SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Injectable Dermal Filler

Device Trade Name: RHA®3

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

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

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P170002/S030

Date of FDA Notice of Approval: October 27, 2023

The original PMA (P170002) for RHA®2, RHA®3 and RHA®4 was approved on October 19, 2017 for injection into the mid-to-deep dermis 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 SSED to support the indication of RHA®2, RHA®3 and RHA®4 for the correction of moderate to severe dynamic facial wrinkles and folds, such as nasolabial folds (NLFs) is available on the CDRH website and is incorporated by reference here. The current supplement was submitted to expand the indication of RHA®3 to include injection into the vermillion body, vermillion border and oral commissures to add volume and fullness to the lips in adults aged 22 years or older.

II. INDICATIONS FOR USE

RHA®3 is indicated for injection into the mid-to-deep dermis 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®3 is indicated for injection in the vermillion body, vermillion border and oral commissures to achieve lip augmentation and lip fullness in adults aged 22 years or older.

III. CONTRAINDICATIONS

- RHA®3 is contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.

- RHA®3 contains trace amounts of gram-positive bacterial proteins, and is contraindicated for patients with a history of allergies to such material.
- RHA®3 should not be used in patients with previous hypersensitivity to local anesthetics of the amide type, such as lidocaine.
- RHA®3 should not be used in patients with bleeding disorders.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in RHA®3 labeling.

V. DEVICE DESCRIPTION

RHA®3 is a viscoelastic, sterile, non-pyrogenic, clear, colorless, and biodegradable gel implant. It is produced with sodium Hyaluronic Acid (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). It contains 0.3% lidocaine hydrochloride to reduce pain on injection.

RHA®3 is supplied in a 1 ml syringe with two 27G ½ inch hypodermic needles.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives to achieve lip volume and lip fullness such as autologous fat transfer, surgery and other soft tissue fillers approved by FDA for lip augmentation.

Each alternative has its own benefits and risks when considering for example, the duration of the treatment, the cost of the treatment, the downtime associated with the treatment, the aesthetic effectiveness of the treatment, the type and duration of the adverse events associated with treatment. 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®3 received FDA approval in 2017 for the correction of moderate to severe dynamic facial wrinkles and folds, such as nasolabial folds (NLFs) (see SSED on the CDRH website under reference P170002). RHA®3 is available in the European Union and in more than 40 countries around the world where it has been approved for a wide range of indications including for lip fullness. It has not been withdrawn from the market for any reason related to its safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

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

Common treatment responses which can occur with the use of RHA®3 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®3 in and outside the United States. The following adverse events were reported as part of post-marketing surveillance on the use of RHA®3 worldwide with a prevalence equal or superior to one occurrence for 100,000 syringes: injection site mass (lumps and bumps), skin swelling, erythema, skin induration, skin edema, vascular complication, inflammatory reaction, pain, allergic reaction andecchymosis.

Additionally, other less frequent adverse reactions have also been reported, including implant migration, granuloma, dermatitis, skin infection, blister, necrosis, fibrosis, pruritus, abscess, overcorrection, skin discoloration/Tyndall effect, telangiectasia, tenderness, urticaria, anaphylactic reaction, injection site cellulitis, influenza-like illness, keloid scarring, overcorrection, numbness, pigmentation disorder, pustules, papules, paresthesia, nerve damage, numbness, visual impairment, neuralgia, wrinkles, hyperthermia, headache, hemorrhage, herpes outbreaks, injection site movement impairment, dry skin, chapped lips, scabs, puffy skin, dizziness.

Delayed-onset inflammation near the site of dermal filler injections is one of the known adverse events associated with dermal fillers. Cases of delayed-onset inflammation have been reported to occur at the dermal filler treatment site following viral or bacterial illnesses or infections, vaccinations, or dental procedures. Typically, the reported inflammation was responsive to treatment or resolved on its own. Additionally, the following rare but serious adverse events that are associated with intravascular injection of other soft tissue filler material in the face have been reported in the literature: vision impairment (acute or permanent), blindness, cerebral ischemia or cerebral hemorrhage leading to stroke, skin necrosis, and damage to underlying facial structures.

In many cases the symptoms resolved without any treatment. Reported treatments included the use of (in alphabetical order): analgesics, antibiotics, antihistamines, anti-inflammatories (NSAID, steroids), anti-viral, implant dissolution (hyaluronidase), drainage, excision, 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 studies, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

RHA®3 was extensively tested and characterized through physical and chemical testing (Table 1), and biocompatibility studies (Table 2). Preclinical testing results were adequate to support initiation of human clinical studies as dermal fillers.

Table 1: Physical and Chemical Testing – Requirements for RHA®3

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 meets specifications	Passed
Residual crosslinker content	To confirm the residual crosslinker content of the gel meets specifications	Passed
Lidocaine content	To confirm the lidocaine concentration of the gel meets specifications	Passed
Impurities deriving from Lidocaine Hydrochloride	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

B. Biocompatibility Studies

Table 2: Summary of biocompatibility studies for RHA®3

Test	Method	ISO Standard	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	Similar level of reactivity as control*. Irritant at 3 days and was non-irritant at Day 25;
Pyrogenicity	Rabbit		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	ISO 10993-3	Non-genotoxic.
Acute systemic toxicity	Mice intraperitoneal study	ISO 10993-11	No evidence of acute systemic toxicity.

Test	Method	ISO Standard	Results
Sub-acute and subchronic systemic toxicity	Intradermal injection in Sprague-Dawley	ISO 10993-11	There was no evidence of systemic toxicity after 4 weeks and 13 weeks of implantation.
Intradermal implantation	Intradermal implantation in rats	ISO 10993-6	The test articles were classified as non-irritant. After 52 weeks, degradation had started.

(*) Note: The control device was an FDA approved Hyaluronic Acid soft tissue filler, with similar characteristics to RHA®3. The control product is legally marketed with similar indications for use.

Stability data have been collected through 36 months at 25°C ± 2°C and 60% ± 5% relative humidity. At each time point, product was characterized via microbiological, physical, chemical, lidocaine hydrochloride content, and lidocaine-related degradant parameters. Conformance of real-time aged product with all specifications was confirmed. RHA®3 dermal filler has a 36 months shelf life.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed one clinical study to establish a reasonable assurance of safety and effectiveness when injecting RHA®3 into the vermillion body, vermillion border, and oral commissures to achieve lip augmentation and lip fullness in adults aged 22 years or over in the U.S. under IDE # G200102. Data from this clinical study was the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Subjects were treated between October 22, 2020, and May 10, 2022. The database for this PMA reflected data collected through June 27, 2022 and included 202 treated subjects with 153 subjects who received injection with RHA®3 and 49 subjects with the control. There were 7 U.S. investigational sites.

The study was a controlled, randomized, double-blinded, between subject, multicenter, prospective clinical study to evaluate the safety and effectiveness of RHA®3 for lip augmentation and lip fullness against a control. Subjects meeting inclusion/exclusion criteria were randomized 3:1 ratio into the treatment or control group. The control was an FDA approved hyaluronic acid soft tissue filler with similar characteristics to RHA®3 and marketed for lip augmentation. The study duration was 14 months and included repeat treatment.

1. Key Clinical Inclusion and Exclusion Criteria

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

- Outpatient, male or female of any race, 22 years of age or older. Female patients of childbearing potential must have a negative urine pregnancy test (UPT) at Visit 1 and practice a reliable method of contraception throughout the study.
- Lip fullness of grade 1 to 3 on the Teoxane Lip Fullness Scale (TLFS ranging from 1 to 5) who desire at least 1 point of correction for upper and/or lower lips *or* has Fitzpatrick skin type V or VI and has lip fullness grade 4 or 5 on the TLFS who desire treatment to the vermillion body for upper and/or lower lips. (The blinded live evaluator (BLE) and treating investigator (TI) must independently assess and agree that this criterion is met; however, concordance of fullness was not required. If the assessments of the TI and the BLE were the same or differed by exactly 1 point on the scale, this difference was considered acceptable. If the assessments differed by 2 points or more on the scale, the subject was not eligible);
- Willing to abstain from facial aesthetic procedures/therapies that could interfere with the study evaluations (e.g., other soft tissue fillers, botulinum toxin injections (frontalis and glabella complex allowed), laser or chemical resurfacing, etc.) 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:

