severity	RHA®4	Control	Total
Firmness	Mild	72 (66.7%)	21 (61.8%)	93 (65.5%)
	Moderate	32 (29.6%)	11 (32.4%)	43 (30.3%)
	Severe	4 (3.7%)	2 (5.9%)	6 (4.2%)
Swelling	Mild	68 (69.4%)	24 (85.7%)	92 (73.0%)
	Moderate	29 (29.6%)	4 (14.3%)	33 (26.2%)
	Severe	1 (1.0%)	0	1 (0.8%)
Lumps/Bumps	Mild	43 (55.8%)	14 (60.9%)	57 (57.0%)
	Moderate	30 (39.0%)	8 (34.8%)	38 (38.0%)
	Severe	4 (5.2%)	1 (4.3%)	5 (5.0%)
Bruising	Mild	55 (74.3%)	15 (93.8%)	70 (77.8%)
	Moderate	17 (23.0%)	1 (6.3%)	18 (20.0%)
	Severe	2 (2.7%)	0	2 (2.2%)
Itching	Mild	15 (88.2%)	2 (100%)	17 (89.5%)
	Moderate	2 (11.8%)	0	2 (10.5%)
	Severe	0	0	0
Discoloration	Mild	24 (75.0%)	6 (100%)	30 (78.9%)
	Moderate	8 (25.0%)	0	8 (21.1%)
	Severe	0	0	0

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 11: CTRs by total duration – initial treatment – 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	RHA4	128 (90.8%)	104 (73.8%)	84 (59.6%)	55 (39.0%)	41 (29.1%)	18 (12.8%)
	Control	44 (95.7%)	33 (71.7%)	25 (54.3%)	20 (43.5%)	14 (30.4%)	4 (8.7%)
	Total	172 (92.0%)	137 (73.3%)	109 (58.3%)	75 (40.1%)	55 (29.4%)	22 (11.8%)
Redness	RHA4	61 (43.3%)	41 (29.1%)	11 (7.8%)	4 (2.8%)	5 (3.5%)	2 (1.4%)
	Control	17 (37.0%)	11 (23.9%)	5 (10.9%)	0	1 (2.2%)	0
	Total	78 (41.7%)	52 (27.8%)	16 (8.6%)	4 (2.1%)	6 (3.2%)	2 (1.1%)
Pain	RHA4	70 (49.6%)	39 (27.7%)	17 (12.1%)	8 (5.7%)	6 (4.3%)	1 (0.7%)
	Control	20 (43.5%)	9 (19.6%)	5 (10.9%)	5 (10.9%)	1 (2.2%)	0
	Total	90 (48.1%)	48 (25.7%)	22 (11.8%)	13 (7.0%)	7 (3.7%)	1 (0.5%)
Tenderness	RHA4	113 (80.1%)	34 (24.1%)	39 (27.7%)	24 (17.0%)	16 (11.3%)	2 (1.4%)
	Control	39 (84.8%)	10 (21.7%)	15 (32.6%)	9 (19.6%)	5 (10.9%)	1 (2.2%)
	Total	152 (81.3%)	44 (23.5%)	54 (28.9%)	33 (17.6%)	21 (11.2%)	3 (1.6%)

Total Duration (days)							
CTR after initial injection	**Group**	**Subjects Experiencing the CTR**	**1-3**	**4-7**	**8-14**	**15-30**	**Last Day Diary**
Firmness	RHA4	108 (76.6%)	34 (24.1%)	35 (24.8%)	19 (13.5%)	20 (14.2%)	6 (4.3%)
	Control	34 (73.9%)	10 (21.7%)	9 (19.6%)	5 (10.9%)	10 (21.7%)	2 (4.3%)
	Total	142 (75.9%)	44 (23.5%)	44 (23.5%)	24 (12.8%)	30 (16.0%)	8 (4.3%)
Swelling	RHA4	98 (69.5%)	47 (33.3%)	32 (22.7%)	13 (9.2%)	6 (4.3%)	1 (0.7%)
	Control	28 (60.9%)	16 (34.8%)	8 (17.4%)	1 (2.2%)	3 (6.5%)	0
	Total	126 (67.4%)	63 (33.7%)	40 (21.4%)	14 (7.5%)	9 (4.8%)	1 (0.5%)
Lumps/	RHA4	77 (54.6%)	30 (21.3%)	13 (9.2%)	12 (8.5%)	22 (15.6%)	15 (10.6%)
Bumps	Control	23 (50.0%)	7 (15.2%)	5 (10.9%)	4 (8.7%)	7 (15.2%)	1 (2.2%)
	Total	100 (53.5%)	37 (19.8%)	18 (9.6%)	16 (8.6%)	29 (15.5%)	16 (8.6%)
Bruising	RHA4	74 (52.5%)	19 (13.5%)	28 (19.9%)	17 (12.1%)	10 (7.1%)	3 (2.1%)
	Control	16 (34.8%)	5 (10.9%)	6 (13.0%)	5 (10.9%)	0	0
	Total	90 (48.1%)	24 (12.8%)	34 (18.2%)	22 (11.8%)	10 (5.3%)	3 (1.6%)
Itching	RHA4	17 (12.1%)	7 (5.0%)	3 (2.1%)	5 (3.5%)	2 (1.4%)	1 (0.7%)
	Control	2 (4.3%)	2 (4.3%)	0	0	0	0
	Total	19 (10.2%)	9 (4.8%)	3 (1.6%)	5 (2.7%)	2 (1.1%)	1 (0.5%)
Discoloration	RHA4	32 (22.7%)	17 (12.1%)	5 (3.5%)	6 (4.3%)	4 (2.8%)	4 (2.8%)
	Control	6 (13.0%)	3 (6.5%)	3 (6.5%)	0	0	0
	Total	38 (20.3%)	20 (10.7%)	8 (4.3%)	6 (3.2%)	4 (2.1%)	4 (2.1%)

Abbreviation: CTR = Common Treatment Response.
All percentages are based on the number of CTR diaries returned by injection by subgroup in the population.
152 subjects were treated with initial injection in RHA®4 group and 141 CTR diaries were returned. 49 subjects were treated with initial injection in Control group and 46 CTR diaries were returned.
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 proportion of diaries having at least 1 CTR were similar after touch-up: 79.8% (75/94) in RHA®4 group against 77.5% (31/40) in the control group. Similarly to initial treatment, 98.8% (83/84) of the diaries contained only CTRs of mild or moderate severity for the RHA®4 group against 90.3% (28/31) in the control group.

CTRs were stratified by Fitzpatrick Skin Type (FST). All FST were appropriately represented with 71% and 29% of subjects with FST I-III and IV-VI, respectively. In the RHA®4 group, 96.0% (97/101) and 77.5% (31/40) of subjects with FST I-III and FST IV-VI, respectively experienced at least 1 CTR. In the control group, 100% (33/33) and 76.9% (10/13) of subjects with FST I-III and FST IV-VI, respectively experienced at least 1 CTR. Tenderness and firmness were the most common CTRs in both FST subgroups in the RHA®4 and control groups.

