SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Injectable Dermal Filler

Device Trade Name: RHA® Redensity™

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

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

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P170002/S012

Date of FDA Notice of Approval: December 22, 2021

The original PMA for RHA®2, RHA®3 and RHA®4 (P170002) was approved on 10/19/2017. The devices are indicated 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 NLF indication is available on the CDRH website and is incorporated by reference here. RHA® Redensity™ is being submitted as a panel-track supplement (P170002/S012) to the RHA® PMA, P170002, to request changes in design or performance of the device, and a new indication for use of the device. The current supplement was submitted for RHA® Redensity™ for injection into the dermis and superficial dermis of the face, for the correction of moderate to severe dynamic perioral rhytids, in adults aged 22 years or older.

II. INDICATIONS FOR USE

RHA® Redensity™ is indicated for injection into the dermis and superficial dermis of the face for, the correction of moderate to severe dynamic perioral rhytids, in adults aged 22 years or older.

III. CONTRAINDICATIONS

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

IV. WARNINGS AND PRECAUTIONS

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

V. DEVICE DESCRIPTION

RHA® Redensity™ is a viscoelastic, sterile, non-pyrogenic, clear, colorless, and biodegradable gel implant of both crosslinked and non-crosslinked hyaluronic acid. It is produced with sodium Hyaluronic Acid (NaHA) with a concentration of 15 mg/g obtained from bacterial fermentation using a *Streptococcus equi* bacterial strain, crosslinked with 1,4-butanediol diglycidyl ether (BDDE) and reconstituted in a physiological buffer (pH 7.3). It contains 0.3% lidocaine hydrochloride to reduce pain on injection.
The product is supplied in a 1 ml syringe, with two 30G ½ inch hypodermic needles.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of moderate to severe dynamic perioral rhytids. Alternatives in the treatment of moderate to severe dynamic perioral rhytids include invasive surgery (face-lift, rhytidectomy, etc.).

Less invasive alternatives include injection of other hyaluronic acid dermal fillers or autologous fat transfer.

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® Redensity™ is the least crosslinked device (combined with noncrossed linked chains) of the RHA® range which also comprises RHA®2, RHA®3 and RHA®4 which received FDA approval in 2017. RHA® Redensity™ is available in the European Union and in more than 40 countries around the world. It has not been withdrawn from marketing 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 effects (e.g., complications) associated with the use of the device.

Common treatment responses which can occur with the use of RHA® Redensity™, and other dermal fillers, include (in alphabetical order): 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 study.

In addition to the common treatment responses noted above, the following adverse events were reported for RHA® Redensity™ as part of the post-marketing surveillance outside the United States. These treatment reactions occurred when RHA® Redensity™ was used for a wide range of indications, including but not limited to perioral rhytids. The following adverse events were reported with a prevalence equal or superior to 1 occurrence for 100,000 syringes: edema, injection site masses (lumps and bumps), inflammatory nodules (papules), skin swelling, skin induration, vascular skin disorder (such as vessel compression/occlusion), pain, ecchymosis, and inflammatory reaction. Additionally, other less frequent adverse reactions have also been reported, and include dermal filler overcorrection, allergic reaction, product misplacement, skin discoloration, skin necrosis, erythema, granuloma, injection site movement impairment, paraesthesia, skin atrophy and tenderness.

In many cases the symptoms resolved without any treatment. Reported treatments and procedures included the use of (in alphabetical order): analgesics, antibiotics, anti-histamines, anti-inflammatories, anti-viral, implant dissolution (hyaluronidase), drainage, excision, incision, massage, and vasodilators. For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

RHA® Redensity™ was extensively tested and characterized through physical and chemical testing (Table 1), and biocompatibility studies (Table 2). Preclinical testing results were adequate to support the initiation of a human clinical study of the dermal filler and to support a PMA.

A. Laboratory Studies

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

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

Test	Purpose	Results
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
Gel content	To ensure gel meets specifications	Passed

B. Biocompatibility Studies

Table 2: Summary of biocompatibility studies for RHA® Redensity™

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	Level of reactivity slightly less than its control*. Slightly irritant at 3 days. RHA® Redensity™ was non-irritant at Day 4.
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.
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 article was classified as non-irritant. No adverse response

Test	Method	ISO Standard	Results
			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 to RHA® Redensity™

The 4 and 13 weeks systemic toxicity studies did not evidence signs of systemic toxicity after short or medium term exposure of RHA® Redensity™. Extensive literature review of the materials used for the manufacturing of RHA® Redensity™ concluded that no studies or reports were found indicating that the materials or their degradation products should pose a significant risk of chronic systemic toxicity in animals or humans. Therefore, there was no biological risks associated with chronic systemic toxicity.
The tumorigenic potential of RHA® Redensity™ was not considered to be a biological risk based on the following data:

- The three-test battery of genotoxicity carried out on RHA® Redensity™ demonstrated that the formulation was not genotoxic
- Absence of known toxicological concerns related to genotoxicity and/or carcinogenicity regarding hyaluronic acid
- While the crosslinker (BDDE) is known to be mutagenic and associated with tumor formation in mice in one study, based on the residual amount of BDDE in the finished product, Teoxane concluded that the carcinogenicity risk related to the presence of the BDDE in RHA® Redensity™ was negligible.

C. Additional Studies

Stability data have been collected for a 36 month period, 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. Conformity of real-time aged product with all specifications was confirmed.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of injection into the dermis and superficial dermis of the face with RHA® Redensity™, for correction of moderate to severe dynamic perioral rhytids, in adults aged 22 years or older. The clinical study investigated the correction of dynamic perioral rhytids which are wrinkles that are intrinsically dynamic wrinkles. Dynamic perioral rhytids are formed upon the subject mouth's movements and grounds of facial expressions. With aging, the repeated perioral movements combined with muscle atrophy and loss of skin elasticity, lead to the genesis of the perioral rhytids in the perioral area. In addition, as a secondary endpoint, the study included the evaluation of the perioral rhytids per the validated modified Glogau scale which further support using the qualitative "dynamic" in the indication.
The study was conducted in the US and in Canada under IDE # G160123. Data from this clinical study was the basis for the PMA supplement approval decision. Results from the clinical study

and the layout of Teoxane proprietary validated Perioral Rhytids Severity Rating Scale (PR-SRS) have been published in the Journal Dermatologic Surgery (Sundaram et al., *Efficacy and Safety of a New Resilient Hyaluronic Acid Filler in the Correction of Moderate-to-Severe Dynamic Perioral Rhytids: A 52-Week Prospective, Multicenter, Controlled, Randomized, Evaluator-Blinded Study.* 2022, Dermatologic Surgery). https://pubmed.ncbi.nlm.nih.gov/34608092/. A summary of the clinical study is presented below.

