SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Injectable Dermal Filler

Device Trade Name: RHA® Redensity™ Mepi
RHA® 2 Mepi
RHA® 3 Mepi
RHA® 4 Mepi

Device Product code: 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/S026

Date of FDA Notice of Approval: October 13, 2023

The original PMA for RHA®2, RHA®3 and RHA®4 (P170002) was approved on October 19, 2017. RHA®2, RHA®3 and RHA®4 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 for RHA®2, RHA®3 and RHA®4 is available on the CDRH website and is incorporated by reference here. RHA® Redensity™ was approved under supplement P170002/S012 on December 22, 2021 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. The SSED to support the perioral rhytids indication for RHA® Redensity™ is available on the CDRH website and is incorporated by reference here.

RHA® Redensity™ Mepi, RHA®2 Mepi, RHA®3 Mepi and RHA®4 Mepi are being submitted as a panel-track supplement (P170002/S026) to the RHA® Redensity™, RHA®2, RHA®3, and RHA®4 PMA (P170002) to request changes in the design or performance of the device. The current supplement was submitted for RHA® Redensity™ Mepi, RHA®2 Mepi, RHA®3 Mepi, and RHA®4 Mepi to modify the device formulation by using 0.3% w/w of mepivacaine instead of 0.3% w/w of lidocaine for pain reduction.

II. INDICATIONS FOR USE

RHA® Redensity™ Mepi 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.

RHA®2 Mepi 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 Mepi 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®4 Mepi is indicated for injection into the deep dermis to superficial subcutaneous tissue for the correction of moderate to severe dynamic facial wrinkles and folds, such as nasolabial folds (NLF), in adults aged 22 years or older.

III. CONTRAINDICATIONS

- RHA® Redensity™ Mepi, RHA®2 Mepi, RHA®3 Mepi and RHA®4 Mepi are contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.
- RHA® Redensity™ Mepi, RHA®2 Mepi, RHA®3 Mepi and RHA®4 Mepi contain trace amounts of gram positive bacterial proteins, and is contraindicated for patients with a history of allergies to such material.
- RHA® Redensity™ Mepi, RHA®2 Mepi, RHA®3 Mepi and RHA®4 Mepi should not be used in patients with previous hypersensitivity to local anesthetics of the amide type, such as lidocaine and mepivacaine.
- RHA® Redensity™ Mepi, RHA®2 Mepi, RHA®3 Mepi and RHA®4 Mepi should not be used in patients with bleeding disorders.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in RHA® Redensity™ Mepi, RHA®2 Mepi, RHA®3 Mepi and RHA®4 Mepi labeling.

V. DEVICE DESCRIPTION

RHA® Redensity™ Mepi, RHA®2 Mepi, RHA®3 Mepi and RHA®4 Mepi are viscoelastic, sterile, non-pyrogenic, clear, colorless, and biodegradable gel implants of both crosslinked and non-

crosslinked hyaluronic acid. They are produced with sodium Hyaluronic Acid (NaHA) with a concentration of 15 mg/g (RHA® Redensity™ Mepi) and 23 mg/g (RHA®2 Mepi, RHA®3 Mepi and RHA®4 Mepi) 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). The devices exist in four formulations, from the least to the most crosslinked:

- RHA® Redensity™ (least cross-linked)
- RHA®2 Mepi
- RHA®3 Mepi
- RHA®4 Mepi (most cross-linked)

RHA® Redensity™ Mepi, RHA®2 Mepi, RHA®3 Mepi and RHA®4 Mepi contain 0.3% mepivacaine hydrochloride to reduce pain on injection.

Syringes contain 1 ml of RHA® Redensity™ Mepi, RHA®2 Mepi, or RHA®3 Mepi.

Syringes contain 1.2 mL of RHA®4 Mepi.

RHA® Redensity™ Mepi and RHA®2 Mepi are supplied with two 30G ½ inch hypodermic needles.