At initial injection, the incidence rate of CTRs was also stratified by volume. 65.8% (100/152) of subjects in RHA®4 group and 83.7% (41/49) in the control group received ≤3 mL. 34.2% (52/152) of subjects in RHA®4 group and 16.3% (8/49) in the control group received >3 mL. Based on the

number of returned diaries, 85.9% (79/92) of subjects in RHA®4 who received ≤3 mL experienced at least 1 CTR against 100% (49/49) for those who received >3 mL. In the control group, 94.7% (36/38) of subjects experienced at least 1 CTR if they received ≤3 mL and 100% (8/8) if they received >3 mL.

When injecting using the multilayering technique (i.e. injection at both depths: subcutaneous and supraperiosteal), the incidence rate of subjects experiencing at least 1 CTR was 94.3% (99/105) in RHA®4 group and 100% (33/33) in the control group. When compared to injections performed at a unique depth (subcutaneous only or supraperiosteal only), no conclusion could be made on the impact of injection depth on CTR occurrence.

After initial injection, in the RHA®4 group, 100% (19/19) of subjects reported a CTR if the administration used needle only, 82.2% (60/73) reported a CTR after cannula injection only, and 100% (49/49) reported a CTR after needle + cannula injection. Rates were similar in the control group with, 100% (7/7) of subjects reported a CTR if the administration used needle only, 93.8% (16/17) reported a CTR after cannula injection only, and 95.7% (23/25) reported a CTR after needle + cannula injection. Overall, the cannula only administration of RHA®4 had the lowest incidence of CTRs out of all administration methods and groups for all 3 injections; initial injection (82.2%, 60/73), touch-up (60.5%, 23/38) and retreatment (74.6%, 47/63).

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.

Adverse Device Effects that occurred in the PMA clinical study

All Adverse Device Effects (Table 12) were the types and frequency of adverse events that are typically experienced following the injection of a dermal filler into the cheeks.
From Visit 1 to Visit 7 (i.e., not including retreatment injections), 84 ADEs were reported (Table 12):

- 23.7% (36/152) subjects (67 events) in the RHA®4 group
- 16.3% (8/49) subjects (17 events) in the control group

Overall, most ADEs were obtained from the diary. In the RHA®4 group (from V1 to V7):

- 62.7% (42/67) of the ADEs were CTRs automatically elevated to AEs because they were present on the last day of the diary.
- 16.4% (11/67) of the ADEs were automatically elevated to AEs because they were reported as "Other" in the diary.
- 12.0% (8/67) of the ADEs were reported from a pre-identified list of AEs in the subject diary but were not a CTR. Out of these 8 ADEs, none were related to visual disturbances.

- 9.0% (6/67) of the ADEs were identified by the TI during a visit.

Table 12: Adverse Events profile overview (initial, touch-up) Visit 1 to Visit 7 – Safety population

From V1 to V7	RHA®4 (N=152)		Control (N=49)		Total (N=201)	
	Number of events	Number of subjects (%)	Number of events	Number of subjects (%)	Number of events	Number of subjects (%)
Overall						
Number of subjects		152		49		201
All AEs	136	68 (44.7%)	43	19 (38.8%)	179	87 (43.3%)
AESIs	10	5 (3.3%)	0	0	10	5 (2.5%)
ADEs	67	36 (23.7%)	17	8 (16.3%)	84	44 (21.9%)
UADEs	0	0	0	0	0	0
Serious AEs	1	1 (0.7%)	2	2 (4.1%)	3	3 (1.5%)
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 as serious.

The type of ADEs were also comparable between RHA®4 and the control groups as shown by Table 13.

Similar safety profiles were observed between treatment groups: a total of 23.7% (36/152) and 16.3% (8/49) subjects in RHA®4 and control groups respectively, experienced at least 1 ADE between Visit 1 and Visit 7.

The most common events were:

- Injection site mass, experienced in 11.2% (17/152) and 6.1% (3/49) subjects in the RHA®4 and control groups, respectively.
- Injection site induration, experienced in 5.3% (8/152) and 10.2% (5/49) subjects in the RHA®4 and control groups, respectively.
- Injection site pain, experienced in 3.3% (5/152) and 2.0% (2/49) subjects in the RHA®4 and control groups, respectively.

There were no noticeable differences of the frequencies of ADEs between the RHA®4 and control groups.

Table 13: ADEs sorted by SOC and PT (Visit 1 to Visit 7 – initial treatment to 52 weeks follow-up excluding retreatment) – Safety population

From V1 to V7	RHA®4 (N=152)		Control (N=49)		Total (N=201)	
SOC PT	Number of events	Number of subjects	Number of events	Number of subjects	Number of events	Number of subjects
Any ADE	**67**	**36 (23.7%)**	**17**	**8 (16.3%)**	**84**	**44 (21.9%)**
General Disorders and Admin. Site Conditions	**55**	**32 (21.1%)**	**13**	**7 (14.3%)**	**68**	**39 (19.4%)**
Injection Site Mass	18	17 (11.2%)	4	3 (6.1%)	22	20 (10.0%)
Injection Site Induration	8	8 (5.3%)	5	5 (10.2%)	13	13 (6.5%)
Injection Site Pain	6	5 (3.3%)	1	1 (2.0%)	7	6 (3.0%)
Injection Site Discoloration	5	5 (3.3%)	0	0	5	5 (2.5%)
Injection Site Bruising	3	3 (2.0%)	0	0	3	3 (1.5%)
Injection Site Swelling	2	2 (1.3%)	1	1 (2.0%)	3	3 (1.5%)
Injection Site Warmth	2	2 (1.3%)	1	1 (2.0%)	3	3 (1.5%)
Injection Site Hypoaesthesia	1	1 (0.7%)	1	1 (2.0%)	2	2 (1.0%)
Mass	2	2 (1.3%)	0	0	2	2 (1.0%)
Administration Site Acne	1	1 (0.7%)	0	0	1	1 (0.5%)
Injection Site Deformation	3	1 (0.7%)	0	0	3	1 (0.5%)
Injection Site Discomfort	1	1 (0.7%)	0	0	1	1 (0.5%)
Injection Site Erythema	1	1 (0.7%)	0	0	1	1 (0.5%)
Injection Site Pruritus	1	1 (0.7%)	0	0	1	1 (0.5%)
Swelling Face	1	1 (0.7%)	0	0	1	1 (0.5%)
Injection Site Discolouration	1	1 (0.7%)	0	0	1	1 (0.5 %)
Injection Site Haematoma	1	1 (0.7%)	0	0	1	1 (0.5 %)
Injection Site Vesicles	0	0	2	1 (2.0 %)	2	1 (0.5 %)
Mass	1	1 (0.7%)	0	0	1	1 (0.5 %)
Swelling Face	0	0	1	1 (2.0 %)	1	1 (0.5 %)
Nervous System Disorders	**6**	**5 (3.3%)**	**2**	**2 (4.1%)**	**8**	**7 (3.5%)**
Headache	6	5 (3.3%)	2	2 (4.1%)	8	7 (3.5%)
Eye Disorders	**4**	**2 (1.3%)**	**0**	**0**	**4**	**2 (1.0%)**
Periorbital pain	2	2 (1.3%)	0	0	2	2 (1.0%)
Eye pain	1	1 (0.7%)	0	0	1	1 (0.5%)
Ocular Hyperaemia	1	1 (0.7%)	0	0	1	1 (0.5%)
Skin and Subcutaneous Tissue Disorders	**2**	**2 (1.3%)**	**0**	**0**	**2**	**2 (1.0%)**
Pruritus	1	1 (0.7%)	0	0	1	1 (0.5%)
Urticaria	1	1 (0.7%)	0	0	1	1 (0.5%)
Musculoskeletal And Connective Tissue Disorders	**0**	**0**	**2**	**1 (2.0%)**	**2**	**1 (0.5%)**
Masticatory pain	0	0	2	1 (2.0%)	2	1 (0.5%)