A. Study Design

Subjects were treated and followed-up between December 20, 2016 and January 8, 2019. The database for this PMA reflected data collected for 150 treated subjects and 52 untreated controls. There were 6 US and 2 Canadian investigational sites.

This study was randomized, blinded, No-Treatment control, multicenter, and prospective. The Treatment group was compared to a No-Treatment group of subjects. The No-Treatment group of subjects were followed until the primary endpoint for the Treatment group was met, at which time the No-Treatment group received their first treatment and subsequently followed the same treatment schedule as the Treatment group. Subjects meeting the inclusion/exclusion criteria were randomized 3:1 to the Treatment or No-Treatment groups.
Overall study duration was 17 months and included retreatment. If deemed necessary by the Treating Investigator (TI), subjects may receive a touch-up treatment 2 weeks after their initial treatment to achieve optimal correction. In addition, subjects were eligible for optional retreatment if necessary at Weeks 12, 16, 24 and 36. Refer to Table 3 for additional information about retreatment. All subjects were offered repeat treatment at 52 weeks after their initial treatment or touch-up treatment and were then followed for another 4 weeks.

1. Key Clinical Inclusion and Exclusion Criteria

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

- Outpatient, male or female of any race, 22 years of age or older.
- Moderate to severe perioral rhytids of grade 2 or 3 on the four-point PR-SRS (ranging from 0-3).
- Willing to abstain from facial aesthetic procedures/therapies that could interfere with study evaluations for the duration of the study.
- Able to follow study instructions and complete all required visits.

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

- Female subjects who were pregnant, breast-feeding, or of childbearing potential and not practicing reliable birth control.
- Known hypersensitivity or previous allergic reaction to any component of the study devices.
- Use of a prohibited treatment/procedure within certain time periods.

- Known sensitivity to local anesthetics of the amide type, history of multiple severe allergies, or history of anaphylactic shock.
- Known susceptibility to keloid formation, hypertrophic scarring or clinically significant skin pigmentation disorders (TI discretion).
- Clinically significant active skin disease within 6 months prior to study entry (TI discretion).
- History of active chronic debilitating systemic disease that in the opinion of the investigator, would make the subject a poor candidate in the study.
- History of connective tissue disease.
- Malignancy (excluding non-melanoma skin cancer) within the past 5 years.
- Need for clinically significant (TI discretion) and continuous medical treatment within 2 weeks prior to initial visit.
- History or presence of condition or feature that may confound the interpretation of the results in the perioral region, for example, tattoo, significant facial hair, acne scaring, prior surgery in the area, potential for active disease or infection flare up such as herpes simplex.
- Herpes simplex lesion flare-ups greater than 6 per year.
- History of skin cancer in the treatment area
- Elective, clinically significant facial procedures that may confound the interpretation of the results in the perioral region prior to study enrollment.
- Clinically active disease or infection in the perioral area or mouth (e.g., dental abscess).
- Subjects with known prolonged bleeding times because of disease or medication.
- 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.
- Have dentures or any device covering all or part of the upper palate, and/or severe malocclusion, dentofacial or maxillofacial deformities, or significant asymmetry of the perioral area.
- Subjects seeking lip augmentation.
- Exposure to any other investigational drug/device within 90 days of entering the study.
- Clinically significant alcohol or drug abuse, or history of poor cooperation or unreliability.

2. Follow-up Schedule

At Visit 1, subjects randomized to the "treatment group" received injections of RHA® Redensity™ into the dermis including the superficial dermis, to treat moderate to severe dynamic perioral rhytids. Injection technique and depth of injection were at the discretion of the Treating Investigator (TI). The TI administered the study device to the upper and lower perioral area, including as necessary, into the vermillion border of the lip. The focus of the study was to treat the perioral rhytids, and there was no augmentation of the lips. The maximum volume of administration was 6.0 mL per treatment session (max 3.0 mL above the upper lip, and max 3.0

below the lower lip).

After 2 weeks, additional touch-up correction with RHA® Redensity™ was provided, if deemed necessary by the TI.

Following any injection (initial, touch-up, retreatment), subjects were given a 14-day diary to daily record Common Treatment Responses (CTR) and any other adverse reactions. 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, 16, 24, 36, and 52 weeks after the last treatment (initial or touch-up) and 4 weeks after a retreatment. Refer to Table 3.

The primary effectiveness endpoint of the study (PR-SRS) was evaluated at 8 weeks by a Blinded Live Evaluator (BLE). Subjects were followed until 52 weeks to evaluate long term safety, safety of retreatment and other secondary endpoints. Subjects were offered optional retreatment if there was a significant loss of correction (i.e., severity of perioral rhytids returned to pre-treatment level) at 12, 16, 24 or 36 weeks after last treatment. Furthermore, retreatment was offered to all subjects attending the study visit at Week 52.

The design included a No-Treatment group of subjects who were followed until the primary endpoint (8 weeks), at which time they received their first treatment and then followed the same treatment schedule as the initial group.

Table 3: Treatment schedule

Treatment group	**No-Treatment group up to primary endpoint**	**No-Treatment group After primary endpoint(5)**
V1 – Visit 1 – Initial injection	V1	V1b
V2 – Visit 2 – 2 weeks	V2	V2b
V3 – Visit 3 – 4 weeks[1]	V3	V3b
V4 – Visit 4 – 8 weeks[2] Primary endpoint	V4	V4b
V5 – Visit 5 – 12 weeks[2,3]	N/A	V5b
V6 – Visit 6 – 16 weeks[2,3]		V6b
V7 – Visit 7 – 24 weeks[2,3]		V7b
V8 – Visit 8 – 36 weeks[2,3]		V8b
V9 – Visit 9 – 52 weeks[4] Exit visit or repeat treatment		V9b
V9x – Visit 9x – 4 weeks after repeat treatment		V9bx

([1]) optional touch up if deemed necessary by the Treating Investigator
([2]) after last treatment may be V1 (initial treatment) or V2 (touch-up treatment)
([3]) optional early repeat treatment in case of significant loss of correction
([4]) repeat treatment offered to all subjects
([5]) No treatment group received treatment after the first 8 weeks of their participation to the study and followed the same schedule as the Treatment group. V1/V1b means that the population of the Treatment group and the No-Treatment group after they had received treatment was pooled.