- Known hypersensitivity or previous allergic reaction to any component of the study or control devices (e.g., gram positive bacterial proteins, hyaluronic acid, lidocaine, etc.);
- Known sensitivity to local anesthetics of the amide type, history of multiple severe allergies, history of anaphylactic shock;
- An outbreak of herpes labialis within 4 weeks of randomization or 4 or more outbreaks in the 12 months prior to randomization;
- Subjects who have either 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;
- Has an active inflammation, infection, cancerous or precancerous lesion, or unhealed wound on the lips, in the area of the mouth, or the area around the mouth;
- Has lip tattoos, facial hair, scar, lumps, or severe lip asymmetry that would interfere with visualization of the lips for the effectiveness assessments as per TI discretion;
- Has dentures or any device covering all or part of the upper palate, and/or severe malocclusion, dentofacial or maxillofacial deformities as judged by the TI;
- Has undergone significant oral surgery or other dental procedures (e.g., orthodontia or implantation) within 6 weeks prior to randomization or is planning to undergo any of these procedures during the study;

- Is planning to undergo during the study or has undergone any type of facial, plastic, nonablative, or reconstructive surgery (e.g., blepharoplasty, face lift, or rhinoplasty) within 6 months before randomization;
- Immunosuppressive therapy, chemotherapy, treatment with biologics or systemic corticosteroids within 3 months before randomization;
- Has a history of or currently has an auto-immune disease;
- Clinically significant alcohol or drug abuse or history of poor cooperation or unreliability;
- Has used any lip plumping, waxing, or antiwrinkle products around the mouth within 10 days before randomization or is planning to use such products during the study;
- Clinically significant (Investigator discretion) active skin disease within 6 months prior to study entry;
- History of bleeding disorders;
- Need for continuous medical treatment within 2 weeks prior to Visit 1;
- Received/used a prohibited treatment/procedure within certain time periods;
- A condition or be in a situation that may put the subject at significant risk, may confound the study results, or may significantly interfere with the subject's participation in the study;
- Study staff or close relative to study staff (e.g., parents, children, siblings, or spouse);

2. Follow-up Schedule

At Visit 1, subjects were randomized to RHA®3 or control treatment group. They received injection in their upper and lower lips. The Treating Investigator (TI) determined the injection technique and depth of injection. The maximum volume of administration was 3 mL per treatment session, with a maximum of 1.5 mL per lip per session. After 4 weeks, subjects may receive additional treatment with the same device as originally injected (RHA®3 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, 12, 24, 36, and possibly 52 weeks after treatment.. Follow-up was initially 36 weeks and was extended to 52 weeks for subjects who agreed to the extension of their participation in the study. The purpose of the study extension from 36 weeks to 52 weeks was to monitor subject's safety and product effectiveness for a longer time. The primary effectiveness endpoint (TLFS) was evaluated at 12 weeks after last treatment. Subjects were followed for 36 or 52 weeks to evaluate the long-term safety, safety

of retreatment and other secondary endpoints of RHA®3. Subjects were offered retreatment 36 or 52 weeks after last treatment. Retreatment was with RHA®3 irrespective of the assigned device at initial and touch-up treatment.

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 Adverse Events (AE) assessments at each visit.

An Adverse Event (AE) is any untoward medical occurrence, unintended disease or effect, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users, or other persons, whether or not related to the study device, the control device or the study procedure.

An Adverse Device Effect (ADE) is any adverse event related to the use of the study device, the control device, or the study procedures. This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the study or the control device. This definition also includes any event resulting from use error or from intentional misuse of the study or the control device.

For each AE identified in the investigation, the TI assess its relationship to the study and the control device and/or to the procedure. The TI must determine whether there is a reasonable possibility that these caused or contributed to an AE to be called an ADE.

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) and lip functionality tests at each visit (function, sensation and movement).

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 lip fullness improvement based on the Teoxane Lip Fullness Scale[1] (TLFS) (Table 3) from pre-injection fullness of the lips treated with the RHA®3 compared to the improvement from pre-injection fullness of the lips treated with the control device, as assessed by the BLE at 12 weeks after Baseline.

Table 3: Teoxane Lip Fullness Scale (TLFS)

Grade	Name	Description
1	Very thin	Upper and lower lips are both very thin and may be inverted with very little to no red lip showing; flat or nearly flat contour in profile view.
2	Thin	Lower lip may be slightly fuller than upper lip with some red lip showing, but overall both lips will be thin; slight contour in profile view.
3	Moderate	Approximately 1/3 upper lip and 2/3 lower lip with moderate red lip showing and slight lower lip pout; mild contour in profile view.
4	Full	Both lips will be full with significant red lip showing and moderate lower lip pout; moderate contour in profile view.
5	Very Full	Both lips will be very full and will likely be the same size with significant red lip showing; upper lip pout and lower lip pout; significant contour in profile view.

The primary effectiveness endpoint was the difference in the Teoxane Lip Fullness Scale (TLFS) change from Baseline to 12 weeks after last injection (initial or touch-up) between subjects treated with RHA®3 and those treated with the control. Assessment of the subject's lip fullness was based on the Teoxane Lip Fullness Scale (TLFS) as rated by the Blinded Live Evaluator. The co-primary endpoint was the proportion of responders with a ≥1-grade point improvement on the TLFS at 12 weeks when compared to pretreatment (Baseline). A change in the TLFS ≥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 TLFS score as rated by the BLE and TI (responder is a change of ≥ 1-grade on the TLFS); Global Aesthetic Improvement (GAI) as assessed by the BLE, TI and subject; impact and effectiveness of study

1 Trevidic, Carey, Benedetto, Joseph, Easton, Antunes and Maffer - *Creation and validation of a photonumeric scale for assessment of lip fullness* – Journal of Cosmetic Dermatology – 2022;21:949-955

treatment from the subjects' perspective, as assessed by the *Satisfaction with lips* and *Satisfaction with outcome* domains of the validated FACE-Q© patient-reported outcome measurement and by the subject satisfaction questionnaire; natural look of the lips as assessed by the BLE, TI and subject; and the natural feel of the lips as assessed by the subject.

With regard to success/failure criteria, the effectiveness of RHA®3 would be demonstrated if the TLFS change from Baseline for subjects treated with RHA®3 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%.

B. Accountability of PMA Cohort

A total of 212 subjects were screened. Ten (10) subjects did not meet the inclusion/exclusion criteria resulting in 202 enrolled subjects. Out of these enrolled subjects:

- 202 subjects (100%) were assigned to the Safety Population,
- 196 subjects (97.0%) to the ITT Population (6 subjects did not have post-Baseline TLFS score assessed by the BLE),
- 181 subjects (89.6%) to the mITT Population (15 subjects had Baseline TLFS score as assessed by the BLE of grade 4 or 5), and
- 169 subjects (83.7%) to the PP Population (12 subjects had a major protocol deviation: primary endpoint visit missed, primary endpoint visit ouf of windows by more than 21 days late, vision assessments were not performed due to COVID-19 and missing CTR diary).

Altogether, 119 subjects (58.9%) consented to enter the study extension (93 subjects (60.8%, 93/153) from the RHA®3 group and 26 subjects (53.1%, 26/49) from the control group) and participate in the study with a follow-up of 52 weeks instead of 36 weeks before being eligible for retreatment.

Table 4: Subject Accountability and Disposition

	RHA®3	**Control**
Screened	212	
Enrolled	202	
Safety population	153	49
ITT population[1]	148	48
mITT population[2]	137	44
PP population	127	42
Number of subjects consenting to enter study extension	93 (60.8%)	26 (53.1%)
Number of subjects who completed the study (V6/36 wks or V7/52 wks)	139 (90.8%)	46 (93.9%)
Number of subjects at primary endpoint visit (V4/12 wks)	146 (95.4%)	47 (95.9%)
Number of subjects at V6/36 wks	142 (92.8%)	46 (93.9%)

	RHA®3	Control
Number of subjects who received repeat treatment at V6/36 wks	24 (15.7%)	12 (24.5%)
Number of subjects at V7/52 wks	88 (57.5%)	25 (51.0%)
Number of subjects who received repeat treatment at V7/52 wks	66 (43.1%)	19 (38.8%)
Number of subjects withdrawn from study	14 (9.2%)	3 (6.1%)
Reason for discontinuation		
A subject or legal representative withdrawal	6 (3.9%)	1 (2.0%)
Lost to follow-up	6 (3.9%)	2 (4.1%)
Other[a]	2 (1.3%)	0

(1) ITT: set contained of all enrolled subjects who received treatment and for whom at least 1 post-Baseline primary effectiveness variable observation was obtained

(2) mITT: set consisted of the ITT Population excluding subjects with Baseline TLFS grade 4 and grade 5 (a few subjects with FST V or VI to be followed for safety only).

All percentages are based on the number of subjects by group in the Safety Population

[a] Other includes pregnancy (1 subject) and moving to another state (1 subject).