RHA®3 Mepi, and RHA®4 Mepi are supplied with two 27G ½ inch hypodermic needles.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of moderate to severe dynamic perioral rhytids or for the correction of moderate to severe dynamic facial wrinkles and folds, such as nasolabial folds (NLF). Alternatives in the treatment of facial wrinkles and folds and 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™ Mepi, RHA®2 Mepi, RHA®3 Mepi and RHA®4 Mepi are only available in the United States. There is no marketing history for these products.

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™ Mepi, RHA®2 Mepi, RHA®3 Mepi, RHA®4 Mepi 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 studies.

Rare but serious adverse events associated with the intravascular injection of soft tissue fillers in the face have been reported and include temporary or permanent vision impairment or blindness, cerebral ischemia or cerebral hemorrhage leading to stroke, skin necrosis, and damage to underlying facial structures.

RHA® Redensity™ Mepi, RHA®2 Mepi, RHA®3 Mepi, RHA®4 Mepi are the exact same products as RHA® Redensity™, RHA®2, RHA®3, RHA®4 respectively except that the RHA® Mepi family of products contains 0.3% of the anesthetic mepivacaine while the RHA® family of product contains 0.3% of the anesthetic lidocaine. Both anesthetics agents are of the same family with the same mechanisms effects. Both have an effect limited in time and are released from the gel within 24 hours. Therefore, post-marketing surveillance data of the RHA® family of products containing lidocaine are applicable to the RHA® Mepi family of products.

The RHA® Mepi family of product has not been commercialized yet but the RHA® family of products has been commercialized since 2015 outside the United States and since 2020 in the United States. The following adverse events have been reported for RHA® family of products as part of the post-marketing surveillance outside the United States. These treatment reactions occurred when RHA® products were used for a wide range of indications, including but not limited to perioral rhytids or nasolabial folds. The following adverse events were reported with a prevalence equal or superior to 1 occurrence for 100,000 syringes: skin edema, injection site masses (lumps and bumps), skin swelling, skin induration, vascular skin disorder (such as vessel compression/occlusion), pain, ecchymosis, erythema, skin discoloration, skin infection and inflammatory reaction.

Additionally, other less frequent adverse reactions have also been reported, and include dermal filler overcorrection, allergic reaction, product misplacement, fibrosis, skin necrosis, papules, granuloma, injection site movement impairment, paraesthesia, urticaria and device migration.

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™ Mepi, RHA®2 Mepi, RHA®3 Mepi and RHA®4 Mepi were 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™ Mepi, RHA®2 Mepi, RHA®3 Mepi and RHA®4 Mepi

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
Mepivacaine content	To confirm the mepivacaine concentration of the gel meets specifications	Passed
Impurities deriving from mepivacaine hydrochloride for RHA® Redensity™ Mepi	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™ Mepi, RHA®2 Mepi, RHA®3 Mepi and RHA®4 Mepi

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.

Test	Method	ISO Standard	Results
Intracutaneous reactivity	Intradermal injection in rabbits.	ISO 10993-10	Level of reactivity similar or slightly less than its control*. RHA® Redensity™ Mepi was non-irritant before Day 3. RHA®2 Mepi was non-irritant at 15 days. RHA®4 Mepi was non-irritant at 20 days.
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 microscopically or macroscopically. After 52 weeks, degradation had started.

(*) Note: The control device was an FDA approved Hyaluronic Acid soft tissue filler, with similar characteristics. The control for RHA® Redensity™ Mepi was RHA® Redensity™, for RHA®2 Mepi was RHA®2 and for RHA®4 Mepi was RHA®4.
Some testing performed with RHA®2 Mepi and RHA®4 Mepi is applicable to RHA®3 Mepi

The 4 and 13 weeks systemic toxicity studies did not evidence signs of systemic toxicity after short or medium term exposure of RHA® Redensity™ Mepi, RHA®2 Mepi and RHA®4 Mepi. Extensive literature review of the materials used for the manufacturing of RHA® Redensity™ Mepi, RHA®2 Mepi, RHA®3 Mepi and RHA®4 Mepi 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™ Mepi, RHA®2 Mepi, RHA®3 Mepi and RHA®4 Mepi was not considered to be a biological risk based on the following data:

- The three-test battery of genotoxicity carried out on RHA® Redensity™ Mepi, RHA®2 Mepi, and RHA®4 Mepi demonstrated that the three formulations were not genotoxic. Results are applicable to RHA®3 Mepi.
- 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™ Mepi, RHA®2 Mepi, RHA®3 Mepi and RHA®4 Mepi was negligible.