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 82.0% (55/67) of ADEs in the RHA®4 group were mild and the remaining were moderate 17.9% (12/67) (Table 14). In the control group, the severity was similar: 76.5% (13/17) were mild and 23.5% (4/17) were moderate. There were no severe ADEs reported in both treatment groups.

Of the 67 ADEs reported between Visit 1 and Visit 7 for the RHA®4 group (after initial and touch-up treatment), 46.3% (31/67) ADEs lasted 1 to 3 days, 82.1% (55/67) ADEs were resolved within 14 days. There was 1 event of injection site mass in the RHA®4 group which lasted more than 90 days. It was mild in severity and resolved without treatment and sequelae. Overall, most ADEs resolved within 30 days and the proportion of subjects with reported ADEs was similar across the 2 treatment groups.

After retreatment, most ADEs also resolved within 30 days. They were all resolved in less than 90 and all ADEs resolved at the time of study exit.

Table 14: ADEs sorted by severity (Visit 1 to Visit 7 – initial treatment to 52 weeks follow-up excluding retreatment) – Safety population

From V1 to V7	RHA®4 (N=152)		Control (N=49)		Total (N=201)	
Severity	Number of events	Number of subjects	Number of events	Number of subjects	Number of events	Number of subjects
Any ADE	**67**	**36 (23.7%)**	**17**	**8 (16.3%)**	**84**	**44 (21.9%)**
Mild	55	32 (21.1%)	13	8 (16.3%)	68	40 (19.9%)
Moderate	12	9 (5.9%)	4	3 (6.1%)	16	12 (6.0%)
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 15: ADEs sorted by duration (Visit 1 to Visit 7 – initial treatment to 52 weeks follow-up excluding retreatment) – Safety population

From Visit 1 to Visit 7			RHA®4 (N= 152)		Control (N= 49)		Total (N= 201)	
	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			**67**	**36 (23.7%)**	**17**	**8 (16.3%)**	**84**	**44 (21.9%)**
		1-3	31	19 (12.5%)	6	4 (8.2%)	37	23 (11.4%)
		4-7	10	9 (5.9%)	3	3 (6.1%)	13	12 (6.0%)
		8-14	14	7 (4.6%)	3	2 (4.1%)	17	9 (4.5%)
		15 - 30	7	6 (3.9%)	4	3 (6.1%)	11	9 (4.5%)
		31 - 90	4	4 (2.6%)	1	1 (2.0%)	5	5 (2.5%)
		>90	1	1 (0.7%)	0	0	1	1 (0.5%)
	N (missing)		67 (0)		17 (0)		84 (0)	
	Mean (SD)		12.4 (28.76)		9.5 (9.06)		11.8 (25.98)	

From Visit 1 to Visit 7			RHA®4 (N= 152)		Control (N= 49)		Total (N= 201)	
	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
	95% CI Mean		5.3-19.4		4.9-14.2		6.1-17.4	
	Min to Max		1 to 227		1 to 36		1 to 227	

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 the category 31 - 90 days.

All Fitzpatrick Skin Types (FST) were appropriately represented, with 71.1% (143/201) and 28.9% (58/201) of subjects being of skin types I-III and types IV-VI, respectively. Proportion of subjects being FST I-III vs IV-VI were similar within treatment groups:

- FST I-III: 70.4% (107/152) and 73.5% (36/49) of subjects in the RHA®4 and control groups, respectively
- FST IV-VI: 29.6% (45/152) and 26.5% (13/49) of subjects in the RHA®4 and control groups, respectively

In RHA®4 treatment group, 22.4% (24/107) and 26.7% (12/45) subjects with FST I-III and with FST IV-VI, respectively, experienced at least 1 ADE. In the control group, 11.1% (4/36) and 30.8% (4/13) subjects with FST I-III and with FST IV-VI, respectively, experienced at least 1 ADE. There were no observed differences in rates of ADEs across FST groups. The ADEs profiles were similar. RHA®4 and control treatment groups present a similar profile. Similar results were found following retreatment.

Table 16: ADE profile overview by Fitzpatrick Skin Type (Visit 1 to Visit 7 – initial treatment to 52 weeks follow-up excluding retreatment) – Safety population

FST	From V1 to V7	RHA®4 (N= 152)		Control (N= 49)		Total (N= 201)	
		Number of events	Number of subjects	Number of events	Number of subjects	Number of events	Number of subjects
I-III	Number of subjects		107		36		143
	Any ADE	45	24 (22.4%)	7	4 (11.1%)	52	28 (19.6%)
IV-VI	Number of subjects		45		13		58
	Any ADE	22	12 (26.7%)	10	4 (30.8%)	32	16 (27.6%)
	p-value		**0.6764**				

Abbreviations: ADE = adverse device effect. N = number of subjects; SAFT = safety (population)
Notes: Number (%) of subjects with at least 1 ADE in the subgroup. All percentages were based on the number of subjects by subgroup in the population. P-values were based on a Fisher exact test, 2-sided at 5% to test independence or not of the subgroup. Only subgroups with at least 10 subjects from the RHA®4 initial treatment group were analyzed.

All ethnicities were appropriately represented, with 19.9% (40/201) and 79.1% (159/201) of subjects being Hispanic and Non-Hispanic or Latino, respectively. There were no observed differences in rates of ADEs across ethnicity groups. RHA®4 and control treatment groups present a similar profile. Similar results were found following retreatment.

Sex was appropriately represented, with 10.4% (21/201) and 89.6% (180/201) of male and female subjects, respectively. There were no observed differences in rates of ADEs across sex. Similar results were found following retreatment.