C. Study Population Demographics and Baseline Parameters

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

The study population included female and male subjects who were ≥ 22 years old. The study ensured that subjects meeting the inclusion criteria were representative of gender and ethnicity of the U.S. population who may use RHA®3 implant for lip augmentation. Subjects had a mean age of approximately 48 years, and most subjects were female (approximately 98% (199/202) of study subjects).

The majority of subjects were Caucasian (86.6% - 175/202), with 8.4% (17/202) of subjects identifying as Black or African American. 22.3% (45/202) 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 73.8% (149/202) and 26.2% (53/202) of subjects had skin types I-III and IV-VI, respectively (and 10% (21/202) of subjects having skin types V/VI).

Table 5: Demographic Characteristics at Baseline

Demographic Variable	RHA®3 *N=153*	Control *N=49*	Total *N=202*
Age (years)			
N (missing)	153 (0)	49 (0)	202 (0)
Mean ± SD	48.8 ± 13.19	48.5 ± 11.69	48.7 ± 12.82
Min, Max	22, 76	22, 68	22, 76
Gender			
N (missing)	153 (0)	49 (0)	202 (0)
Male	2 (1.3%)	1 (2.0%)	3 (1.5%)

Demographic Variable	RHA®3 *N=153*	Control *N=49*	Total *N=202*
Female	151 (98.7%)	48 (98.0%)	199 (98.5%)
Race[a]			
N (missing)	153 (0)	49 (0)	202 (0)
American Indian or Alaska Native	2 (1.3%)	1 (2.0%)	3 (1.5%)
Asian	4 (2.6%)	1 (2.0%)	5 (2.5%)
Black or African American	15 (9.8%)	2 (4.1%)	17 (8.4%)
Nat. Hawaiian, Other Pacific Islander	2 (1.3%)	0 (0.0%)	2 (1.0%)
White	130 (85.0%)	45 (91.8%)	175 (86.6%)
Ethnicity			
N (missing)	153 (0)	49 (0)	202 (0)
Hispanic or Latino	32 (20.9%)	13 (26.5%)	45 (22.3%)
Not-Hispanic or Latino	118 (77.1%)	35 (71.4%)	153 (75.7%)
Not available	3 (2.0%)	1 (2.0%)	4 (2.0%)
Fitzpatrick Skin Type			
N	153 (0)	49 (0)	202 (0)
I-III	**114 (74.5%)**	**35 (71.5%)**	**149 (73.8%)**
I	10 (6.5%)	7 (14.3%)	17 (8.4%)
II	46 (30.1%)	9 (18.4%)	55 (27.2%)
III	58 (37.9%)	19 (38.8%)	77 (38.15%)
IV-VI	**39 (25.5%)**	**14 (28.6%)**	**53 (26.2%)**
IV	22 (14.4%)	10 (20.4%)	32 (15.8%)
V	10 (6.5%)	3 (6.1%)	13 (6.4%)
VI	7 (4.6%)	1 (2.0%)	8 (4.0%)

The most common injection technique for all injection sessions (i.e., initial, touch-up, retreatment) and both treatment groups was linear threading, either as a stand-alone technique or in combination with other techniques such as multiple punctate pools or fan like injection.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the cohort of 202 subjects available for up to 52 week evaluation. The common treatment responses for this study are presented below in Table 6 to Table 8. Adverse device effects are reported in Table 9 to Table 12.

Safety of the RHA®3 implant when injected into the lips 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, lip functionality at each visit and measurement of injection site pain.

Common Treatment Responses After Initial Treatment

CTR data for initial treatment are presented in Table 6 to Table 8 below. CTRs for touch-up and repeat treatment were of the same proportions.

Out of the 202 subjects, 195 subjects completed and returned their diaries, with 147/153 in the RHA®3 group and 48/49 in the control group. Out of those subjects, 187 (95.9% - 187/195) experienced at least 1 CTR: 95.2% (140/147) of the subjects in the RHA®3 group and 97.9% (47/48) of the 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 swelling (experienced by 92.8% (181/195) of subjects overall who retrieved their diaries), lumps/bumps (78.5% (153/195) of subjects overall who retrieved their diaries), firmness (78.5% (153/195) of subjects overall who retrieved their diaries) and tenderness (77.9% (152/195) of subjects overall who retrieved their diaries) (Table 6).

For the RHA®3 group, within the diaries having at least one CTR, 78% (109/140) of the subjects reported CTRs of mild or moderate severity, while 22% (31/140) of the subjects reported at least one CTR of severe severity (Table 7). This proportion was similar in both treatment groups: 22% (31/140) for RHA®3 and 23% (11/47) for the control.

The most frequent severe CTR reported was swelling (28 in RHA®3 and 9 in the control group). Swelling being the most frequent severe CTR is consistent and anticipated from previous similar studies following an injection into the lips.

All severe CTRs did not last more than 8 days, except for one RHA®3 subject who experienced severe tenderness and severe firmness which had a maximum duration of 14 days.

In the RHA®3 group, 278 CTRs lasted up to 14 days (84% - 278/329) and 51 lasted between 15 and 30 days (16% - 51/329) (Table 8). In the control group, 84 CTRs lasted up to 14 days (89% - 84/94) and 10 lasted between 15 and 30 days (11% - 10/94).

19% of the subjects (37/195) reported at least one CTR on the last day of the diary: 20% in the RHA®3 group (30/147) against 15% in the control group (7/48) (Table 8).

62% of subjects overall (125/202) received a touch-up, with 58% in the RHA®3 group (89/153) against 74% in the control group (36/49) (Table 14). Following touch-up, 88 out of 89 subjects in the RHA®3 group returned a diary, and 33 out of 36 subjects in the control group returned a diary. From these diaries returned after touch-up, the proportions of the subjects having at least one CTR were similar after touch-up: 82% (72/88) in RHA®3 group against 79% (26/33) in the control group.

Similar to initial treatment, 96% (69/72) of the subjects reported only CTRs of mild or moderate severity for the RHA®3 group against 88% (23/26) in the control group.

Table 6: CTRs incidence rate – Initial treatment – Safety population

CTR	RHA®3	Control	Total
Number of subjects	153	49	202
Number of CTR diaries retrieved	147	48	195
At least 1 CTR	140 (95.2%)	47 (97.9%)	187 (95.9%)
Redness	81 (55.1%)	28 (58.3%)	109 (55.9%)
Pain	77 (52.4%)	31 (64.6%)	108 (55.4%)
Tenderness	114 (77.6%)	38 (79.2%)	152 (77.9%)
Firmness	115 (78.2%)	38 (79.2%)	153 (78.5%)
Swelling	134 (91.2%)	47 (97.9%)	181 (92.8%)
Lumps/Bumps	115 (78.2%)	38 (79.2%)	153 (78.5%)
Bruising	102 (69.4%)	25 (52.1%)	127 (65.1%)
Itching	39 (26.5%)	9 (18.8%)	48 (24.6%)
Discoloration	65 (44.2%)	20 (41.7%)	85 (43.6%)

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

Table 7: CTRs by Maximum Severity after initial treatment with RHA®3 and the control device – Safety population

CTR	Severity	RHA®3	Control	Total
Number of subjects		153	49	202
Number of CTR diaries retrieved		147	48	195
At least 1 CTR	Mild	58 (41.4%)	17 (36.2%)	75 (40.1%)
	Moderate	51 (36.4%)	19 (40.4%)	70 (37.4%)
	Severe	31 (22.1%)	11 (23.4%)	42 (22.5%)
Redness	Mild	49 (60.5%)	17 (60.7%)	66 (60.6%)
	Moderate	23 (28.4%)	9 (32.1%)	32 (29.4%)
	Severe	9 (11.1%)	2 (7.1%)	11 (10.1%)
Pain	Mild	53 (68.8%)	15 (48.4%)	68 (63.0%)
	Moderate	21 (27.3%)	14 (45.2%)	35 (32.4%)
	Severe	3 (3.9%)	2 (6.5%)	5 (4.6%)
Tenderness	Mild	69 (60.5%)	17 (44.7%)	86 (56.6%)
	Moderate	35 (30.7%)	20 (52.6%)	55 (36.2%)
	Severe	10 (8.8%)	1 (2.6%)	11 (7.2%)
Firmness	Mild	56 (48.7%)	17 (44.7%)	73 (47.7%)
	Moderate	47 (40.9%)	18 (47.4%)	65 (42.5%)
	Severe	12 (10.4%)	3 (7.9%)	15 (9.8%)
Swelling	Mild	61 (45.5%)	21 (44.7%)	82 (45.3%)
	Moderate	45 (33.6%)	17 (36.2%)	62 (34.3%)
	Severe	28 (20.9%)	9 (19.1%)	37 (20.4%)
Lumps/Bumps	Mild	58 (50.4%)	24 (63.2%)	82 (53.6%)
	Moderate	46 (40.0%)	10 (26.3%)	56 (36.6%)
	Severe	11 (9.6%)	4 (10.5%)	15 (9.8%)
Bruising	Mild	51 (50.0%)	18 (72.0%)	69 (54.3%)
	Moderate	34 (33.3%)	6 (24.0%)	40 (31.5%)
	Severe	17 (16.7%)	1 (4.0%)	18 (14.2%)
Itching	Mild	31 (79.5%)	7 (77.8%)	38 (79.2%)
	Moderate	6 (15.4%)	1 (11.1%)	7 (14.6%)
	Severe	2 (5.1%)	1 (11.1%)	3 (6.3%)
Discoloration	Mild	39 (60.0%)	12 (60.0%)	51 (60.0%)
	Moderate	19 (29.2%)	7 (35.0%)	26 (30.6%)
	Severe	7 (10.8%)	1 (5.0%)	8 (9.4%)

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.