C. Additional Studies

Stability data of RHA® Redensity™ Mepi, RHA®2 Mepi, RHA®3 Mepi and RHA®4 Mepi have been collected for 24 month period at 25°C ± 2°C and 60% ± 5% relative humidity. At each time point, product was characterized via microbiological, physical, chemical, mepivacaine hydrochloride content, and mepivacaine-related degradant parameters. Conformity of real-time aged product with all specifications was confirmed.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

Overview of Safety and Effectiveness Clinical Studies

RHA® Redensity™ Mepi, RHA®2 Mepi, RHA®3 Mepi, and RHA®4 Mepi are strictly identical to approved dermal filler RHA® Redensity™, RHA®2, RHA®3, and RHA®4, respectively, except for the small amount of anesthetic medicine they contain: RHA® Redensity™ Mepi, RHA®2 Mepi, RHA®3 Mepi, and RHA®4 Mepi contain 0.3% w/w of *mepivacaine* while RHA® Redensity™, RHA®2, RHA®3, and RHA®4 contain 0.3% w/w of *lidocaine*. Both anesthetics, mepivacaine and lidocaine, are of the same family with the same mechanisms of effects and overall safety profiles. RHA® Redensity™ Mepi and RHA® Redensity™ are injected in the same location and have the exact same indication. RHA®2, RHA®3, RHA®2 Mepi and RHA®3 Mepi are injected in the same location, into the mid-to-deep dermis and have the exact same indication. RHA®4 and RHA®4 Mepi are injected in the same location, both into the deep dermis to superficial subcutaneous and have the exact same indication. For all products, the anesthetic is released from the gel within approximately 24 hours and the anesthetic effect lasts for an average of 3 to 4 hours. Accordingly, the long term safety and effectiveness conclusions that were drawn for RHA® Redensity™, RHA®2, RHA®3, and RHA®4, were leveraged to support the long term safety and effectiveness of RHA® Redensity™ Mepi, RHA®2 Mepi, RHA®3 Mepi, and RHA®4 Mepi. The safety and effectiveness conclusions for RHA® Redensity™ Mepi, RHA®2 Mepi, RHA®3 Mepi, and RHA®4 Mepi, were extrapolated from clinical studies as follows:

- The long term safety and effectiveness of RHA® Redensity™ Mepi were evaluated in a clinical study of RHA® Redensity™.
- The long-term safety and effectiveness of RHA®2 Mepi and RHA®3 Mepi were evaluated in a clinical study using RHA®2 and RHA®3, respectively.
- The long-term safety and effectiveness of RHA®4 Mepi were evaluated in a clinical study using RHA®4.

These clinical studies are summarized below:

A. Safety and Effectiveness of RHA® Redensity™ Mepi

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 safety data of this clinical study are presented in the SSED available on the CDRH website under approved supplement P170002/S012 on December 22, 2021.

B. Safety and Effectiveness of RHA® 2 Mepi, RHA®3 Mepi and RHA®4 Mepi

The applicant performed two clinical studies to establish a reasonable assurance of safety and effectiveness of injection into the mid to deep dermis with RHA®2 and RHA®3 under IDE G140028 (Study 1302) or deep dermis to superficial subcutaneous tissue with RHA®4 under IDE G140106 (Study 1402) for the correction of moderate to severe dynamic facial wrinkles and folds, such as nasolabial folds (NLFs) in adults aged 22 years or over. Data from these clinical studies were the basis for the original PMA approval decision for RHA®2, RHA®3 and RHA®4.

The safety data of these two clinical studies are presented in the SSED available on CDRH website under original approval of P170002 on October 19, 2017.