The median age was 56 years old with 52.2% (105/201) of subjects aged 22 to 56 years old and 47.8% (96/201) of subjects older than 56 years old. In the RHA®4 group, 19.8% (16/81) of subjects 56 years old or younger experienced an ADE against 28.2% (20/71) of subjects older than 56 years old. Subjects in the control group had a similar incidence rate of ADEs as subjects of the same age in the RHA®4 group. Similar results were found following retreatment.

The number of subjects who experienced ADEs analyzed by subgroup of volume were divided into: ≤3 mL (141 subjects) and/or with >3 to ≤6 mL (115 subjects) and >6 mL (18 subjects). A subject may be counted more than once because a subject may be reported after experiencing an ADE following initial treatment and then again after touch-up (in another bracket of volume).
Most subjects were injected with ≤3 mL (141 subjects) and/or with >3 to ≤6 mL (115 subjects). The incidence of ADEs between study groups was similar for subjects injected with these 2 volume ranges. Incidence rates for subjects injected with: ≤3 mL were 36 events in 20/100 subjects (20.0%) in RHA®4 group and 12 events in 7/41 subjects (17.1%) in control group; >3 to ≤6 mL were 29 events in 17/90 subjects (18.9%) in RHA®4 group and 5 events in 3/25 subjects (12.0%) in control group. Only 18 subjects received >6 mL to ≤9 mL and only 1 of them (in the RHA®4 group) developed an ADE, however only 3 subjects in the control group received this volume.

Similarly, the depth of injection may be different after initial treatment and touch-up and a subject may experience an ADE after both and be counted twice in different injection depth sub-groups. The analyses with relatively small and disproportionate number of subjects treated per depth of injection (subcutaneous only and supraperiosteal only) does not allow any meaningful conclusions regarding the incidence rate of ADEs per injection depths. However, for subjects injected with the multilayering technique (both subcutaneously and supraperiosteally), the incidence of ADEs was similar between treatment groups, with 33 (27.0%, 33/122) subjects in the RHA®4 group and 7 (17.5%, 7/40) subjects in the Control group.

Subjects were injected using several administration methods: needle only, cannula only or both. The administration method may have been different between initial and touch-up treatments. Because of the high number of combinations of administration methods, the analysis of the ADEs incidence rate by method of administration was no conclusive.
Similarly, 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.

Adverse Events of Special Interests (AESI)
Eleven events of visual disturbances (vision blurred, headache, blepharospasm, photopsia, periorbital pain, ocular hyperemia, eye pain, periorbital pain, blurred vision, pain around the eyes, intermittent floaters in the eye) in five subjects were reported as Adverse Events of Special Interests (AESI). All were in subjects randomly assigned to RHA®4 group including one event after retreatment. All events were mild. None were related to device. Four events from two subjects were related to the injection procedure. None of the subjects required treatment or outside interventions, except for one subject who experienced blurred vision which was mild and unlikely related to the study device or procedure, who used lubricating eye daily drops for 3 days. All events resolved without sequalae or the TI considered that no additional follow-up was necessary.

There were no Serious Adverse Events (SAE) that were device related and no Unanticipated Adverse Device Effects (UADE). There were no deaths, and no subjects prematurely withdrew due to an ADE.

Pain at injection
Injection pain during injection (initial, touch-up 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 study device injections was similar between treatment groups, with 7.2 ± 17.32 and 5.5 ± 14.96 in the RHA®4 and the Control groups, respectively. Injection site pain was reduced to 2.6 ± 9.01 mm and 1.9 ± 7.40 mm in the RHA®4 and the Control groups, respectively by 5 minutes post-injection. Pain after 15 minutes was 1.3 ± 5.33 and 0.4 ± 2.86 in the RHA®4 and the Control groups, respectively. Pain after 30 minutes was 1.1 ± 5.87 and 0.0 ± 0.00 in the RHA®4 and the Control groups, respectively.

Similar findings were observed following touch-up and retreatment injections.

2. Effectiveness Results

The analysis of effectiveness was based on the per-protocol (PP) population of 131 subjects who received treatment with RHA®4 and 42 who received treatment with the control. A supportive analysis was also performed in the intent-to-treat (ITT) population of 152 subjects who received treatment with RHA®4 and 49 subjects who received treatment with the control.

The primary effectiveness endpoint was to assess the effectiveness (non-inferiority) of RHA®4 versus the control on adding volume in the midface region 8 weeks after the last treatment (initial or touch-up). For the primary endpoint, the change from Baseline for subjects treated with RHA®4 had to be statistically non-inferior to the change from Baseline for subjects treated with the control at 8 weeks after the last treatment as assessed by the Blinded Live Evaluator (BLE) using the TMVDS. The difference in the TMVDS change from Baseline to 8 weeks was used to establish non-inferiority.

As shown in Table 17, subjects treated with RHA®4 had a mean TMVDS change at week 8 from Baseline of -1.3, and subjects treated with Control had a similar TMVDS change of -1.3.

Table 17: TMVDS Grade Change from Baseline at primary endpoint (week 8)

Category (PP Population)	**RHA®4 (N=131)**	**Control (N=42)**
TMVDS change from Baseline at Visit 3		
N	131	42
Mean (SD)	-1.3 (0.80)	-1.3 (0.65)
95% CI Mean	-1.5 - -1.2	-1.5 - -1.1
Min to Max	-3 to 1	-2 to 0
Bootstrap method		
Estimate of difference in means RHA4 – Control	0.02	
95% CI for difference in means	-0.22 – 0.25	
Category (ITT Population*)	**RHA®4 (N=152)**	**Control (N=49)**
TMVDS change from Baseline at Visit 3		
N	152	49
Mean (SD)	-1.3 (0.75)	-1.3 (0.61)
95% CI Mean	-1.4 - -1.2	-1.5- -1.1
Min to Max	-3.0 - -1.0	-2.0- -1.0
Bootstrap method		
Estimate of difference in means RHA4 – Control	0.01	
95% CI for difference in means	-0.20-0.22	

Abbreviations: ANCOVA = analysis of covariance; BLE = blinded live evaluator; CI = confidence interval; n = number of observations; N = number of subjects; PP = per population; SD = standard deviation; TMVDS = Teoxane Midface Volume Deficit Scale

Baseline is defined as the last non missing measurement preceding the initial treatment.

Difference in means was calculated by Bootstrap estimate using 1,000 samples. 95% CI was based on the percentile interval. A non-parametric model was used as all assumptions needed to use an ANCOVA model were not met.

*In the ITT population, missing values were imputed using mean imputation before bootstrapping. 19 subjects (15 RHA4, 4 Control) were missing primary endpoint data in the ITT population.

When repeated with the ITT population, the TMVDS change from Baseline assessed by BLE at 8 weeks was similar to that of PP population in RHA®4 and Control groups, respectively, with -1.3 in both treatment groups.