3. Clinical Endpoints

Safety was evaluated through a 14-day patient Common Treatment Response (CTR) diary (after each injection), assessment of lip function, measurements of injection site pain, and Adverse Events (AEs) assessments at each visit. Subjects recorded the presence, duration, and severity of CTRs that may occur following the injection of RHA® Redensity™, for the first 14 days after each treatment (initial, touch-up, and retreatment(s)) in a patient diary. CTRs that were present on the last day of diary entry, regardless of severity and duration, were automatically recorded as AEs. The TI assessed all AEs and recorded the description (sign, symptom, or diagnosis), duration, seriousness, severity, cause and relationship to the study device and action taken. For statistical analysis, the maximal severity reported for the AE was recorded, even if the AE presented as being less severe at some point during the event.

Effectiveness was measured by assessing the aesthetic improvement from pre-injection (Baseline), based on Teoxane validated and proprietary Perioral Rhytids Severity Rating Scale (PR-SRS) (Table 4 and Figure 1), as evaluated by the BLE at 8 weeks after baseline. A subject was considered to be a PR-SRS responder if he/she presented with ≥1-point improvement from pre-treatment (Baseline).

Table 4: Perioral Severity Rating Scale (PR-SRS)

Grade	Name	Description
0	Absent	No lines
1	Mild	Shallow lines
2	Moderate	Deeper lines
3	Severe	Deepest lines

Figure 1: Teoxane PR-SRS scale

The primary effectiveness objective was to demonstrate superiority of RHA® Redensity™ implant versus No-Treatment at 8 weeks based on the responder rate. A PR-SRS change of ≥ 1-grade was considered clinically significant.

Secondary/exploratory effectiveness endpoints included evaluation and comparison of perioral rhytids severity in the RHA® Redensity™ treatment group versus No-Treatment control, using the validated FACE-Q© patient-reported outcome measurement, Global Aesthetic Improvement (GAI) as assessed by the BLE, TI and subject, subject satisfaction, and Natural Look and Feel as assessed by the subject. Blinded Live Evaluators and the TI at each site evaluated dynamic wrinkles through use of the modified Glogau Scale. Validation data was provided to support the use of the modified Glogau Scale.

Development and validation of the TEOXANE Perioral Rhytid-Severity Rating Scale (PR-SRS)

Photographs used for the creation of TEOXANE PR-SRS (TEO 04-2016) were obtained from subjects with a wide range of severity of their perioral rhytids. Subjects had given authorization for the release of their photograph and the photographs were taken by a qualified photographic vendor to ensure consistency and reproducibility of the process. A group of experts in facial aesthetics with relevant experience used approximately 171 photographs to develop the 4 grades of the scale and identify the photographs that would be representative of each grade. Each grade was given a number with a photograph as a frontal view. The photograph was cropped to keep only the mouth and the perioral area showing the perioral rhytids. A minimal text description was added to complement the scale as shown in Figure 1.

The group of experts who developed the scale selected a set of 48 photographs to serve as the validation set and covering the full range of the grades. A "true" rating was assigned for each photograph of the validation set by the group of scale developers. Another independent group of experience Board certified dermatologists and plastic surgeons were selected and trained to validate the scale and were called the "Scale Validation group".

Two cycles of validation were performed at least 14 days apart to assess Intra-Rater consistency, as well as Inter-Rater agreement by each member of the Scale Validation group. For each of the validation cycle, the photographs were randomized in different order.
The Intra-Rater Kappa Statistics were all ≥0.9144 (overall 0.9416). The Inter-Rater Kappa Statistic was 0.7765.
The validation process was performed a second time with photographs of subjects from a wider range of ethnic diversity. The overall Intra-Rater Kappa was 0.9501 and Inter-Rater Kappa was 0.8642. In addition, a supplementary analysis was performed to assess the percentage agreement with the "true" grades. Agreement with the true grade was 91.7% the first time and 95.3% the second time the validation was performed.
As both the Intra-Rater and the Inter-Rater kappa scores met their pre-determined acceptance criteria the validation was performed, the proprietary TEOXANE PR-SRS scale TEO 04-2016 was demonstrated to be repeatable and reproducible. The scale was considered validated and suitable for use for various clinical studies, including evaluation of primary endpoint to measure the effectiveness of the injection of RHA® Redensity™ for the correction of moderate to severe perioral rhytids.

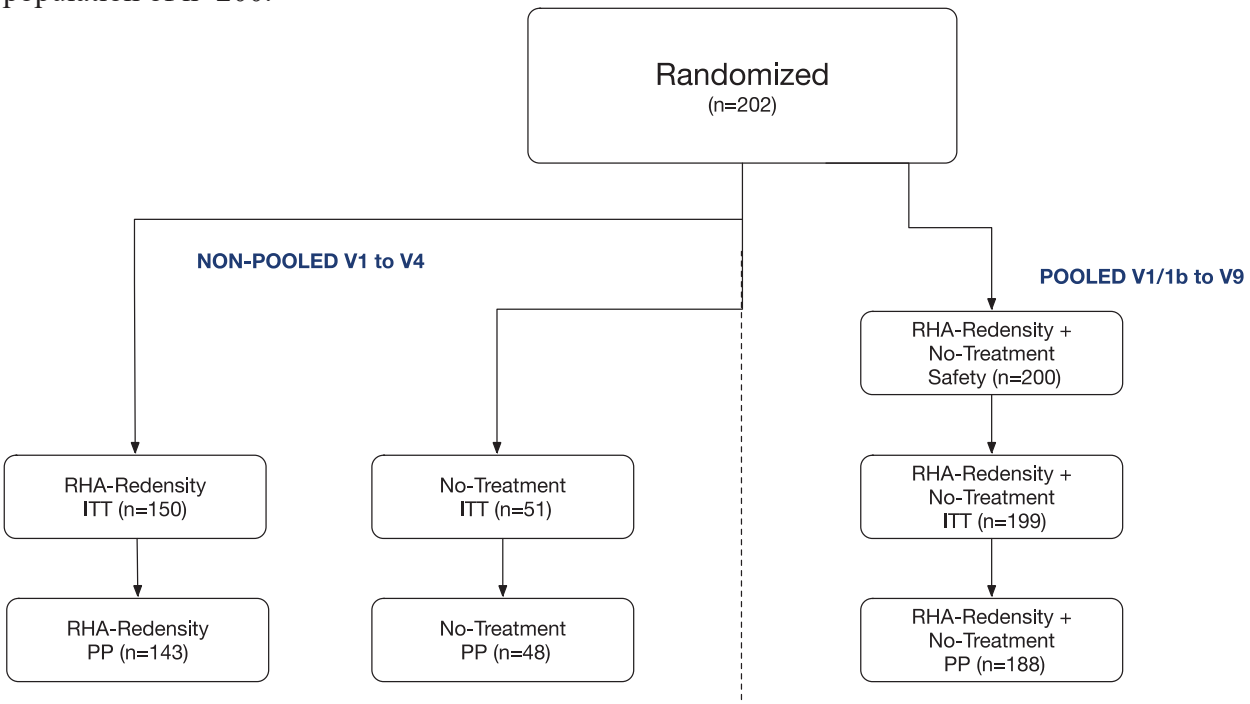
B. Accountability of PMA Cohort

A total of 202 subjects were randomized with 150 subjects allocated to RHA® Redensity™ and 52 subjects allocated to No-Treatment control (non-pooled populations) (Figure 2).
As the latter subjects were injected with RHA® Redensity™ after the evaluation of the primary endpoint, both groups were then co-evaluated for other effectiveness and safety endpoints, making up the "pooled population".