Overview of Clinical Studies to Evaluate Reduction in Pain

Two clinical studies were performed to demonstrate non-inferiority of pain reduction for the mepivacaine-containing devices (RHA® Redensity™ Mepi, RHA®2 Mepi, RHA®3 Mepi, and RHA®4 Mepi) when compared to the respective lidocaine-containing devices (RHA® Redensity™, RHA®2, RHA®3, and RHA®4):

- The applicant performed a clinical study to demonstrate the non-inferiority of RHA® Redensity™ Mepi to RHA® Redensity™ in terms of reducing pain at time of injection when injected into the perioral rhytids under IDE G190055. A summary of the clinical study is presented below, beginning in part C.

- The applicant performed a clinical study to demonstrate the non-inferiority of RHA®4 Mepi to RHA®4 in terms of reducing pain at time of injection when injected into the nasolabial folds under IDE G190118. Due to similarities in the formulation of RHA®2 Mepi, RHA®3 Mepi, and RHA®4 Mepi, results of the clinical study evaluating pain reduction of RHA®4 Mepi (G190118) were leveraged to demonstrate non-inferiority of RHA®2 Mepi and RHA®3 Mepi in terms of reducing pain at time of injection. A summary of the clinical study is presented, below beginning in part G.

C. Study Design for RHA® Redensity™ Mepi for Study G190055 to Evaluate Effectiveness of RHA® Redensity™ Mepi in Reducing Pain

The applicant performed an additional clinical study to demonstrate the safety and effectiveness of RHA® Redensity™ Mepi under IDE G190055. The purpose of this clinical study was to compare RHA® Redensity™ Mepi containing mepivacaine with RHA® Redensity containing lidocaine in terms of reducing pain during injection into the perioral rhytids. The goal was to show that RHA® Redensity™ Mepi was non inferior to RHA® Redensity™ in reducing pain as felt by the subject during injection assessed immediate after injection of each side using a 100 mm Visual Analog Scale (VAS). The duration of the effectiveness of the anesthetic agent (mepivacaine or lidocaine) is less than a day. The study lasted 30 days.

Subjects in IDE G190055 were treated between October 30, 2019 and January 22, 2020. The database reflected data collected for 30 subjects who were randomized and completed the study. There were three U.S. investigational sites.

The clinical study was a randomized, double blinded, within-subject (split-face) study in which the perioral rhytids of one side of the mouth were injected with RHA® Redensity™ Mepi and the perioral rhytids on the other side of the mouth were injected with the control device RHA® Redensity™ (with lidocaine). The primary effectiveness objective was to demonstrate the non-inferiority of RHA® Redensity™ Mepi (with mepivacaine) versus the control (RHA® Redensity™ with lidocaine) in terms of reducing pain during device injection into the perioral rhytids. Primary endpoint was injection site pain felt during injection of one side of the mouth assessed by the subject immediately following injection with RHA® Redensity™ Mepi (with mepivacaine), compared to the injection site pain felt during injection into the contralateral side of the mouth assessed immediately following injection with RHA® Redensity™ with lidocaine. RHA® Redensity™ Mepi and RHA® Redensity™ are completely identical except for 0.3% mepivacaine replacing 0.3% lidocaine. The study duration was 4 weeks and could be extended to 8 weeks for subjects who presented an unresolved clinically significant device related Adverse Event.

Subjects received treatment for their perioral rhytids with RHA® Redensity™ Mepi on one side and RHA® Redensity™ (the control) on the other side of their mouth. The order of injection and the side were assigned randomly. To minimize potential interference between the effect of the anesthetic agents of each study device, left and right perioral areas were separated by a "no treatment zone" defined as the area between the philtral columns (approximately 8 mm). Similarly, a no treatment zone of the lower perioral area was defined as the ~8 mm area directly below the upper perioral no treatment zone.

Subjects assessed their pain at time of injection and several times up to 60 minutes post injection using a 100 mm Visual Analog Scale (VAS). Subjects reported their Common Treatment Responses on a 30-day diary and the duration of the anesthetic effect and returned 30 days later for a final Visit 2. The treating investigator performed effectiveness and safety assessments at each visit, including during a call 3 days after treatment. Subjects performed effectiveness and satisfaction assessments when compared to Baseline, prior to injection.