Table 18 presents the TMVDS responder rate as assessed by BLE at week 8. In RHA®4 group, 114 (87.0%) subjects were considered as responders at week 8, whereas 38 (90.5%) subjects responded to Control treatment. The co-primary endpoint would support non-inferiority if the Control device responder rate was ≥70%. The threshold was chosen at ≥70% to make sure the Control device was an effective comparator, to determine the good effectiveness of the tested device (i.e., RHA®4). This assures that RHA®4 would be non-inferior to an effective control device at 8 weeks after last treatment. More than 90% of subjects treated with the Control device were responders, the co-primary was therefore met.

Table 18: Responder rate (BLE) at primary endpoint (Week 8) – PP population

Responders	RHA®4 (N=131)	Control (N=42)
N	131	42
Responder[a] [95% CI]	114 (87.0%) [80.2 – 91.7%]	38 (90.5%) [77.9 – 96.2%]
Not Responder	17 (13.0%)	4 (9.5%)
Difference in responder rate (RHA4 – Control) [95% CI]	-3.5% [-12.4 – 9.9%]	

Abbreviations: BLE = blinded live evaluator; CI = confidence interval; PP = per population; N = number of subjects; TMVDS = Teoxane Midface Volume Deficit Scale

Baseline was defined as the last non-missing measurement preceding the initial treatment. To successfully achieve the co-primary endpoint, the proportion of responders with a ≥1 grade point on the TMVDS at Visit 3 when compared to pretreatment for the control device should be ≥70%. The 95% CI for responder and for difference in responder rate were obtained using Wilson method.

All percentages are based upon the total number of subjects by group with non-missing data for the TMVDS at Week 8 (Visit 3).

a: Responder: Improvement from Baseline of ≥1 grade TMVDS

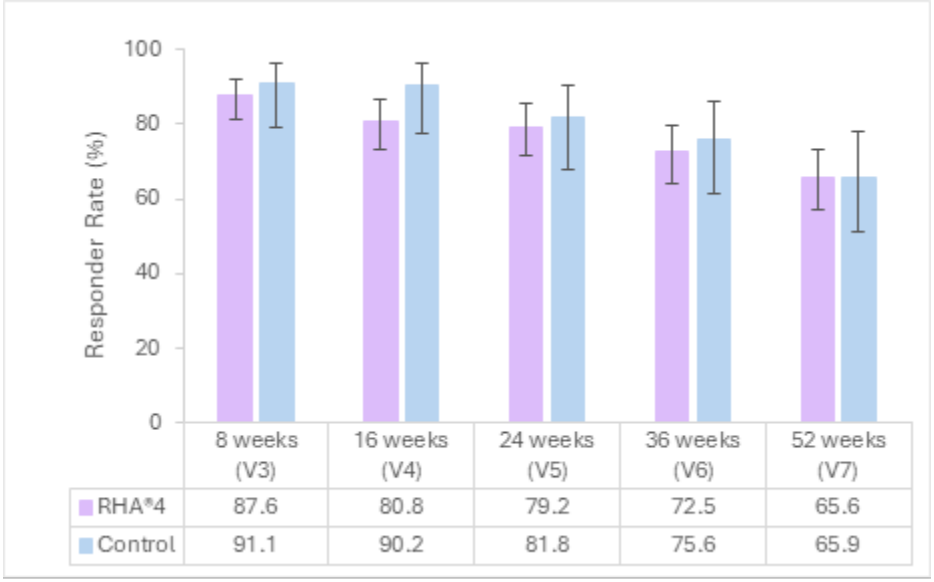
When repeated with the ITT population, the responder rate of the Control was ≥70% at 8 weeks after last treatment confirming the criteria of the co-primary endpoint.

At 8 weeks after last treatment, as the upper bound of the confidence intervals of the TMVDS of the Change from Baseline of RHA®4 was < 0.5 and the lower bound of the responder rate of the Control was ≥70% (PP and ITT), treatment with RHA®4 is non-inferior to treatment with Control.

RHA®4 demonstrated non-inferiority to the Control device based on TMVDS change from Baseline at 8 weeks after last treatment in both the PP and ITT analysis populations.

All secondary endpoints were performed using ITT population as observed (no imputation).

Figure 1: TMVDS rate of responders (≥1-grade difference from Baseline), as assessed by the Blinded Live Evaluator, thought the follow-up period – Observed ITT population



Descriptive only – The 95% confidence intervals presented have not been adjusted for multiple comparisons.

The responder rate of RHA®4 was similar to the responder rate of the Control throughout the course of the study (52 weeks after last treatment). Overall, we observed an expected decrease in the change from Baseline in TMVDS over time on both treatment groups. Results showed that subjects injected with RHA®4 were able to sustain volume augmentation over time, as the volumizing effect was still visible in approximately 65% of subjects at 1-year post treatment. To achieve this effect, 75% (114/152) of subjects were injected (Table 8) with the multilayering technique (subcutaneous and supraperiosteal layers) for their initial treatment, and 64.6% (62/96) for their touch-up treatment.

The analysis grade (Table 19) change from Baseline showed that 5.8% and 0% of subjects in RHA®4 and Control groups respectively had their midface volume deficit decrease by 3 grades (Grade 3 to Grade 0).

Table 19: Shift table of TMVDS Grade Change from Baseline (BLE) at 8 weeks – Observed ITT population

Treatment	Grade at Baseline	Grade at Post-Baseline					
		Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
RHA4	Grade 0	0	0	0	0	0	0
	Grade 1	0	0	0	0	0	0
	Grade 2	10 (7.3%)	32 (23.4%)	8 (5.8%)	1 (0.7%)	0	51 (37.2%)
	Grade 3	8 (5.8%)	35 (25.5%)	35 (25.5%)	8 (5.8%)	0	86 (62.8%)
	Grade 4	0	0	0	0	0	0
	Total	18 (13.1%)	67 (48.9%)	43 (31.4%)	9 (6.6%)	0	137 (100%)
Control	Grade 0	0	0	0	0	0	0
	Grade 1	0	0	0	0	0	0

Treatment	Grade at Baseline	Grade at Post-Baseline					
		Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
	Grade 2	3 (6.7%)	10 (22.2%)	3 (6.7%)	0	0	16 (35.6%)
	Grade 3	0	15 (33.3%)	13 (28.9%)	1 (2.2%)	0	29 (64.4%)
	Grade 4	0	0	0	0	0	0
	Total	3 (6.7%)	25 (55.6%)	16 (35.6%)	1 (2.2%)	0	45 (100%)

The GAI score assessed after RHA®4 injection into the midface (Table 20) were reported as improved or much improved for at least 94% of subjects as assessed by the BLE, 100% of subjects as assessed by the TI and 95% of the subjects as assessed by the subjects at 8 weeks after Baseline. The GAI score remained high at, at least 75% when assessed by the BLE, 86% when assessed by the TI and 81% when assessed by the subject 52 weeks after Baseline.