Table 8: CTRs by duration after initial treatment with RHA®3 and the control device

			Total Duration (days)				
CTR at initial injection	**Group**	**Subjects Experiencing the CTR**	**1-3**	**4-7**	**8-14**	**15-30**	**Last Day Diary**
Any CTR	RHA®3	140 (95.2%)	111 (75.5%)	100 (68.0%)	67 (45.6%)	51 (34.7%)	30 (20.4%)
	Control	47 (97.9%)	40 (83.3%)	33 (68.8%)	11 (22.9%)	10 (20.8%)	7 (14.6%)
	Total	187 (95.9%)	151 (77.4%)	133 (68.2%)	78 (40.0%)	61 (31.3%)	37 (19.0%)
Redness	RHA®3	81 (55.1%)	42 (28.6%)	18 (12.2%)	15 (10.2%)	6 (4.1%)	0
	Control	28 (58.3%)	19 (39.6%)	6 (12.5%)	3 (6.3%)	0	0
	Total	109 (55.9%)	61 (31.3%)	24 (12.3%)	18 (9.2%)	6 (3.1%)	0
Pain	RHA®3	77 (52.4%)	40 (27.2%)	19 (12.9%)	10 (6.8%)	8 (5.4%)	0
	Control	31 (64.6%)	20 (41.7%)	9 (18.8%)	2 (4.2%)	0	0
	Total	108 (55.4%)	60 (30.8%)	28 (14.4%)	12 (6.2%)	8 (4.1%)	0
Tenderness	RHA®3	114 (77.6%)	37 (25.2%)	32 (21.8%)	27 (18.4%)	18 (12.2%)	3 (2.0%)
	Control	38 (79.2%)	16 (33.3%)	13 (27.1%)	6 (12.5%)	3 (6.3%)	1 (2.1%)
	Total	152 (77.9%)	53 (27.2%)	45 (23.1%)	33 (16.9%)	21 (10.8%)	4 (2.1%)
Firmness	RHA®3	115 (78.2%)	32 (21.8%)	26 (17.7%)	27 (18.4%)	30 (20.4%)	11 (7.5%)
	Control	38 (79.2%)	12 (25.0%)	18 (37.5%)	4 (8.3%)	4 (8.3%)	3 (6.3%)
	Total	153 (78.5%)	44 (22.6%)	44 (22.6%)	31 (15.9%)	34 (17.4%)	14 (7.2%)
Swelling	RHA®3	134 (91.2%)	45 (30.6%)	43 (29.3%)	32 (21.8%)	14 (9.5%)	1 (0.7%)
	Control	47 (97.9%)	25 (52.1%)	17 (35.4%)	2 (4.2%)	3 (6.3%)	0
	Total	181 (92.8%)	70 (35.9%)	60 (30.8%)	34 (17.4%)	17 (8.7%)	1 (0.5%)
Lumps/	RHA®3	115 (78.2%)	30 (20.4%)	23 (15.6%)	17 (11.6%)	45 (30.6%)	27 (18.4%)
Bumps	Control	38 (79.2%)	13 (27.1%)	14 (29.2%)	2 (4.2%)	9 (18.8%)	7 (14.6%)
	Total	153 (78.5%)	43 (22.1%)	37 (19.0%)	19 (9.7%)	54 (27.7%)	34 (17.4%)
Bruising	RHA®3	102 (69.4%)	29 (19.7%)	34 (23.1%)	33 (22.4%)	6 (4.1%)	1 (0.7%)
	Control	25 (52.1%)	12 (25.0%)	10 (20.8%)	2 (4.2%)	1 (2.1%)	0
	Total	127 (65.1%)	41 (21.0%)	44 (22.6%)	35 (17.9%)	7 (3.6%)	1 (0.5%)
Itching	RHA®3	39 (26.5%)	22 (15.0%)	8 (5.4%)	4 (2.7%)	5 (3.4%)	1 (0.7%)
	Control	9 (18.8%)	5 (10.4%)	4 (8.3%)	0	0	0
	Total	48 (24.6%)	27 (13.8%)	12 (6.2%)	4 (2.1%)	5 (2.6%)	1 (0.5%)
Discoloration	RHA®3	65 (44.2%)	25 (17.0%)	18 (12.2%)	15 (10.2%)	7 (4.8%)	3 (2.0%)
	Control	20 (41.7%)	13 (27.1%)	5 (10.4%)	2 (4.2%)	0	0
	Total	85 (43.6%)	38 (19.5%)	23 (11.8%)	17 (8.7%)	7 (3.6%)	3 (1.5%)

Abbreviation: CTR = Common Treatment Response.
All percentages are based on the number of CTR diaries retrieved by injection by subgroup in the population.
153 subjects were treated with initial injection in RHA3 group and 147 CTR diaries were retrieved. 49 subjects were treated with initial injection in Restylane-L group and 48 CTR diaries were retrieved.

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 (ADEs)

All Adverse Device Effects observed (Table 9) were types of events that are typical for the injection of a dermal filler into the lips and were observed at frequencies of that are typical for the injection of a dermal filler into the lips.

Table 9 below summarizes all AEs (including ADE, AESI, SAE) for the entire study period (from Visit 1 to Visit 6B/7B: initial + touch-up + retreatment). Of the 144 ADEs experienced in the RHA®3 group in the entire study period, 108 were from V1 to V6/V7 (i.e. prior to retreatment), and 36 were associated with retreatment.

Overall, most adverse events were obtained from the diary. In the RHA®3 group prior to retreatment (from V1 to V6-36 wks/V7-52 wks):

- 36% (39/108) of the ADEs were CTRs automatically elevated to AEs because they were present on the last day of the diary.
- 31% (34/108) of the ADEs were automatically elevated to AEs because they were reported as "Other" in the diary.
- 25% (27/108) of the ADEs were identified by the TI during a visit.
- 7% (8/108) 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.

The type of ADEs were also comparable between RHA®3 and the control groups as shown in Table 10 below.

Table 9: Adverse Events Overview (from initial treatment to exit visit – V1 to V6B/V7B* - including retreatment) – RHA®3 versus the control device

All Study Periods	RHA®3 (N=153)		Control (N=49)		Total (N=202)	
	Number of events	Number of subjects (CI)	Number of events	Number of subjects (CI)	Number of events	Number of subjects (CI)
Overall						
Number of subjects		153		49		202
All AEs	207	75 (49.0%)	70	22 (44.9%)	277	97 (48.0%)
AESIs	1	1 (0.7%)	0	0	1	1 (0.5%)
ADEs	144	63 (41.2%)	50	15 (30.6%)	194	78 (38.6%)
Serious AEs	0	0	1	1 (2.0%)	1	1 (0.5%)

All Study Periods	RHA®3 (N=153)		Control (N=49)		Total (N=202)	
	Number of events	Number of subjects (CI)	Number of events	Number of subjects (CI)	Number of events	Number of subjects (CI)
Fitzpatrick skin type I-III						
Number of subjects		114		35		149
All AEs	162	57 (50.0%)	56	15 (42.9%)	218	72 (48.3%)
AESIs	1	1 (0.9%)	0	0	1	1 (0.7%)
ADEs	111	48 (42.1%)	44	12 (34.3%)	155	60 (40.3%)
Serious AEs	0	0	0	0	0	0
Fitzpatrick skin type IV-VI						
Number of subjects		39		14		53
All AEs	45	18 (46.2%)	14	7 (50.0%)	59	25 (47.2%)
AESIs	0	0	0	0	0	0
ADEs	33	15 (38.5%)	6	3 (21.4%)	39	18 (34.0%)
Serious AEs	0	0	1	1 (7.1%)	1	1 (1.9%)

Abbreviations: ADE = adverse device effect; AE = adverse event; AESI = adverse event of special interest; CI = confidence interval; N = number of subjects; SAE = serious adverse event; UADE = unanticipated adverse device effect

Note: 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 occurred 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. Adverse events with a missing relationship were counted as related. A device related serious AE was a related AE also considered as serious.