The control group was the perioral area of the same subject injected with RHA® Redensity™ which has been approved for the same indication and is identical to RHA® Redensity™ Mepi except for the anesthetic in the formulation, wherein RHA® Redensity™ includes lidocaine and RHA® Redensity™ Mepi includes mepivacaine for pain reduction. RHA® Redensity™ is legally marketed in the United States.

1. Key Clinical Inclusion and Exclusion Criteria

Enrollment in the pivotal study G190055 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 Perioral Rhytid Severity Rating Scale (PR-SRS) (ranging from 0-3).
- Perioral rhytids of the same PR-SRS grade on the left and right sides of the mouth.
- 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 (Treating Investigator (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, RHA® Redensity Mepi with mepivacaine was administered in the perioral area in a randomly selected sequence (first or second injection) and side of the mouth and RHA® Redensity™ with lidocaine was administered in the perioral area to the other side. Both upper perioral rhytids were quadrants injected first, prior to injection of either lower perioral rhytids quadrants. Injection into the lower quadrants was only to improve cosmetic results. Immediately after injection of an upper perioral quadrant, subjects rated injection site pain experienced **during injection** using a 100 mm Visual Analog Scale (VAS). Injection site pain in each side of the mouth was also assessed at 15, 30, 45 and 60 minutes after the upper quadrant was injected.
Additionally, subjects assessed anesthetic sensation on each side of the face every hour until normal sensation returned; the time for return to normal sensation was recorded.

Subjects attended Visit 2 (30 days post-injection) where effectiveness and safety assessments were conducted. Subjects who presented with an unresolved clinically significant device related Adverse Event (AE) at Visit 2 received the optional follow-up phone call no later than 30 days after Visit 2. If the clinically significant AE remained unresolved, the Investigator requested that the subject attend the optional in-clinic follow-up visit (i.e., Visit 3) within 5 working days. Follow-up of the clinically significant AE continued until the AE was resolved or the TI determined that additional follow-up was not necessary.

At study exit (i.e., Visit 2, optional follow-up phone call, or Visit 3), subjects were offered treatment with a commercially available dermal filler approved for injection into the perioral rhytids if they presented with wrinkles/lines in the no-treatment zone.

3. Clinical Endpoints

Injection site pain was measured on each side of the face during the injection (primary endpoint) as well as at 15, 30, 45 and 60 minutes post-injection. The duration of the anesthetic effect on each

side of the face was also followed on the patient diary. Lip functionality testing was conducted pre- and post-injection and at each follow-up visit. It included: lip function, lip sensation and lip movement.
For safety evaluations, post-injection Common Treatment Responses (CTRs) including visual disturbances were assessed on a 30-Day patient CTR diary. Assessment of visual disturbances (Snellen visual acuity, confrontational visual fields test and ocular) motility were assessed by the TI at each visit.
CTRs that were present on the last day of diary entry, regardless of severity and duration, were automatically recorded as AEs. Adverse Events (AEs) were assessed by the TI at each visit and during a call 3 days after treatment. 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.

The primary effectiveness objective was to demonstrate the non-inferiority of RHA® Redensity™ Mepi with mepivacaine versus the control (RHA® Redensity™ with lidocaine) in terms of reducing pain during device injection into the perioral area. Pain during injection was based on the 100 mm Visual Analog Scale (VAS), as assessed by subjects immediately after injection of each side. The primary effectiveness assessment consisted in comparing the injection site pain felt during injection of one perioral area upper quadrant assessed by the subject immediately following injection with RHA® Redensity™ Mepi (with mepivacaine) with the injection site pain felt during injection into the contralateral perioral area upper quadrant assessed immediately following injection with RHA® Redensity™ (with lidocaine). Statistical analysis of the primary endpoint was performed using paired one-sided tests, with a significance level of 0.05, either parametric or non-parametric as appropriate.