Table 20: GAIS as assessed by BLE, TI and subject – Observed ITT population

		RHA®4 (N=152)	Control (N=49)
GAI (BLE)			
V3 (W8)	N	137	45
	GAIS responder	129 (94.2%)	44 (97.8%)
V7 (W52)	N	128	44
	GAIS responder	97 (75.8%)	30 (68.2%)
GAI (TI)			
V3 (W8)	N	137	45
	GAIS responder	137 (100%)	45 (100%)
V7 (W52)	N	128	44
	GAIS responder	111 (86.7%)	37 (84.1%)
GAI (Subject)			
V3 (W8)	N	136	45
	GAIS responder	130 (95.6%)	43 (95.6%)
V7 (W52)	N	128	44
	GAIS responder	104 (81.3%)	34 (77.3%)

The change from Baseline and the responder rate of the TMVDS score as rated by the IPR were assessed 8 weeks after last treatment (initial or touch-up). At Baseline the TMVDS grade was similar between RHA®4 and the Control groups. And the change from Baseline and responder rate 8 weeks after last treatment was similar between RHA®4 and Control group. The results of the IPR are consistent with those observed by the BLE and TI.

Table 21: Change from Baseline and Responder Rate per IPR, 8 weeks after last treatment – Observed ITT population

Visit	Sample Characteristics/Category/ Responders	RHA®4 (N = 152)	Control (N = 49)
Baseline	n (missing)	136 (16)	45 (4)
	Mean (SD)	2.9 (0.85)	2.8 (0.94)
V3 (W8)	n (missing)	136 (1)	45 (0)
	Mean change from Baseline (SD)	-1.1 (0.91)	-1.0 (0.72)

Visit	Sample Characteristics/Category/ Responders	RHA®4 (N = 152)	Control (N = 49)
	Responder	110 (80.9%)	37 (82.2%)

Abbreviations: IPR = independent photo review; N = number of subjects; n = number of observations; SD = standard deviation; TMVDS = Teoxane Midface Volume Deficit Scale

Note: Baseline is defined as the last non-missing measurement preceding the initial treatment. Responder: Improvement from Baseline of ≥1 grade TMVDS. For subjects lost-to-follow-up or not present at the visit for the TMVDS assessment, missing values were not imputed. No imputation was performed for secondary endpoint analysis. All percentages were based upon the total number of subjects by group with non-missing data for the TMVDS at the specific visit.

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 *Satisfaction with cheeks* at rest and when smiling domain of the validated FACE-Q© patient-reported outcome measurement questionnaire.

At all time points, for all subjects in RHA®4 treatment group, scores were higher than pre-injection scores, indicating subject-perceived improvement in the appearance of their cheeks (including when they smiled). For the *Satisfaction with cheeks* domain at rest, the mean score increased from 32 to more than 84 at 8 weeks and stayed high to more than 70 at 52 weeks (Figure 2). For the *Satisfaction with cheeks* domain when smiling, the mean score increased from 31 to more than 86 at 8 weeks and remained high, above 70 at 52 weeks (Figure 3). The satisfaction of the appearance of the cheeks was maintained during dynamic movement. The mean score at rest and when smiling was always greater than 70 throughout the follow-up period.

Figure 2: FACE-Q – Satisfaction with Cheeks – at rest - Observed ITT population

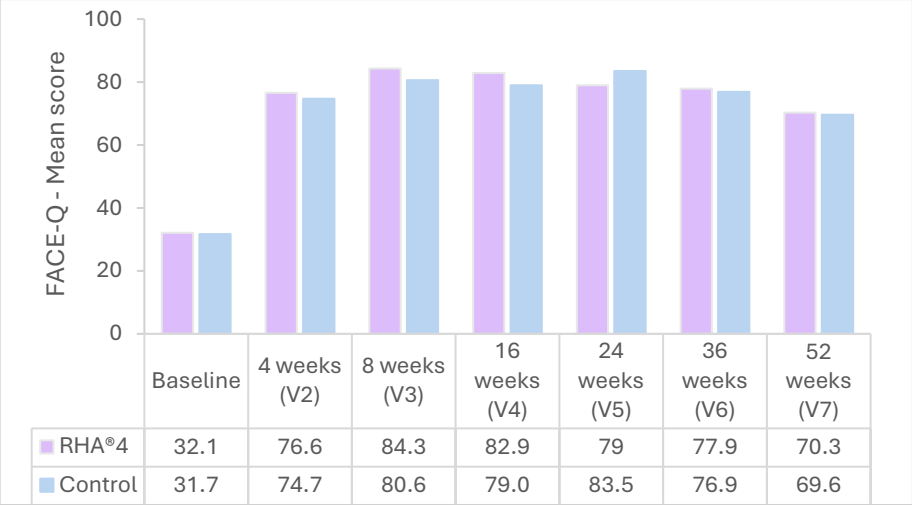
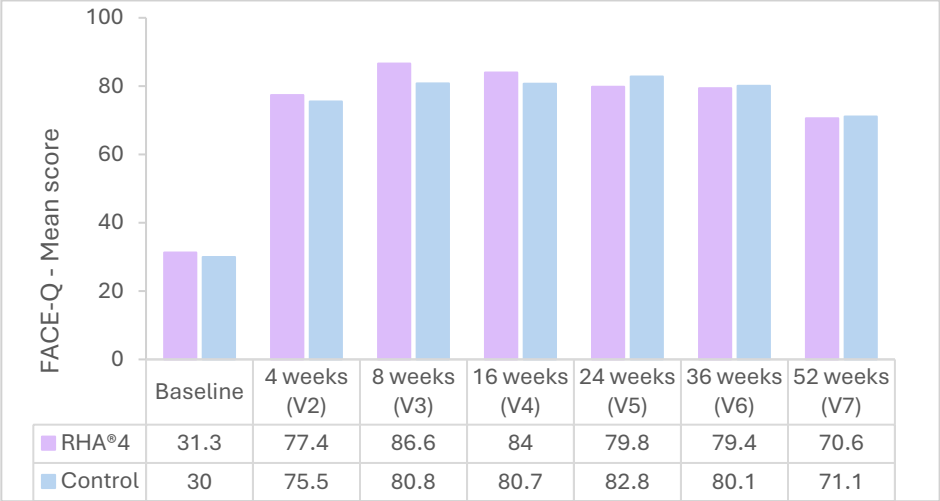