*V6B: 4 weeks after retreatment 36 weeks after last treatment and V7B: 4 weeks after retreatment 52 weeks after last treatment

Similar safety profiles were observed between treatment groups (Table 10 below): a total of 34.0% (52/153) and 24.4% (12/49) subjects in the RHA®3 group and the control group, respectively, experienced at least one ADE between Visit 1 and Visit 6/7 (up to retreatment). In the RHA®3 group, eight (8) ADEs (7.4% - 8/108) were reported from the pre-identified list of AEs in the subject diary: 1 event of dizziness, 4 events of change to chewing and drinking, 2 events of sensitivity to hot/cold to liquids and foods and 1 event of crusty or scabby skin. All of the eight (8) ADEs were mild in severity and resolved without sequalae.

All ADEs experienced by both treatment groups were typical of the expected signs and symptoms observed following an injection of a hyaluronic acid-based dermal filler (Table 10). The ADEs with an overall incidence of >5% were:

- Injection site mass: 14.4% (22/153) and 16.3% (8/49) of subjects originally assigned to the RHA®3 and control groups, respectively, experienced at least 1 event.

- Injection site swelling: 9.2% (14/153) and 12.2% (6/49) of subjects originally assigned to the RHA®3 and control groups, respectively, experienced at least 1 event.
- Injection site induration: 5.2% (8/153) and 6.1% (3/49) of subjects originally assigned to the RHA®3 and control groups, respectively, experienced at least 1 event.

Table 10: ADEs sorted by SOC and PT (from initial treatment to 36 or 52 weeks follow-up excluding retreatment – V1 to V6/V7*): Safety population

From V1 to V6/7	RHA®3 (N=153)		Control (N=49)		Total (N=202)	
SOC PT	Number of events	Number of subjects	Number of events	Number of subjects	Number of events	Number of subjects
Any ADE	**108**	**52 (34.0%)**	**38**	**12 (24.5%)**	**146**	**64 (31.7%)**
General Disorders and Admin. Site Conditions	**100**	**49 (32.0%)**	**36**	**12 (24.5%)**	**136**	**61 (30.2%)**
Injection Site Mass	26	22 (14.4%)	9	8 (16.3%)	35	30 (14.9%)
Injection Site Swelling	15	14 (9.2%)	6	6 (12.2%)	21	20 (9.9%)
Injection Site Induration	10	8 (5.2%)	3	3 (6.1%)	13	11 (5.4%)
Injection Site Bruising	7	7 (4.6%)	1	1 (2.0%)	8	8 (4.0%)
Injection Site Reaction	5	5 (3.3%)	2	2 (4.1%)	7	7 (3.5%)
Injection Site Deformation	6	5 (3.3%)	0	0	6	5 (2.5%)
Injection Site Erosion	3	2 (1.3%)	4	3 (6.1 %)	7	5 (2.5%)
Injection Site Exfoliation	5	3 (2.0%)	4	2 (4.1 %)	9	5 (2.5%)
Injection Site Pain	3	3 (2.0%)	2	2 (4.1 %)	5	5 (2.5%)
Injection Site Hypoaesthesia	8	4 (2.6%)	0	0	8	4 (2.0 %)
Injection Site Discomfort	2	2 (1.3%)	0	0	2	2 (1.0 %)
Injection Site Hyperaesthesia	2	2 (1.3%)	0	0	2	2 (1.0 %)
Injection Site Movement Impairment	1	1 (0.7%)	1	1 (2.0 %)	2	2 (1.0 %)
Injection Site Paraesthesia	3	2 (1.3%)	0	0	3	2 (1.0 %)
Injection Site Scab	1	1 (0.7%)	1	1 (2.0 %)	2	2 (1.0 %)
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 %)
Infections and Infestations	**4**	**4 (2.6%)**	**0**	**0**	**4**	**4 (2.0 %)**
Injection Site Infection	3	3 (2.0%)	0	0	3	3 (1.5 %)
Herpes Zoster	1	1 (0.7%)	0	0	1	1 (0.5 %)
Nervous System Disorders	**4**	**3 (2.0%)**	**1**	**1 (2.0%)**	**5**	**4 (2.0 %)**
Headache	2	1 (0.7%)	1	1 (2.0 %)	3	2 (1.0 %)
Dizziness	1	1 (0.7%)	0	0	1	1 (0.5 %)
Dyskinesia	1	1 (0.7%)	0	0	1	1 (0.5 %)
Skin and Subcutaneous Tissue Disorders	**0**	**0**	**1**	**1 (2.0 %)**	**1**	**1 (0.5 %)**
Pruritus	0	0	1	1 (2.0 %)	1	1 (0.5 %)

Abbreviations: ADE = adverse device effect; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; PT = preferred term; SOC = system organ class; V = visit
All percentages are based on the number of subjects by group in the population.
Adverse device effects were coded using MedDRA version 25.0.
Adverse device effects are displayed by descending subject frequency of SOC, then descending subject frequency of PT within SOC in the Total column, then alphabetically.
*V6: 36 weeks after last treatment and V7: 52 weeks after last treatment

The majority (85%) of ADEs (92/108) in the RHA®3 group were mild and the remaining (15%) were moderate (16/108) (Table 11). There were no severe ADEs in either group. In the control group, the severity of ADEs was similar: 71% (27/38) were mild and 29% (11/38) were moderate (Table 11).

Of the 108 ADEs reported between Visit 1 to Visit V6/V7 for the RHA®3 group (after initial and touch-up treatment), 36% (39/108) of ADEs lasted one (1) to three (3) days, 67% (72/108) of ADEs were resolved within 14 days. There were four (4) and two (2) events of injection site mass in the RHA®3 and control groups, respectively, lasting more than 90 days. There was one (1) event of mass in the RHA®3 group lasting more than 90 days. Overall, most ADEs resolved within 30 days and the proportion of subjects with reported ADEs was similar across the 2 treatment groups (Table 12).

Table 11: ADE by Severity (from initial treatment to 36 or 52 weeks follow-up excluding retreatment – V1 to V6/V7): Safety population

From V1 to V6/7 SOC PT	Severity	RHA®3 (N=153)		Control (N=49)		Total (N=202)	
		Number of events	Number of subjects	Number of events	Number of subjects	Number of events	Number of subjects
Any ADE		**108**	**52 (34.0%)**	**38**	**12 (24.5%)**	**146**	**64 (31.7%)**
	Mild	92	49 (32.0%)	27	10 (20.4%)	119	59 (29.2%)
	Moderate	16	13 (8.5%)	11	7 (14.3%)	27	20 (9.9%)
	Severe	0	0	0	0	0	0

Table 12: ADE by Duration (from initial treatment to 36 or 52 weeks follow-up excluding retreatment – V1 to V6/V7): Safety population

From Visit 1 to Visit 6/7		RHA®3 (N= 153)		Control (N= 49)		Total (N= 202)	
System Organ Class	Duration of AE (days)	Number of events	Number of subjects	Number of events	Number of subjects	Number of events	Number of subjects
Any ADE		**108**	**52 (34.0%)**	**38**	**12 (24.5%)**	**146**	**64 (31.7%)**
	1-3	**39**	**19 (12.4%)**	**17**	**8 (16.3%)**	**56**	**27 (13.4%)**
	4-7	**20**	**12 (7.8%)**	**3**	**2 (4.1%)**	**23**	**14 (6.9%)**
	8-14	**13**	**11 (7.2%)**	**4**	**4 (8.2%)**	**17**	**15 (7.4%)**
	15 - 30	**13**	**12 (7.8%)**	**7**	**5 (10.2%)**	**20**	**17 (8.4%)**

From Visit 1 to Visit 6/7			RHA®3 (N= 153)		Control (N= 49)		Total (N= 202)	
System Class	Organ	Duration of AE (days)	Number of events	Number of subjects	Number of events	Number of subjects	Number of events	Number of subjects
		31 - 90	**18**	**13 (8.5%)**	**5**	**3 (6.1%)**	**23**	**16 (7.9%)**
		>90	**5**	**5 (3.3%)**	**2**	**2 (4.1%)**	**7**	**7 (3.5%)**

Nine (9) ADEs following the retreatment were still ongoing at the end of the study (i.e., one month after retreatment) and were the typical and expected signs and symptoms observed following the injection of a dermal filler (6 lumps/bumps, 1 swelling, 2 firmness). They were mild in severity (8/9), except for one subject who experienced moderate lumps/bumps after retreatment with RHA®3 which resolved one month later.