One subject randomized to No-Treatment control received treatment and was placed in the Safety population for safety evaluations, but not included in the Intent-To-Treat (ITT) or Per Protocol (PP) populations for effectiveness analyses resulting in an ITT population (non-pooled population) with 201 subjects (RHA® Redensity™ n=150, No-Treatment control n=51). A total of 7 subjects were excluded from the RHA® Redensity™ PP population, and 3 subjects were excluded from the No-Treatment control, resulting in a PP population sample size of n=191 (Non-Pooled population; RHA® Redensity™ n=143, No-Treatment control n=48).

For the pooled population, 3 subjects were excluded from the pooled ITT population (n=199). A further 11 subjects were excluded from the RHA® Redensity™ PP population resulting in a pooled PP population sample size of n=188.

The Safety population consists of all subjects who received at least one treatment with the study device. Of the 202 randomized subjects, 2 subjects did not receive treatment, resulting in a Safety population of n=200.



Legend: "V" stands for "Visit". Refer to Table 3 for the description of the treatment schedule
V1/1b means the population from the Treatment group and the population from the No-Treatment group after they received treatment

Figure 2: Disposition of subjects

C. Study Population Demographics and Baseline Parameters

The mean age of subjects was approximately 61 years, with the majority of subjects being female (98%) and Caucasian (96%). All Fitzpatrick skin types were appropriately represented with approximately 72.8% and 27.2% of subjects being of skin types I-III and types IV-VI, respectively. There were no statistically significant or notable differences between the demographics of the subject population enrolled in the US (n=163) compared to the population enrolled in Canada (n=39).

More than 27% of subjects in the study presented Fitzpatrick skin type IV to VI which is representative of real-world experience as it is consistent with the American Society of Plastic Surgeons (ASPS) data: of the 13.3M cosmetic minimally invasive procedures that took place in 2020, 78% were for soft tissue fillers in Caucasian patients, 5% were in African-American, 5% in Asian/Pacific Islander, 10% in Hispanic and 1% in other patients.
(https://www.plasticsurgery.org/documents/News/Statistics/2020/plastic-surgery-statistics-full-report-2020.pdf)

Table 5: Demographic characteristics at Baseline

Demographic Variable	RHA® Redensity™ *n=150*	No-Tx *n=52*
Age (years)		
Mean ± SD [95% CIs]	61.6 ± 7.2 [60.4, 62.7]	60.7 ± 7.6 [58.6, 62.8]
Min, Max	38, 81	46, 77
Gender		
Female	147 (98.0%)	51 (98.1%)
Male	3 (2.0%)	1 (1.9%)
Race		
White	143 (95.3%)	52 (100.0%)
Black or African American	4 (2.7%)	0 (0.0%)
American Indian or Alaska Native	1 (0.7%)	0 (0.0%)
Asian	2 (1.3%)	0 (0.0%)
Nat. Hawaiian, Other Pacific Islander	0 (0.0%)	0 (0.0%)
Other	0 (0.0%)	0 (0.0%)
Ethnicity		
Hispanic or Latino	25 (16.7%)	10 (19.2%)
Not-Hispanic or Latino	125 (83.3%)	42 (80.8%)
Fitzpatrick Skin Type		
I	18 (12.0%)	6 (11.5%)
II	37 (24.7%)	13 (25.0%)
III	55 (36.7%)	18 (34.6%)
IV	29 (19.3%)	12 (23.1%)
V	8 (5.3%)	3 (5.8%)
VI	3 (2.0%)	0 (0.0%)

The overall total mean volume of RHA® Redensity™ injected to achieve optimal correction results was 2.8 ml. The proportion of subjects who received touch-up treatment with RHA® Redensity™ at Week 2 was 68.1%.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the Safety pooled population (i.e. population from the Treatment group + population of the No-Treatment group after their received treatment after the primary endpoint). The Common Treatment Responses for this study are presented below in Table 6 and Table 7. Adverse effects are reported in Table 8 and Table 9.

Safety of the RHA® Redensity™ product was evaluated through a 14-day patient Common Treatment Response (CTR) diary which was completed after each injection, AE assessments and lip functionality at each visit, and measurement of injection site pain.

Common Treatment Responses (CTR) after Initial Treatment

CTR data for initial treatment are presented in Table 6 and Table 7 below. Similar findings were noted following touch-up and retreatments.

Nearly all subjects (87.9%, 175/199 after initial treatment) reported at least 1 CTR. The most frequently reported CTR were bruising (77.4%, 154/199), swelling (73.4%, 146/199), redness (65.8% 131/199), firmness (57.8%, 115/199) and lumps/bumps (57.8%, 115/199). Other common CTRs were tenderness (52.8%, 105/199), discoloration (47.2%, 94/199), pain (27.1%, 54/199) and itching (15.6%, 31.199). For the majority of CTRs that occurred with initial treatment, severity was reported as "Mild" or "Moderate". More than 76% of the CTRs had resolved by Day 7. Nearly 90% of CTRs had resolved by Day 14 without treatment. Other than lumps/bumps, each type of CTR that was present on the last day of the 14-Day diary was present in less than 10% of subjects. For nearly all CTRs (more than 92%), the maximal severity reported was "Mild" or "Moderate". Less than 6% of each CTR type was assessed by the subject as severe except for bruising. For bruising, a total of 24 (12.1%) of subjects assessed this CTR as "severe". However, of the Bruising CTRs that were elevated to AE status (because they were present on the last day of the diary), all were deemed by the Investigator (clinical interpretation) as mild other than 3 that were deemed as moderate. None of the Bruising AEs were deemed by the Investigators as being "severe". Similar findings were noted regarding touch-up and repeat treatments.