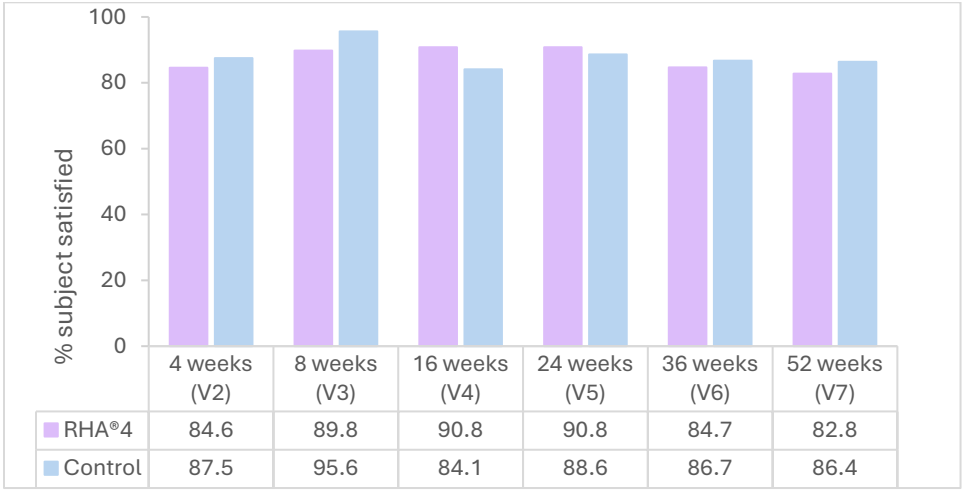
Figure 3: FACE-Q – Satisfaction with Cheeks – when smiling – Observed ITT population



	Baseline	4 weeks (V2)	8 weeks (V3)	16 weeks (V4)	24 weeks (V5)	36 weeks (V6)	52 weeks (V7)
RHA®4	31.3	77.4	86.6	84	79.8	79.4	70.6
Control	30	75.5	80.8	80.7	82.8	80.1	71.1

In the RHA®4 group, responder rates based on subject satisfaction were maintained above >82% throughout the study, with 82.8% of subjects still satisfied 1 year after the last treatment (Week 52). Similar results were found in the Control group, with subject satisfaction responder rates above >84%. Both RHA®4 and its Control demonstrated high degree of satisfaction with the treatment across all time points.

Figure 4: Subject satisfaction (satisfied or very satisfied) – Observed ITT population



	4 weeks (V2)	8 weeks (V3)	16 weeks (V4)	24 weeks (V5)	36 weeks (V6)	52 weeks (V7)
RHA®4	84.6	89.8	90.8	90.8	84.7	82.8
Control	87.5	95.6	84.1	88.6	86.7	86.4

Teoxane validated NLF-WSRS scale was used to assess any change of the severity of the nasolabial folds (NLFs) following the treatment of the midface. NLF-WSRS change from Baseline and the responder rate were also assessed by the BLE at each visit.
The responder rate in RHA®4 group was 24.8% at 8 weeks and 17.2% at 52 weeks after last treatment. In the Control group, the responder rate was 33.3% at 8 weeks and 22.7% at 52 weeks after last treatment.

Teoxane validated TIOHS scale was used to assess any change in the severity of the infraorbital hollows following the treatment of the midface. TIOHS change from Baseline and the responder rate were also assessed by the BLE at each visit.
The responder rate in RHA®4 group was 39.4% at 8 weeks and 25.0% at 52 weeks after last treatment. In the Control group, the responder rate was 53.3% at 8 weeks and 22.7% at 52 weeks after last treatment.

Table 22: TIOHS responder rate (BLE) – Observed ITT population

Visit	RHA®4	Control
Week 8	39.4% (54/137)	53.3% (24/45)
Week 16	36.9% (48/130)	36.6% (15/41)
Week 24	30.0% (39/130)	24.4% (19/44)
Week 36	30.5% (40/131)	24.4% (11/45)
Week 52	25.0% (32/128)	22.7% (10/44)

Naturalness of cheek was assessed by the Teoxane Midface Naturalness Subject Questionnaire (TMNSQ). At 8 weeks, more than 88% of subjects in both RHA®4 and Control groups "agreed" or "strongly agreed" with each statement of the TMNSQ:

- At rest my cheeks look natural
- At rest my skin of my cheeks is radiant
- When I am smiling, my cheeks look natural
- I can not perceive restriction in the movement of my cheeks when I am smiling
- I can not perceive restriction in the movement of my cheeks when I am kissing
- When I touch my cheeks, I can not feel the dermal filler
- My facial expressions have not changed from before treatment

At 52 weeks, more than 70% of subjects in both study groups "agreed" or "strongly agreed" with all of the statements.

3. Subgroup Analyses

The following baseline characteristics were evaluated for potential association 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 from Baseline of the TMVDS and responder rate of TMVDS at Week 8 as well as the incidence rate of ADEs. No statistical tests were performed. Results are descriptive only. The study was not specifically powered for subgroup analyses.

Safety

Subgroup Analysis of Adverse Events (ADEs)
Fitzpatrick Skin Type (FST):
No differences in ADE incidence rates were observed between FST I-III and IV-VI subgroups in the RHA®4 treatment group. The incidence rates in each FST subgroup were similar between RHA®4 and the Control groups.

Ethnicity:
Non-Hispanic/Latino subjects had slightly higher ADE incidence rates compared to Hispanic/Latino subjects (26.7% vs 12.9%). A similar trend was observed in the control group.

Sex:
Small differences in ADE incidence rates between male and female subjects were not clinically significant and may not be representative due to the limited number of male subjects.

Age:
No age-related differences in ADE incidence rates were observed between younger (≤56 years) and older (>56 years) subjects.

Injection Volume:
ADE incidence rates were similar across volume subgroups and consistent with the overall study population.

Administration Method:
The variability in injection methods (needle only, cannula only, or combined) across individual injections, along with disproportionate subgroup sizes, prevented meaningful conclusions about the impact of administration method on ADE incidence.

Injection Technique:
No meaningful conclusions could be drawn regarding injection technique impact on ADE incidence.

Injection Depth:
Since most subjects received multilayering injections (subcutaneous and supraperiostal) with few receiving single-depth injections, no meaningful conclusions could be made about injection depth impact on ADE incidence.

Effectiveness at primary endpoint

Subgroup Analysis Effectiveness Results
Fitzpatrick Skin Type (FST):
Analysis of FST I-III versus IV-VI subgroups showed similar effectiveness. TMVDS change from baseline (-1.3 vs -1.3) and responder rates (86.0% vs 89.5%) were comparable between groups, indicating FST did not impact RHA®4 effectiveness.

Ethnicity:
Hispanic subjects showed slightly higher responder rates (96.3%, 26/27) compared to non-Hispanic subjects (84.5%, 87/103) with comparable TMVDS change from baseline (-1.4 vs -1.3).

Sex:
Male subjects had higher responder rates (100%, 14/14) than female subjects (85.5%, 100/117) with TMVDS change from baseline (-1.5 vs -1.3). However, males comprised only 10.7% (14/131) of the study population.

Age:
Subjects ≤56 years showed greater TMVDS improvement (-1.4 vs -1.2) and higher responder rates (97.2%, 69/71) compared to subjects >56 years (75.0%, 45/60).

Administration Method:
Needle-only injections comprised of only ~15% of treated subjects (TMVDS change -1.8, responder rate ~95%). Cannula-only and combination needle/cannula methods showed similar outcomes (TMVDS change ~ -1.3, responder rate ~85%). No conclusion can be drawn.