Secondary effectiveness endpoints included the comparison of the PR-SRS severity on each side of the mouth and comparing them to Baseline using Teoxane validated 4-grade photonumeric scale measuring the severity of the Perioral Rhytids (Perioral Rhytids Severity Rating Scale) (see Table 3 and Figure 1 below). Other secondary effectiveness endpoints included the Subject FACE-Q Assessment (Perioral Rhytids domain) at Baseline and Visit 2, patient satisfaction assessment at Visit 1 after treatment and at Visit 2 and the Global Aesthetic Improvement (GAI) assessment by the subject and the TI at Visit 1 after treatment and at Visit 2. The total volume required to achieve Optimal Cosmetic Result (OCR) was also reported for each device.

Teoxane validated and proprietary Perioral Rhytids Severity Rating Scale (PR-SRS)

Table 3: Teoxane Perioral Rhytid 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

D. Accountability of PMA Cohort for RHA® Redensity™ Mepi for Study G190055

At the time of the database lock, the 30 subjects who were randomized and enrolled, all (100%) completed the study. Each subject was injected with RHA® Redensity™ Mepi in one side of the perioral area and RHA® Redensity™ in the other side of the perioral area. There were no subjects who dropped out or were lots to follow-up prior to the final study visit.

There were no major protocol deviations reported in the study. As such, the intent to treat (ITT) and per protocol (PP) populations consisted of all randomized/enrolled subjects (i.e. n=30). The Safety (SAFT) population consisted of all study subjects that were randomized and received treatment with at least one of study device, i.e. n=30.

E. Study Population Demographics and Baseline Parameters for Study G190055

Subjects had a mean age of 64.3 years, an average BMI of 26.3, and all subjects were female and Caucasian. Fitzpatrick skin types were represented with 76.7% of subjects having skin types I-III, and 23.3% of subjects having skin types IV. Fitzpatrick skin types V and VI were not represented. Fitzpatrick skin type is a classification intended to reflect individual sun sensitivity and not race or phenotypic features. Ethnicity was well represented with 36.7% of subjects identifying as Hispanic or Latino and 63.3% as Non-Hispanic or Latino.

Table 4: Demographic characteristics at Baseline

Demographic Variable	*n=30*
Age (years)	
N	30
Mean ± SD [95% CIs]	**64.3 ± 8.2 [61.2, 67.3]**
Median (P25, P75)	**65.5 (57.2, 71.0)**
Min, Max	**48.0 - 78.0**
Missing values	0
BMI (kg/m²)	
N	30
Mean ± SD [95% CIs]	26.3 ± 4.6 [24.6, 28.0]
Median (P25, P75)	25.5 (24.2, 29.7)
Min, Max	17.4 - 34.3
Missing values	0
Gender	
N	30
Male	0 (0.0%)
Female	30 (100%)
Missing values	0
Race	
N	30
Caucasian	30 (100%)
Black or African American	0 (0.0%)
American Indian or Alaska Native	0 (0.0%)
Asian	0 (0.0%)
Nat. Hawaiian, Other Pacific Islander	0 (0.0%)
Other	0 (0.0%)
Missing values	0
Ethnicity	
N	30
Hispanic or Latino	11 (36.7%)
Non-Hispanic or Latino	19 (63.3%)

Demographic Variable	*n=30*
Unknown	0 (0.0%)
Missing values	0
Fitzpatrick Skin Type	
N	30
I-III	**23 (76.7%)**
I	1 (3.3%)
II	11 (36.7%)
III	11 (36.7%)
IV-VI	**7 (23.3%)**
IV	7 (23.3%)
V	0 (0.0%)
VI	0 (0.0%)
Missing values	0

In the upper quadrants, the overall total mean volume of RHA® Redensity™ Mepi injected to achieve optimal correction results was 0.27 ± 0.09 ml. It was 0.27 ± 0.08 ml for RHA® Redensity™.
In the lower quadrants, the overall total mean volume of RHA® Redensity™ Mepi injected to achieve optimal correction results was 0.23 ± 0.13 ml. It was 0.22 ± 0.10 ml for RHA® Redensity™.