Table 6: CTRs by Severity after initial treatment - V1/1b – Pooled Analysis

		Maximum Severity within 14 Days			
CTR	**≥1 CTR**	**Mild**	**Moderate**	**Severe**	**# of subjects with no CTR**
Redness	131 (65.8%)	84 (42.2%)	42 (21.1%)	5 (2.5%)	68 (34.2%)
Pain	54 (27.1%)	39 (19.6%)	13 (6.5%)	2 (1.0%)	145 (72.9%)
Tenderness	105 (52.8%)	83 (41.7%)	19 (9.5%)	3 (1.5%)	94 (47.2%)
Firmness	115 (57.8%)	79 (39.7%)	33 (16.6%)	3 (1.5%)	84 (42.2%)
Swelling	146 (73.4%)	85 (42.7%)	49 (24.6%)	12 (6.0%)	53 (26.6%)
Lumps/Bumps	115 (57.8%)	71 (35.7%)	34 (17.1%)	10 (5.0%)	84 (42.2%)
Bruising	154 (77.4%)	65 (32.7%)	65 (32.7%)	24 (12.1%)	45 (22.6%)
Itching	31 (15.6%)	26 (13.1%)	3 (1.5%)	2 (1.0%)	168 (84.4%)
Discoloration	94 (47.2%)	49 (24.6%)	34 (17.1%)	11 (5.5%)	105 (52.8%)

All percentages are calculated based on 199, which is the total number of subjects who provided diary answers after V1/1b.

V1/1b means all the subjects at Visit 1 (V1) from the Treatment group after their initial treatment and at Visit 1b (V1b) from all subjects of the No-Treatment group once they received their initial treatment (V1b) after reaching the primary endpoint at V4 (8 weeks). See Table 3 for visit schedule. In other words, V1/1b subjects are all subjects pooled from the entire study who received an initial treatment (from the Treatment and No-Treatment group)

Of the 945 CTRs that occurred with initial treatment, 722 (76.4%) had resolved by post-injection Day 7. Other than Lumps/Bumps, each type of CTR (e.g., redness, tenderness etc.) was present on the last day of the 14-Day diary for less than 10% of the subjects. For Lumps/Bumps, 26 (13.1%) subjects presented with this CTR on the last day of the diary. Similar findings were noted regarding touch-up and repeat treatments.

Table 7: CTRs by Duration – Initial Treatment – V1/1b – Pooled analysis

	Duration (days)			
CTR	**1-3**	**4-7**	**8-14**	**CTR Last Day Diary**
Redness	78 (39.2%)	35 (17.6%)	18 (9.0%)	8 (4.0%)
Pain	38 (19.1%)	10 (5.0%)	6 (3.0%)	1 (0.5%)
Tenderness	55 (27.6%)	29 (14.6%)	21 (10.6%)	10 (5.0%)
Firmness	63 (31.7%)	24 (12.1%)	28 (14.1%)	18 (9.0%)
Swelling	72 (36.2%)	40 (20.1%)	34 (17.1%)	10 (5.0%)
Lumps/Bumps	53 (26.6%)	29 (14.6%)	33 (16.6%)	26 (13.1%)
Bruising	30 (15.1%)	64 (32.2%)	60 (30.2%)	15 (7.5%)
Itching	21 (10.6%)	8 (4.0%)	2 (1.0%)	3 (1.5%)
Discoloration	39 (19.6%)	34 (17.1%)	21 (10.6%)	5 (2.5%)

All percentages are calculated on n=199, which is the total number of subjects who provided diary answers after V1/1b

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 (14-day rule). Overall, for CTRs that were automatically elevated to the level of an AE after 14 days, the TI determined that none of the AEs were of "severe" intensity.

Treatment Related Adverse Events (TRAEs)

All Treatment-Related Adverse Events (TRAEs) were the types and frequency of events that are typically experienced following the injection of a dermal filler, 81.7% of those were based on CTR diary entries (present on the last diary day - Table 7), 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 TRAEs were reported). There was no late onset of TRAEs, and no events were deemed to be a granuloma.

Adverse Events incidence rates were not negatively correlated with higher Fitzpatrick skin type.

Table 8 and Table 9 sums up all Treatment Related Adverse Events which occurred throughout the study, i.e. following initial, touch-up or retreatment injections.

Table 8: Treatment Related Adverse Events Overview – V1/1b to V9 – Pooled Analysis

AEs from V1/1b to V9		RHA® Redensity™/No-Tx Pooled
Any TRAE (N=200)	**Subjects**	**73 (36.5%)**
	Events	186
Hispanics/Latino (N=34) any TRAE	**Subjects**	**7 (20.6%)**
	Events	17
Non-Hispanic/Non-Latino (N=166) any TRAE	**Subjects**	**66 (39.8%)**
	Events	169
Age 38-60 years old (N=91) any TRAE	**Subjects**	**33 (36.3%)**
	Events	86
Age 61-81 years old (N=109) any TRAE	**Subjects**	**40 (36.7%)**
	Events	100
Fitzpatrick I-III (N=146) any TRAE	**Subjects**	**46 (31.5%)**
	Events	88
Fitzpatrick IV-VI (N=54) any TRAE	**Subjects**	**18 (33.3%)**
	Events	41
Any TRSAE (N=200)	**Subjects**	**0 (0.0%)**
	Events	0
Any UADE (N=200)	**Subjects**	**0 (0.0%)**
	Events	0

All TRAEs observed throughout the study (including repeat treatment) per the system organ classes (SOC) of General Disorders and Administration Site Conditions are summarized in Table 9.

Table 9: Treatment-Related AEs - V1/V1b to V9 – Pooled Analysis

TRAEs V1/V1b to V9		RHA® Redensity™/No-Tx Pooled	
SOC	**PT**	n=200	**Events**
Any TRAE		**73 (36.5%)**	**186**
Gastrointestinal disorders		**1 (0.5%)**	**1**
	Lip swelling	1 (0.5%)	1
General disorders and administration site conditions		**70 (35.0%)**	**167**
	Deformity	1 (0.5%)	1
	Injection site bruising	21 (10.5%)	27
	Injection site discolouration	12 (6.0%)	12
	Injection site erythema	10 (5.0%)	11
	Injection site hypoaesthesia	3 (1.5%)	4
	Injection site induration	22 (11.0%)	26
	Injection site irritation	1 (0.5%)	1
	Injection site mass	34 (17.0%)	42
	Injection site movement impairment	1 (0.5%)	1
	Injection site pain	12 (6.0%)	19
	Injection site paraesthesia	1 (0.5%)	1
	Injection site pruritus	5 (2.5%)	6
	Injection site scab	1 (0.5%)	1
	Injection site swelling	12 (6.0%)	15
Infections and infestations		**1 (0.5%)**	**2**

TRAEs V1/V1b to V9		RHA® Redensity™/No-Tx Pooled	
SOC	**PT**	n=200	**Events**
	Oral herpes	1 (0.5%)	2
Nervous system disorders		**9 (4.5%)**	**13**
	Headache	7 (3.5%)	9
	Hypoaesthesia	1 (0.5%)	1
	Muscle contractions involuntary	1 (0.5%)	2
	Paraesthesia	1 (0.5%)	1
Skin and subcutaneous tissue disorders		**3 (1.5%)**	**3**
	Acne	1 (0.5%)	1
	Needle track marks	1 (0.5%)	1
	Skin wrinkling	1 (0.5%)	1

Includes all AEs, including those temporarily associated with Repeat-Treatment.