For subjects aged 22-40 years, higher rates of ADEs were observed in RHA®3 group (24%, 35/144) when compared to control group (4%, 2/50). The opposite trend was observed for subjects aged 50-60 years where rates of ADEs were lower in RHA®3 group (29%, 42/144) than in the control group (60%, 30/50). There were no trends of ADEs related to age.

Table 13: ADE Profile Overview by Age Group (initial, touch-up and retreatment) Visit 1 to Visit 6B/V7B* – Safety Population

All Study Periods	RHA®3 (N=153)		Control (N=49)		Total (N=202)	
	Number of events (%)[a]	Number of subjects (%)[b]	Number of events (%)[a]	Number of subjects (%)[b]	Number of events (%)[a]	Number of subjects (%)[b]
Overall						
Number of subjects		153		49		202
ADEs	144	63 (41.2%)	50	15 (30.6%)	194	78 (38.6%)
Age 22-≤40 years						
Number of subjects		42		13		55
ADEs	35 (24.3%)	18 (42.9%)	2 (4.0%)	1 (7.7%)	37 (19.0%)	19 (34.5%)
Age 40-≤50 years						
Number of subjects		33		11		44
ADEs	36 (25.0%)	11 (33.3%)	7 (14.0%)	3 (27.3%)	43 (22.2%)	14 (31.8%)
Age 50-≤60 years						

All Study Periods	RHA®3 (N=153)		Control (N=49)		Total (N=202)	
	Number of events (%)[a]	Number of subjects (%)[b]	Number of events (%)[a]	Number of subjects (%)[b]	Number of events (%)[a]	Number of subjects (%)[b]
Number of subjects		50		18		68
ADEs	42 (29.2%)	20 (40.0%)	30 (60.0%)	8 (44.4%)	72 (37.1%)	28 (41.2%)
Age >60 years						
Number of subjects		28		7		35
ADEs	31 (21.5%)	14 (50.0%)	11 (22.0%)	3 (42.9%)	42 (21.6%)	17 (48.6%)

Abbreviations: ADE = adverse device effect; N = number of subjects.
[a] Percentages are based on the number of events in the population
[b] Percentages are based on the number of subjects by group in the population
*V6B: 4 weeks after retreatment 36 weeks after last treatment and V7B: 4 weeks after retreatment 52 weeks after last treatment

Adverse Event of Special Interest (AESI)

One event of mild blurred vision was reported as an Adverse Event of Special Interest (AESI). It was assessed as Unlikely related to the study treatment and did not motivate referral to an eye specialist. The event resolved without sequelae within 24 hours.

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.

Lip functionality

Lip functionality assessments were conducted by the TI pre- and post-injection at each injection and at each follow-up visit. The lip functionality testing included Lip function, Lip sensation and Lip movement tests.

- Lip function: Ability to suck liquid through a straw.

Lip function (use of straw) was assessed as to whether the subject could properly use a straw for drinking liquids (yes/no response, based on "can the subject drink/suck through a straw effectively"). 92.8% (142/153) of subjects in RHA®3 group and 91.8% (45/49) of subjects in the control group were able to use a straw post-injection. All subjects (100%) could use a straw at Visit 2 and thereafter.

- Lip Sensation: Ability to feel the change in the lip sensation to touch, using the two following tests:

- the monofilament test (i.e., a subject's ability to feel the sensation of a monofilament at three points on the upper lip and three points on the lower lip) and
- the cotton wisp test (i.e., a subject's ability to feel the sensation of a cotton wisp at three points on the upper lip and three points on the lower lip).

The proportion of touch-points that subjects could feel at Visit 1 post-injection was similar between treatment group, with >91.5% (140/153) of subjects for RHA®3 and >91.8% (45/49) of subjects for the control able to feel monofilament or cotton wisp. For both tests, the proportion of touch-points that subjects could feel at Visit 2 was >99.3% for both treatment groups and in all quadrants, and 100% at all the following study visits for both treatment groups and in all quadrants.

- Lip Movement: Ability to pronounce correctly (based on 10 words per subject).

After the initial treatment at Visit 1, subjects treated with RHA®3 pronounced 98.7% of words correctly (1510/1530 words pronounced) and subjects treated with the control pronounced 98.0% of words correctly (480/490 words pronounced). All subjects (100%) in both treatment groups pronounced the words correctly at the subsequent visits (V2-4 wks to V6-36 wks/V7-52 wks), confirming full recovery of Baseline lip movement after RHA®3 and control treatments.

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 9.0 ± 14.88 and 8.8 ± 14.30 in the RHA®3 and the control groups, respectively. Injection site pain was reduced to 2.2 ± 6.76 mm and 1.5 ± 4.66 mm in the RHA®3 and the control groups, respectively by 5 minutes post-injection. Pain after 15 minutes was 0.7 ± 2.43 and 1.5 ± 5.92 in the RHA®3 and the control groups, respectively. Pain after 30 minutes was 0.5 ± 2.97 and 0.7 ± 4.09 in the RHA®3 and the control groups, respectively.

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

Extent of exposure

The maximum volume allowed was 3.0 mL per injection session.

The average volume injected for initial treatment was nearly identical between treatment groups with volumes of 1.43±0.47 mL and 1.43±0.48 mL in the RHA®3 and the control groups, respectively. Similar volumes were injected at initial treatment for upper and lower lips, in both treatment groups. Injection volumes used

for touch-up treatment in both lips were slightly higher in the control group, with 0.71±0.43 mL compared to 0.60±0.38 mL in the RHA®3 group.

The number of treatment sessions needed to obtain optimal cosmetic results (OCR) was slightly higher for the control device than with the RHA®3 implant formulations as shown by Table 14 below.

Volumes injected to achieve Optimal Correction Results (OCR) (i.e. initial and touch-up treatment) were comparable in both treatment groups with slightly higher volumes in both lips noted for the control group: a total volume of 1.78±0.64 mL and 1.95±0.73 mL was used in the RHA®3 and the control groups, respectively.

Volume injected at retreatment (with RHA®3 only) at the end of the study was also similar between treatment groups, with 1.03±0.46 mL for RHA®3 and 1.03±0.41 mL in subjects initially assigned to receive the control device. No meaningful difference was observed between volumes injected in the upper and lower lip.

Table 14: Number of subjects for each treatment session – Safety population

Treatment	RHA®3 (N=153)	Control (N=49)	Total (N=202)
Initial treatment	153 (100%)	49 (100%)	202 (100%)
Touch-up treatment	89 (58.2%)	36 (73.5%)	125 (61.9%)
Retreatment	90 (58.8%)	30 (61.2%)	120 (59.4%)
Number of subjects receiving 1 treatment (i.e., only initial treatment)	42 (27.5%)	9 (18.4%)	51 (25.2%)
Number of subjects receiving all 3 injections (initial, touch-up and retreatment)	68 (44.4%)	26 (53.1%)	94 (46.5%)

All percentages are based on the number of subjects by group in the population.
Retreatment includes subjects injected at Visit 6 (36 weeks) or at Visit 7 (52 weeks). At retreatment injection, all subjects received RHA®3

2. Effectiveness Results

The analysis of effectiveness was based on 137 subjects who received treatment with RHA®3 and 44 who received treatment with the control.

The primary effectiveness endpoint was to assess the effectiveness (non-inferiority) of RHA®3 versus the control on adding volume and fullness to the lips in subjects seeking lip augmentation, 12 weeks after the last treatment (initial or touch-up). For the primary endpoint, the change from Baseline for subjects treated with RHA®3 had to be statistically non-inferior to the change from Baseline for subjects treated with the control at 12 weeks after the last treatment as assessed by the Blinded Live Evaluator (BLE) using the TLFS. The difference in the TLFS change from Baseline to 12 weeks was used to establish non-inferiority.

As shown by Table 15, subjects treated with RHA®3 had a mean TLFS change at week 12 from Baseline of 1.0, while subjects treated with the control had a TLFS change of 0.8. The estimated difference in means (RHA®3 minus control) analyzed

by the Bootstrap method was 0.19 (95% CI: -0.03 – 0.42). Since the lower bound CI of -0.03 was >-0.5, treatment with RHA®3 was shown to be non-inferior to the control treatment.