Injection Volume:
TMVDS changes were similar across volume subgroups (≤3 mL: -1.4; >3-6 mL: -1.2; >6-9 mL: -1.3). All volume groups achieved ≥80% responder rates at 8 weeks post-treatment.

Site Variability:
While inter-site differences existed in TMVDS changes and responder rates, these differences were consistent across treatment groups, indicating site-specific rather than product-related effects.

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 G210086 included 8 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XII. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

None

XIII. 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.

XIV. CONCLUSION DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

Primary Efficacy: RHA®4 demonstrated non-inferiority to its control at 8 weeks post-treatment for cheek augmentation and midface contour correction in adults ≥22 years. The RHA®4 treatment group achieved a 92.0% responder rate at 8 weeks after final injection. Both treatment groups showed ≥1-grade average TMVDS improvement from Baseline, confirming RHA®4's effectiveness. Results showed that subjects injected with RHA®4 were able to sustain volume augmentation over time, as the volumizing effect was still visible in approximately 65% of subjects at 1-year post treatment (with a non-inferiority margin of ≥0.5 and the proportion of responders among subjects treated with the Control was ≥70%).

B. Safety Conclusions

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

The most frequent CTRs were tenderness, firmness, swelling and lumps/bumps. The majority of subjects had their CTRs resoled by Day 14. The maximum severity reported of nearly all CTRs (more than 90%) was mild or moderate.
All treatment-related Adverse Events were mostly mild, with some that were moderate. No severe treatment-related Adverse Events were reported after all treatments (initial, touch-up and retreatment). Most of the treatment-related Adverse Events were typical of the expected signs and symptoms observed following an injection of hyaluronic acid-based dermal filler, such as: injection site mass, injection site induration and injection site pain. Other reported treatment-related Adverse Events such as headache, periorbital pain or pruritus are less typical but not unexpected following dermal filler's injection. Most treatment-related Adverse Events were based on the subject's diary entries (CTRs) and fewer than 10% were identified by the TI. Most treatment-related adverse events resolved within 14 days. There were no treatment-related serious Adverse Events.

Overall Safety: RHA®4 treatment in the midface using multilayering technique (i.e. combination of subcutaneous and supraperiosteal depths of injection) and injected with needle and/or cannula,

was safe and well-tolerated. No deaths, treatment-related serious adverse events, or unexpected adverse device effects were reported.

Subgroup Analysis: Adverse device effect incidence rates across all subgroups (Fitzpatrick skin type, ethnicity, age, injection volume, depth, and administration method) were consistent with the overall study population.

Adverse Device Effects Characteristics:
• All events were typical of dermal filler injections
• Onset was temporally associated with recent injection
• All events were mild to moderate in severity (no severe events reported)
• No late-onset adverse device effects occurred
• No granulomas were observed
• Resolution of Adverse Device Effects: >45% resolved within 3 days, >80% within 14 days

The safety profile demonstrates that RHA®4 is well-tolerated with predictable, mild-to-moderate adverse effects that resolve quickly.

C. Benefit-Risk Determination

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 clinical benefit of RHA®4 for cheek augmentation and/or correction of age-related midface contour deficiencies was demonstrated based on Blinded Live Evaluator, Treating Investigator assessments and patient reported outcomes from the clinical study IDE G210086.

- The primary endpoint was met. Based on BLE assessment, the TMVDS change from Baseline for subjects treated with RHA®4 was statistically non-inferior to the change from Baseline for subjects treated with the Control at 8 weeks after the last treatment (initial or touch-up).
- Most subjects treated with RHA®4 were responders on the TMVDS (i.e. ≥ 1-point improvement) through 12 months when assessed by the Blinded Live Evaluator (nearly 80% at 6 months and >65% at 12 months.
- RHA®4 provided high level of aesthetic improvement with consistently high responder rates across multiple assessment scales.
    - The TMVDS responder rate at 6 months was >79% and >81% as assessed by the BLE and the TI respectively and remained above 65% for both at 12 months after last treatment. These results were consistent with the TMVDS responder rate as assessed by the IPR which was >80% at 8 weeks after last treatment.
    - The GAIS responder rate was more than 85% as assessed by both the BLE and the TI at 6 months after last treatment and remained above 75% at 12 months.

- Subject satisfaction exceeded 82% throughout the study and remained at 82.8% at 12-month post treatment. The GAIS score as assessed by the subject was maintained >80% throughout the study period.
- Subjects with the RHA®4 treatment group had higher FACE-Q *Satisfaction with cheeks* scores through 12 months compared to pre-injection scores, indicating subject-perceived improvement in the appearance of their cheeks (at rest and when smiling).
- Naturalness Assessment: using the Teoxane Midface Naturalness Subject Questionnaire (TMNSQ), >89% of subjects at week 8 and 77% at 12 months agreed or strongly agreed that their results appeared natural (at rest and when smiling), their skin looked radiant, and their facial experience was positive.
- Nasolabial folds: NLF-WSRS responder rates exceeded 24% at week 8 and 17% at 12 months
- Infraorbital hollows: TIOHS responder rates reached ~ 40% at week 8 and >28% at 12 months

These results demonstrate RHA®4's effectiveness for midface enhancement with sustained aesthetic improvement and high patient satisfaction.

The probable risks of RHA®4 device are also based on data collected in a clinical study conducted to support PMA approval as described above.

The benefit-risk ratio of RHA®4 for cheek augmentation and/or correction of age-related midface contour deficiencies is favorable.

1. 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 *Satisfaction with cheeks* at rest and when smiling domain of the validated FACE-Q© patient-reported outcome measurement
- Subject satisfaction survey
- Teoxane Midface Naturalness Subject Questionnaire

In conclusion, given the available information above, the data support the use of RHA®4 for injection into the subcutaneous to supraperiosteal layers for cheek augmentation and/or correction of age-related midface contour deficiencies 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 this device when used in accordance with the indications for use. The primary effectiveness data showed that RHA®4 was non-inferior to its Control and the subgroup analyses and secondary endpoints showed similarities of the results between groups. From a safety perspective, the observed incidence rates of ADEs between RHA®4 and its Control were similar and the observed incidence rate of ADEs in each subgroup showed that they were similar to the ADE rates determined for the entire population. Therefore, the risks associated with the injection of RHA®4 when considering the benefits (as assessed by the TMVDS Change from Baseline and responder rates assessed by the BLE, TI and IPR, the patient reported outcomes assessed by the GAIs, FACE-Q, and the Teoxane Midface Naturalness Subject and subject satisfaction questionnaires) are reasonable and the ratio benefits / risks is favorable. The data in this application support the reasonable assurance of safety and effectiveness of this device 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.

XV. CDRH DECISION

CDRH issued an approval order on September 18, 2025.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XVI. 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.

XVII. REFERENCES

None