For pooled analysis, only AEs onset on or after initial study treatment are included. Therefore, for No-Treatment group, all AEs with onset date before initial treatment, i.e. V1b date, are excluded from this summary table.

From Visit 1/1b to 9 (Pooled Data), the most common TRAEs were related to the system organ classes (SOC) of General Disorders and Administration Site Conditions where 70 (35.0%) subjects experienced a total of 186 events (Table 8). The events occurring at the highest frequencies were Injection Site Mass (17.0%), Injection Site Induration (11.0%), and Injection Site Bruising (10.5%). Of the 186 Treatment-Related AEs, the vast majority 152 (81.7%) were the results of CTRs that were automatically elevated to Adverse Events with the 14-day rule (i.e. they were still present on the last day of the patient 14-day diary). All other AEs were either reported on the diary by the subject or identified by the TI during a scheduled visit.

All TRAEs appeared to be temporally associated with the recent study device injection. The duration of TRAEs varied from 1 to 90 days except for two:

- a discoloration event at the injection site identified by the TI as a TRAE and which persisted for 384 days. The TI indicated that the discoloration presented as a "Tyndall effect". A "Tyndall effect" is different from hyperpigmentation as it is a bluish discoloration caused by the blue light spectrum scattered by the colloid particle in subjects with very thin skin when the filler is injected too superficially.
- an involuntary muscle contraction (fasciculation, left upper lip) which appeared after re-treatment at Visit 9. It was mild in severity and no treatment was provided. It was persistent and had not improved at the study exit. The investigator followed up three months later and the subject stated it resolved 2 months prior

There were no late onset TRAEs and no events were deemed to be a granuloma.
Additionally, all TRAEs were mild or moderate in severity (no severe events were reported), and the vast majority were typical of the expected signs and symptoms observed following a dermal filler injection. Importantly, none of the TRAEs were considered by the Investigator to be "clinically significant".

There were no reports of TRAEs or Unexpected Adverse Device Effects, no deaths, and no subjects prematurely withdrew due to a Treatment-Related Adverse Event.

Pain at injection

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". The average level of pain noted during initial study device injections was 19.9 mm ± 19.7. Pain appeared to diminish rapidly. At 15-minutes post-injection the average level of pain noted was 3.1 mm ± 8.3. Similar pain response was noted with touch-up injections, repeat-treatments.

Lip functionality

Lip functionality was assessed evaluating lip movements and lip sensation. The mean proportion of words pronounced correctly at every visit following an injection was 100% of pre-injection levels. Lip sensation was first assessed blind-folded with a monofilament. The proportion of touch-points that subjects could feel before the initial injection was 99.8% and immediately post injection was 80.3%. It was back up to 100% at the Visit 2 weeks later. Lip sensation was also assessed blind-folded with a cotton wisp. The proportion of touch-points that subjects could feel before initial injection was 99.9% and immediately post injection was 81.9%. It was back up to 100% at the Visit 2 weeks later.

Lip functionality was assessed at each visit and pre- and post-injection. It included testing:

- Lip function: ability to suck liquid through a straw
- Lip sensation: ability to feel change of lip sensation with a monofilament and cotton wisp at different locations
- Lip movement: ability to pronounce specific letters and words

All subjects were able to perform the tests successfully pre-injection and at every visit thereafter. 10% to 20% of subjects had difficult sucking through a straw, feeling the mono-filament and cotton wisp, or pronouncing certain words, right after injection. All subjects were from the same site and it was likely related to having received pre-injection additional anesthesia. All those subjects successfully completed the tests at subsequent visits.

Extent of exposure

In the pooled population at Week 2, 137 (68.1%) subjects received a Touch-up Treatment (ITT population). At Week 52, 142 (75.5%) subjects received repeat treatment (ITT population). At visits where it was an option (week 12, 16, 24 or 36), a total of 35 (~17.6%) subjects received an early retreatment. Overall, a total of 154 (76.7%) subjects received repeat Treatment, while a total of 23 (11.6%) subjects who received both early retreatment and repeat treatment at the end of the study.

Table 10: Number of treatment sessions

	RHA® Redensity™/No-Tx Pooled N=199
Subjects receiving Touch-up at V2/V2b (Week 2)	137 (68.1%)
Subjects receiving early retreatment	35 (17.6%)
Subjects receiving repeat treatment at V9/V9b (Week 52)	142 (75.5%)

For each individual subject, for any given injection session, the same injection technique was used for both perioral rhytids. However, the injection technique could be different between the injection sessions of a given subject.

The injection techniques employed in the study were quite variable. In the pooled population, at some timepoint during the study, 91.0% of subjects received injections via linear threading/multiple puncture, and 70.6% received injections via multiple puncture. Other injection techniques were used at much lower frequencies.

2. Effectiveness Results

Primary endpoint

The analysis of effectiveness was based on the ITT population. Only data from the study up to the primary endpoint were taken into account. The No-Treatment control group was not pooled for the primary endpoint. Key effectiveness outcomes are presented in Table 11.

Table 11: PR-SRS Responder Rate (BLE) at 8 weeks after baseline (primary outcome)

PR-SRS Responder Rate (BLE)		RHA® Redensity™ n=150	No-Tx n=51	P-value
V4 (W8)	**N**	**150**	**51**	
	Responder	121 (80.7%) [73.4%, 86.7%]	4 (7.8%) [2.2%, 18.9%]	<.0001
	Not Responder	29 (19.3%)	47 (92.2%)	
	Missing values	0	0	

ITT population – BLE assessments – Last Observation Carried Forward (LOCF)
BLE: Blind Live Evaluator

A responder was defined as a subject having a ≥1-grade improvement on the PR-SRS (BLE assessment) at 8 weeks after last treatment (i.e., initial or touch-up treatment), compared with the pre-treatment assessment (Baseline). To successfully achieve the co-primary endpoint: 1) the responder rate for subjects with RHA® Redensity™ must be statistically superior to the responder rate for the No-Treatment control, and; 2) the responder rate for subjects treated with RHA® Redensity™ must be ≥70% and; 3) the difference between the responder rate for subjects treated with RHA® Redensity™ and the No-Treatment group must be ≥50 points.