Table 15: TLFS Grade Change from Baseline (BLE) at primary endpoint (Week 12) – mITT population

Category	RHA®3 (N=137)	Control (N=44)
TLFS change from Baseline at Week 12		
n	137	44
Mean (SD)	1.0 (0.65)	0.8 (0.70)
95% CI Mean	0.9 - 1.1	0.6 - 1.0
Min to Max	0 to 3	-1 to 2

Abbreviations: BLE = blinded live evaluator; CI = confidence interval; mITT = modified intent to treat; n = number of observations; N = number of subjects; SD = standard deviation; TLFS = Teoxane Lip Fullness Scale
Baseline is defined as the last non missing measurement preceding the initial treatment.
For achieving the non-inferiority, the lower confidence limit of a 95% CI of difference at Visit 4 must be > 0.5.
For subjects lost-to-follow-up or not present at the primary endpoint visit for the TLFS assessment, missing value is imputed using the mean of TLFS grade data at the specific visit for the applicable treatment arm and applicable Baseline TLFS grade.

Table 16: Responder rate (BLE) at primary endpoint (Week 12) – Grades 1, 2 & 3 at Baseline– mITT population

Responders	RHA®3 (N=137)	Control (N=44)
N	137	44
Number of Responders (rate %) [95% CI]	107 (78.1%) [70.5 84.2%]	29 (65.9%) [51.1 - 78.1%]
Number of Not Responders (rate %)	30 (21.9%)	15 (34.1%)

Abbreviations: BLE = blinded live evaluator; CI = confidence interval; mITT = modified intent to treat; N = number of subjects; TLFS = Teoxane Lip Fullness Scale
Responder: Improvement from Baseline of ≥ 1 grade TLFS.
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 TLFS at Visit 4 when compared to pretreatment for the control device should be ≥70%.
95% CI for responder was obtained using Wilson method.
All percentages are based upon the total number of subjects by group with non-missing data for the TLFS at Week 12 (Visit 4).
For subjects lost-to-follow-up or not present at the primary endpoint visit for the TLFS assessment, missing value is imputed using the mean of TLFS grade data at the specific visit for the applicable treatment arm and applicable Baseline TLFS grade.

When considering all subjects with grades 1, 2 and 3 at Baseline, the responder rate for the control device was 65.9% (29/44) with 95% confidence interval [51.1%, 78.1%] as shown in Table 16. Since the responder rate of the control is less than 70%, the pre-specified study success criteria were not met.

A sub-analysis of the responder rate broken down by the grade at Baseline, grade 1 & 2 or grade 3 (Table 17), showed that the responder rate of the co-primary

endpoint was met for grade 1 & 2 at Baseline which is is aligned with the inclusion criteria of the study that led to the approval of the control device. The responder rate of the control was 88.9% (24/27) with 95% confidence interval [71.9%, 96.1%] when grade at Baseline was 1 & 2..

The responder rates at Week 12 for subjects with grade 3 at Baseline were the lowest with 62.3% (43/69) and 29.4% (5/17) in RHA®3 and control groups, respectively (subjects starting with fuller lips).

Table 17: TLFS responder rate (BLE) at primary endpoint (week 12) – Post-hoc analysis with subjects TLFS Grade 1&2 at Baseline and Grade 3 at Baseline – mITT population

Responders	RHA®3	Control
N	68	27
Number of Responders (rate %) [95% CI] for grade 1 & 2 at Baseline	64 (94.1%) [85.8 – 97.7%]	24 (88.9%) [71.9 – 96.1%]
Number of Not Responders for grade 1 & 2 at Baseline (rate %)	4 (5.9%)	3 (11.1%)
N	69	17
Number of Responders (rate %) [95% CI] for grade 3 at Baseline	43 (62.3%) [50.5-72.8%]	5 (29.4%) [13.3-53.1%]
Number of Not Responders for grade 3 at Baseline (rate %)	26 (37.7%)	12 (70.6%)

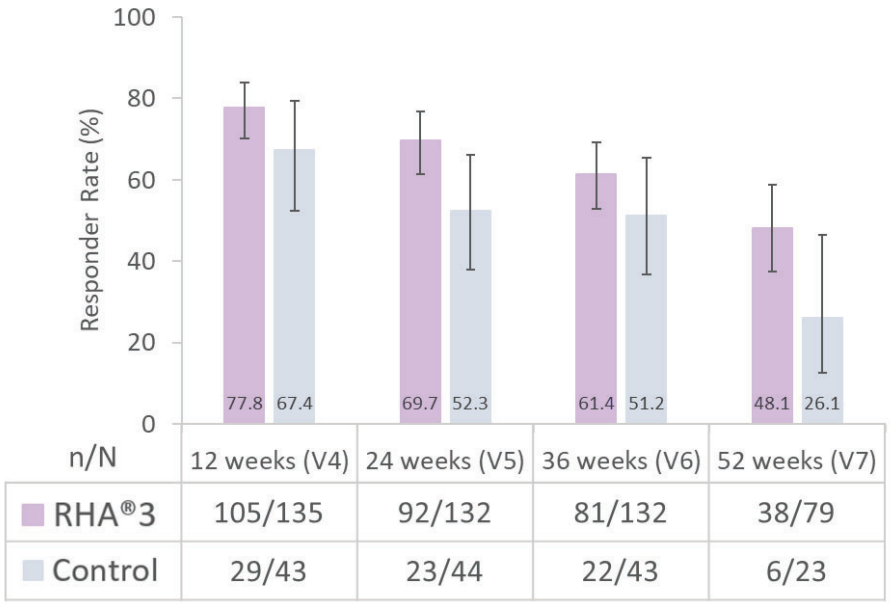
Abbreviations: BLE = blinded live evaluator; CI = confidence interval; mITT = modified intent-to-treat; N = number of subjects; TLFS = Teoxane Lip Fullness Scale

Responder: Improvement from Baseline of ≥ 1 grade TLFS.

95% CI for responder rate was obtained using Wilson method.

All percentages are based upon the total number of subjects by group with non-missing data for the TLFS at Week 12.

Figure 1: TLFS rate of responders (≥1-grade difference from Baseline), as assessed by the Blinded Live Evaluator, throughout the follow-up period (mITT population)



n/N	12 weeks (V4)	24 weeks (V5)	36 weeks (V6)	52 weeks (V7)
RHA®3	105/135	92/132	81/132	38/79
Control	29/43	23/44	22/43	6/23

As anticipated, the responder rate decreased with time, i.e., lip fullness decreased (Figure 1). The responder rate of RHA®3 consistently trended above the responder rate of the control.

The GAI score assessed after RHA®3 injection into the lips (Table 18) were reported as improved or much improved for at least 99% (143/135) of subjects as assessed by the BLE, 100% (135/135) of subjects as assessed by the TI and 92% (125/135) of the subjects as assessed by the subjects at 12 weeks after Baseline. At 52 weeks after Baseline, the GAI score was reported as improved or much improved for at least 73% (58/79) of subjects when assessed by the BLE, 87% (71/81) of subjects when assessed by the TI and 77% (63/81) of subjects when assessed by the subject.

Table 18: GAI scores reported as improved and much improved by the BLE, TI and subjects at 12 and 52 weeks after Baseline – mITT population

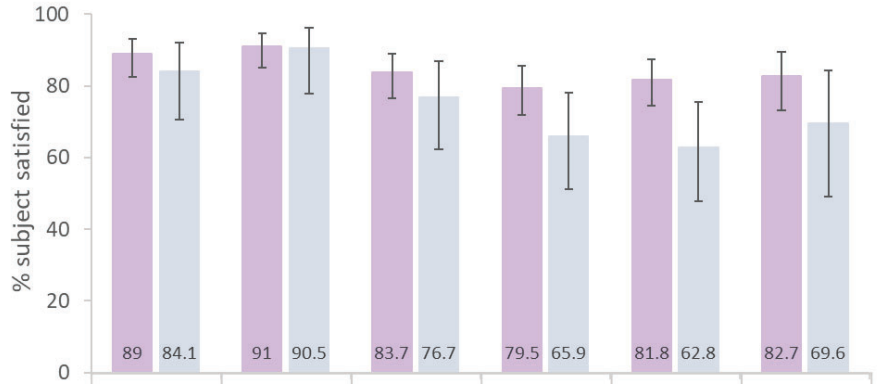
		RHA®3 (N=137)	Control (N=44)
GAI (BLE)			
V4 (W12)	N	135	43
	GAIS responder	134 (99.3%)	41 (95.3%)
V7 (W52)	N	79	23
	GAIS responder	58 (73.4%)	11 (47.8%)
GAI (TI)			

		RHA®3 (N=137)	Control (N=44)
V4 (W12)	N	135	43
	GAIS responder	135 (100%)	42 (97.7%)
V7 (W52)	N	81	23
	GAIS responder	71 (87.7%)	16 (69.6%)
GAI (Subject)			
V4 (W12)	N	135	43
	GAIS responder	125 (92.6%)	34 (79.1%)
V7 (W52)	N	81	23
	GAIS responder	63 (77.8%)	16 (69.6%)

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 lips* and *Satisfaction with outcome* domains of the validated FACE-Q© patient-reported outcome measurement questionnaire. At all time points, for all subjects in RHA®3 treatment group, scores were higher than pre-injection scores, indicating subject-perceived improvement in the appearance of their lips (including when they smiled) and generally with the outcome of their treatment. For the *Satisfaction with lips* domain, the mean score improved from 32 to more than 69, and for *Satisfaction with outcome* domain, the mean score was always greater than 73 (due to the design of the question specific to outcome, there were no Baseline scores), throughout the follow-up period.