Results showed that the PR-SRS responder rates at Week 8 were 80.7% and 7.8% for the RHA® Redensity™ and No-Treatment groups, respectively ($p<0.0001$; ITT population). The analyses concluded that superiority of RHA® Redensity™ over No-Treatment control was demonstrated. The rate of responders throughout the study is summarized in Table 12.

Table 12: PR-SRS Responder Rate (BLE) throughout the study (pooled data)

	Week 8	Week 12	Week 16	Week 24	Week 36	Week 52
N	194	184	183	188	188	188
Responder	156 (80.4%)	156 (80.4%)	147 (80.3%)	137 (72.9%)	131 (69.7%)	125 (66.5%)
Not Responder	38 (19.6%)	28 (15.2%)	36 (19.7%)	51 (27.1%)	57 (30.3%)	63 (33.5%)

ITT population at the respective follow-up visits (Treatment group and No-Treatment group after treatment pooled)
Rate of responders: ≥1-grade difference from pre-treatment on the PR-SRS

Rate of responders up to 52 weeks:

The superiority of RHA® Redensity™ over No-Treatment control was confirmed with secondary outcome measures, and the durability of RHA® Redensity™ was demonstrated through secondary/exploratory outcome measures.

Throughout the follow-up period, RHA® Redensity™ continued to provide a clinically significant improvement of the perioral rhytids. The rate of responders (≥1-grade on the PR-SRS scale) remained high over time. It slowly decreases to 66.5% 52 weeks after injection which is consistent with the reduced effect of the dermal fillers over time.

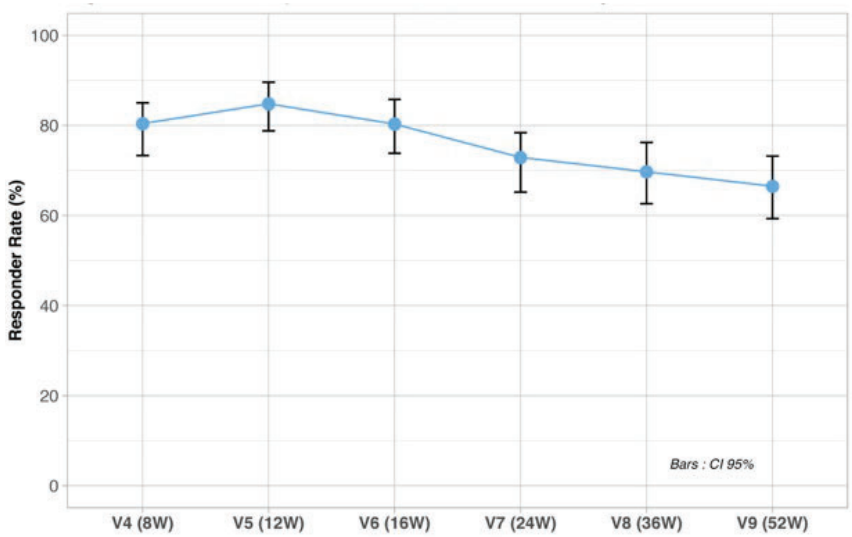


Figure 3: PR-SRS rate of responders, as assessed by the Blinded Live Evaluator, throughout the follow-up period

Secondary/exploratory endpoints (ITT, pooled analysis)

Secondary/exploratory endpoints included the evaluation of the Treating Investigators of the subject's perioral rhytids per the PR-SRS scale, Glogau assessment by the TI and BLE and the assessment of Global Aesthetic Improvement (GAI) by the BLE, TI and subject. Effectiveness endpoints included several patient reported outcome measures such as Subject Satisfaction, FACE-Q©, and natural look and feel assessments.

The rate of responders on the PR-SRS as assessed by the TI followed the same trend as when assessed by the BLE. It was 94.9% at 8 weeks and 79.3% at 52 weeks after initial treatment (pooled analysis). The proportions of subjects with GAI scores of "improved" or "much improved" resulted in consistent trends and outcomes. For the BLE, TI and subjects at 8 weeks it was 92.3%, 98.5% and 94.9% respectively and at 52 weeks after initial treatment 80.9%, 91.0% and 83.0%, respectively. The Glogau rate of responders for the severity of the wrinkling by the BLE and the TI at 8 weeks after initial or touch-up treatment was 63.0% and 68.4% respectively. At 52 weeks, the Glogau rate of responders was 47.3% and 45.2% as assessed by the BLE and the TI respectively. Patient reported outcomes were very high throughout the study. More than 90% of the subjects reported to be satisfied or very satisfied 4 weeks, 8 weeks and 12 weeks after initial treatment and the rate of satisfaction remained at more than 88% at 52 weeks. The FACE-Q© scores on a scale of 0 to 100, were 22.8 at Baseline, 69.3 after 8 weeks and 59.0 after 52 weeks after initial treatment. There was a mean score change of more than 36 points from Baseline throughout the follow-up period based on the six questions of the FACE-Q© Perioral Rhytids Domain. Subjects reported being less bothered by the number and depth of lines, how noticeable lines were after treatment with RHA® Redensity™, being less bothered by how perioral lines looked compared to other people their age, how old the lines made them look, and how their lines appeared when their lips are puckered. At all time points, subject reported outcomes were higher than pre-injection scores, indicating that subject-perceived improvement in the appearance of their perioral rhytids.

3. Subgroup Analyses

Treatment cohorts were stratified based on Fitzpatrick skin type. Common Treatment Reactions and Treatment-Related AE incidence rates were not negatively correlated with higher Fitzpatrick skin type. From Visit 1/1b to 9 (Pooled Data), 54 (37.0%) subjects with skin type I-III experienced at least 1 Treatment-Related AE. In subjects with skin type IV-VI, at least 1 Treatment-Related AE was noted in 19 (35.2%) subjects.