Subject satisfaction was similar between RHA®3 and the control device with a trend of higher satisfaction with RHA®3 versus control with time (Figure 2). More than 83% (113/135) of subjects reported to be satisfied or very satisfied 12 weeks after initial treatment with RHA®3 and the rate of satisfaction remained more than 79% throughout the study. Both RHA®3 and its control demonstrated high degree of satisfaction with the treatment across all time points.

Figure 2: Subject satisfaction (satisfied or very satisfied) (mITT population)



n/N	4 weeks (V2)	8 weeks (V3)	12 weeks (V4)	24 weeks (V5)	36 weeks (V6)	52 weeks (V7)
RHA®3	121/136	122/134	113/135	105/132	108/132	67/81
Control	37/44	38/42	33/43	29/44	27/43	16/23

3. Subgroup Analyses

Treatment cohorts were stratified based on Fitzpatrick skin type, ethnicity and age groups.

As there were a small number of male subjects (1.5% - 3/202), no subgroup analysis could be performed by sex. The indication which is for lip fullness is not an indication that would typically be sought after by male patients. Hence the limited number of male subjects in the study is representative of the user population and does not impact the conclusions of the study.

Safety

Subgroup analysis of ADEs by Fitzpatrick skin type (FST) showed that FST were not correlated with treatment group and there were similar trends of rate of ADEs in RHA®3 treatment group between Fitzpatrick skin type I-III and IV-VI.
Similarly, subgroup analysis of ADEs by ethnicity showed that ethnicity was not correlated with treatment group and there were similar trends of rate of ADEs in RHA®3 treatment group between Hispanic and Non-Hispanic subjects.

Subgroup analysis of ADEs by age showed that that age was not correlated with treatment group and there were similar trends of rate of ADEs in RHA®3 treatment group between age subgroups.

Effectiveness at the primary endpoint

Subgroup analysis by Fitzpatrick skin type (I-III vs IV-VI) of the TLFS change from Baseline and the responder rate at the primary endpoint showed that the TLFS

change from Baseline and the responder rate were not impacted by Fitzpatrick skin type.

Similar analysis by ethnicity (Hispanic vs non-Hispanic) showed that the TLFS change from Baseline and responder rate at the primary endpoint were slightly lower for non-Hispanic (71.4%, 75/105) than for Hispanic (100%, 30/30) subjects.

Similar analysis by age groups showed that TLFS change from Baseline and responder rate at the primary endpoint were similar for all age groups.

Comparative safety and effectiveness assessments between genders could not be adequately conducted due to the small number of male subjects enrolled into the study.

4. Pediatric Extrapolation

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

E. 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 G200102 included 7 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.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

None

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

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

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The TLFS was used in live evaluations to assess effectiveness. Overall intra- and inter-rater agreement for the TLFS were above the threshold commonly used to demonstrate validity of a scale. However, when the intra- and inter-rater agreement of each grade were assessed on a grade-by-grade basis, the validation study demonstrated that the intra- and inter-rater agreement did not meet the FDA requirements used to demonstrate validity at Grade 4. As such, there is uncertainty about the validity of the effectiveness scale for Grade 4. A post-approval validation study, outlined in Section XIV, is intended to address this uncertainty.

Study results demonstrated that RHA®3 was non-inferior to its control at 12 weeks after treatment for lip augmentation and lip fullness in terms of mean change from Baseline when administered as an initial treatment followed by optimization of correction via optional touch-up treatment in adults aged 22 years or older.

However, although proportion of responders at 12 weeks after RHA®3 treatment was above 70% (78.1%, 107/137), subjects treated with the control had a 65.9% (29/44) responder rate 12 weeks after treatment, which was below the ≥70% threshold of the co-primary endpoint. Post-hoc analysis showed that by limiting the analysis to subjects with a Baseline TLFS grade of 1 and 2 (and thus, excluding subjects with TLFS grade 3 at Baseline) to be consistent with how the control had been studied to obtain its approval, responder rates were 94.1% (64/68) and 88.9% (24/27) in the RHA®3 and control groups, respectively, as assessed by BLE. The responder rate of subjects with grade 3 at Baseline was higher in RHA®3 group than in the control group: 62.3% (43/69) and 29.4% (5/17) respectively.

Lastly, RHA®3 injected into the lips provided high levels of aesthetic improvement, responder rates were high, as assessed by the BLE and the TI, and showed a decrease over time, indicating an expected loss of treatment effect with time. Subject satisfaction was maintained above 79% throughout the study, with 82.7% of subjects satisfied one (1) year after the treatment. Improvement of FACE-Q scores with *Satisfaction with Lips* and *Satisfaction with outcome* remained steady and above Baseline throughout the study.

B. Safety Conclusions

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

Study treatment with RHA®3 appeared to be safe and well tolerated. There were no reports of deaths, Serious Adverse Events that were treatment related or Unexpected Adverse Device Effects in the study.

Adverse Device Effects rates were not negatively correlated with Fitzpatrick skin type or with ethnicity.

All Adverse Device Effects were types of events that are typical for the injection of dermal fillers, the onset of all events was temporally associated with a recent injection of a study device, and all events were mild or moderate in intensity (no severe Adverse Device Effects were reported). There were no late onset Adverse Device Effects, and no events were deemed to be a granuloma. 36% (39/108) of the Adverse Device Effects were resolved in 3 days and 67% (72/108) in 14 days.

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 study was randomized, double blinded, between subject, multicenter and prospective, utilizing a scale (TLFS) assessed by a Blinded Live Evaluator to determine the primary effectiveness endpoint. This study design reduces bias for determining an aesthetic outcome. Study results demonstrated that RHA®3 was non-inferior to its control at 12 weeks after treatment for lip augmentation and lip fullness in terms of mean change from Baseline when administered as an initial treatment followed by optimization of correction via optional touch-up treatment in adults aged 22 years or older. Adverse Device Effects were all typical and expected in association with injection of a dermal filler, and did not occur at rates different from those expected. Subjects reported high levels of satisfaction with their results, as assessed by multiple evaluation tools. Long term benefit and risks determinations related to male subjects were supported and leveraged by the prior clinical studies of RHA®3 with lidocaine. No new or unanticipated risks or adverse events were identified.

Patient Perspectives

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 lips* and *Satisfaction with outcome* domains of the validated FACE-Q© patient-reported outcome measurement
- Subject satisfaction survey

In conclusion, given the available information above, the data support the use of RHA®3 for injection in the vermillion body, vermillion border and oral commissures to achieve lip augmentation and lip fullness in adults aged 22 years or over, and 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 benefits and

risks of dermal fillers are sufficiently well understood for patients to make informed decisions about their use.

XIV. CDRH DECISION

CDRH issued an approval order on October 27, 2023.

The final conditions of approval cited in the approval order are summarized below.

The Post-Approval Study for the validation of the Teoxane Lip Fullness Scale (TLFS) will include two protocols:

- Live scale validation
- Photographic scale validation

Subjects will follow these demographic requirements (for photographic and live validation):

- All grades of the scale should be represented
- At least 20% of subjects with Fitzpatrick Skin Type (FST) IV-VI
- At least 10% of subjects with FST V/VI including subjects with FST V and FST VI
- At least 10% of subjects of Hispanic ethnicity
- At least 3% of subjects of Asian descent

Live validation:

- 80 to 150 subjects
- 5 to 15 independent scale evaluators

Photographic validation:

- 75 to 150 subject photographs
- 3 to 8 independent scale evaluators

Each validation will include two sessions 14 to 30 days apart.

Data analysis and acceptance criteria for photographic and live validation:

- Intra-rater kappa per Cichetti-Allison formula: overall mean (all raters) >0.70 (2-sided 95% confidence interval for information)
- Inter-rater: Intraclass Correlation Coefficient (ICC): overall criteria ICC >0.70 (2-sided 95% confidence interval for information)
- Percentage of intra-rater and inter-rater exact agreement:
  - Overall (all raters, all grades): ≥70% 2-sided 95% confidence interval for information)
  - For each grade all raters): ≥70% 2-sided 95% confidence interval for information)

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

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.