The responder rate at 8 weeks after last treatment was also analyzed by race and age as shown in Table 13

Table 13 : PR-SRS Responder Rate (BLE) at 8 weeks after baseline by race and age (primary outcome)

PR-SRS Responder Rate (BLE)		RHA® Redensity™	No-Tx	P-value
Hispanic/Latino				
V4 (W8)	**N = 35**	**25**	**10**	
	Responder	25 (100%) [86.3%, 100.0%]	1 (10.0%) [0.3%, 44.5%]	<.0001
	Not Responder	0 (0.0%)	9 (90.0%)	
	Missing values	0	0	
Non-Hispanic/Non-Latino				
V4 (W8)	**N = 166**	**125**	**41**	
	Responder	96 (76.8%) [68.4%, 83.9%]	3 (7.3%) [1.5%, 19.9%]	<.0001
	Not Responder	29 (23.2%)	38 (92.7%)	
	Missing values	0	0	
Age 38-60 years old				
V4 (W8)	**N = 91**	**66**	**25**	

PR-SRS Responder Rate (BLE)		RHA® Redensity™	No-Tx	P-value
	Responder	58 (87.9%) [77.5%, 94.6%]	2 (8.0%) [1.0%, 26.0%]	<.0001
	Not Responder	8 (12.1%)	23 (92.0%)	
	Missing values	0	0	
Age 61-81 years old				
V4 (W8)	**N =110**	**84**	**26**	
	Responder	63 (75.0%) [64.4%, 83.8%]	2 (7.7%) [0.9%, 25.1%]	<.0001
	Not Responder	21 (25.0%)	24 (92.3%)	
	Missing values	0	0	

ITT population – BLE assessments – Last Observation Carried Forward (LOCF)

Treatment cohorts were stratified based on ethnicity Hispanics / Non-Hispanics. The primary effectiveness, secondary effectiveness and safety endpoints, including the endpoints reflecting the perspective of the subject, were comparable between Hispanics and Non-Hispanics.

Treatment cohorts were stratified based on age group 38-60 years old and 61-81 years old. The primary effectiveness, secondary effectiveness and safety endpoints of the two age-groups were very similar. The only noticeable difference was the injected volume to achieve optimal correction (initial treatment and touch-up) was 2.68 mL for subjects in the 38-60 years old group versus 3.37 mL for subjects in the 61-81 years old group. The overall total mean volume of RHA® Redensity™ injected to achieve optimal correction results was 2.8 mL.

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

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 G160123 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.

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 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

Study results clearly demonstrated that RHA® Redensity™ is statistically superior to No-Treatment for the correction of dynamic perioral rhytids when administered as an initial treatment followed by optimization of correction via an optional touch-up treatment. PR-SRS (BLE assessment) responder rates at Week 8 were 80.7% and 7.8% for the RHA® Redensity™ and No-Treatment groups, respectively ($p<0.0001$; ITT population).

The superiority and durability of RHA® Redensity™ over No-Treatment control was confirmed with secondary/exploratory outcome measures.

Lastly, study device 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. Each treatment group presented very high subject satisfaction rates throughout the study (i.e., 90.8% at 8 weeks and 88.3% at 52 weeks of subjects satisfied or very satisfied with RHA® Redensity™, ITT pooled population)

B. Safety Conclusions

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

Study treatment with RHA® Redensity™ appeared to be safe and well tolerated. There were no reports of deaths, Treatment-Related Serious Adverse Events (TRSAE) or Unexpected Adverse Device Effects (UADE) in the study.

The Common Treatment Responses (redness, pain, tenderness, firmness, swelling, lumps/bumps, bruising, itching or discoloration) were rated by the subject on their 14-day diary. Most of them were rated as "mild" or "moderate". Of the 945 reported CTRs, 7.6% (72/945) had a maximum severity rated as "severe" by the subject at some point in their diary. Of those CTRs, bruising was the most frequent as 12.1% (24/199) of the subjects reported "severe" bruising at one time on their diary. 27 events of bruising were still present on the last day of the diary, thus were elevated to TRAE status irrespective of their severity. The TI assessed them all to be mild except for 3 which were considered moderate. None were assessed by the TI to be severe.

Importantly, 81.7% of the TRAEs were based on the elevation of Common Treatment Responses that were present on the last diary day, and were typical and expected signs and symptoms observed following the injection of a dermal filler.

All Treatment-Related Adverse Events were types of events that are typically experienced following the injection of a dermal filler, the onset of all events was temporally associated with a recent injection of a study device, and all events were mild or moderate in intensity (no severe Treatment-Related Adverse Events were reported in any of the treatment groups). There were no late onset Treatment-Related Adverse Events, and no events were deemed to be a granuloma.

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, and prospective, utilizing a validated scale (PR-SRS) assessed by Blinded Live Evaluators (BLE) to determine the primary effectiveness endpoint. This is a study design that reduces bias for determining an aesthetic outcome. Superiority was confirmed versus the No-Treatment control group at 8 weeks after the last treatment: 80.7% (121/150 in the treatment group) were responders and the effect lasted through 1 year with the majority of participants still responders (66.5%, 125/188 pooled data) after 52 weeks. The findings of the primary effectiveness assessment were supported by the secondary endpoints. Indeed, subjects reported high levels of satisfaction with their results, as assessed by multiple evaluation tools.

Patient Perspective

Patient perspectives considered during the study included:

- Global Aesthetic Improvement (GAI) as assessed by the subject
- Impact and effectiveness of study treatment from the subjects' perspective as assessed by the perioral rhytid domain of the validated FACE-Q© patient-reported outcome measurement
- Subject satisfaction survey
- Natural look and feel survey

At 8 weeks after the last treatment, the subjects and the BLE assessments of the GAIs in the treatment group were 95.9% and 92.5% respectively and it remained at 83.0% and 80.9% at 1 year. The improvement of the FACE-Q assessment of the perioral rhytid area overall means score from baseline to 8 weeks and up to 52 weeks after treatment was statistically significant ($p<0.0001$). The proportion of subjects who experienced a natural look and feel after study treatment and up to 1 year was greater than 83.6%. Subject satisfaction was 88.3% (166/188) at week 52 after last treatment.

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

Most of the subjects experienced Common Treatment Responses (CTRs) which included bruising, swelling, firmness, lumps/bumps, redness, tenderness, discoloration, pain and itching. Subjects rated CTRs as predominantly mild in severity with a majority (76.4%) resolving within 1 week.
Treatment-Related Adverse Events were all typical and expected in association with injection of a dermal filler, and did not occur at rates different from those expected.

Based on the safety and effectiveness conclusions drawn from the pivotal clinical studies, it is reasonable to conclude that the benefits of the use of RHA® Redensity™, outweigh the risks when used in accordance with the Instructions For Use.

In conclusion, given the available information above, the data support that for the correction of moderate to severe dynamic perioral rhytids 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 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 December 22, 2021.

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.