F. Safety and Effectiveness Results for Study G190055

1. Safety Results for Study G190055

The analysis of safety was based on the Safety cohort of 30 subjects who were randomized and all completed the study. The Common Treatment Responses for this study are presented below in Table 5 and Table 6.

Safety of RHA® Redensity™ Mepi was evaluated through a 30-day patient Common Treatment Response (CTR) diary which was completed after the injection individually for each side of the mouth, AE assessments at each visit, lip functionality and visual disturbances before and after injection and at each visit and measurement of injection site pain at time of injection and up to 60 minutes after injection for each side of the face.

Common Treatment Responses (CTR)

A total of 25 (83.3%) and 24 (80.0%) of the 30 subjects in the RHA® Redensity™ Mepi and RHA® Redensity™ groups, respectively, experienced at least one CTR. The proportions of subjects experiencing at least one CTR of each category (e.g., Bruising, Lumps/Bumps, etc.) was similar between treatment groups with the majority (220/226, 97.4%) of CTRs resolving in 14 days or fewer.

Of the 226 CTRs that occurred following study treatments (including the CTRs reported in the "other" CTR category by the subjects), 220 (97.4%) had a cumulative duration of 14 days or less (i.e., 141 [62.4%] 1-3 days, 60 [26.5%] 4-7 days, and 19 [8.4%] 8-14 days). Six (2.7%) CTRs had a cumulative duration of 15-30 days (i.e., 2 [0.9%] 15-21 days and 4 [1.8%] 22-30 days).

Five (5) CTRs from three (3) subjects were recorded on the last day of the diary, and each was elevated to a Treatment-Related AE. In total, 3 (10.0%) and 2 (6.7%) subjects in the RHA® Redensity™ Mepi and RHA® Redensity™ groups recorded CTRs on the last day of the dairy. Specifically, on the last day of the CTR diary:

- 2 subjects reported firmness with RHA® Redensity™ Mepi and RHA® Redensity™
- 1 subject reported lumps/bumps with RHA® Redensity™ Mepi

On the last day of the diary when they were automatically elevated to Treatment-Related AEs (TRAEs), all CTRs were mild in severity and deemed by the Investigators to be not clinically significant.

Two subjects recorded symptoms in the "other" CTR category, which were processed as AEs. Specifically:

- One subject experienced injection site soreness on both sides of the mouth of moderate severity. Both events resolved within 2 days.
- One subject experienced needle marks on both sides of the mouth that were of mild severity. Both resolved within 4 days.

Table 5: CTRs by Duration

CTR	Group	≥1 CTR	Cumulative Duration (days) 1-3	4-7	8-14	15-21	22-30	CTR Last Day Diary
At least 1 CTR	**RHA® Redensity™ Mepi**	**24 (80.0%)**	**-**	**-**	**-**	**-**	**-**	**3 (10.0%)**
	RHA® Redensity™	**25 (83.3%)**	**-**	**-**	**-**	**-**	**-**	**2 (6.7%)**
Bruising	RHA® Redensity™ Mepi	12 (40.0%)	4 (13.3%)	7 (23.3%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	RHA® Redensity™	16 (53.3%)	3 (10.0%)	11 (36.7%)	2 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Discoloration	RHA® Redensity™ Mepi	10 (33.3%)	7 (23.3%)	3 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	RHA® Redensity™	10 (33.3%)	7 (23.3%)	3 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Firmness	RHA® Redensity™ Mepi	14 (46.7%)	9 (30.0%)	2 (6.7%)	1 (3.3%)	1 (3.3%)	1 (3.3%)	2 (6.7%)
	RHA® Redensity™	19 (63.3%)	11 (36.7%)	4 (13.3%)	2 (6.7%)	1 (3.3%)	1 (3.3%)	2 (6.7%)
Itching	RHA® Redensity™ Mepi	4 (13.3%)	3 (10.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	RHA® Redensity™	2 (6.7%)	1 (3.3%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lumps/Bumps	RHA® Redensity™ Mepi	15 (50.0%)	11 (36.7%)	3 (10.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)	1 (3.3%)
	RHA® Redensity™	17 (56.7%)	5 (16.7%)	8 (26.7%)	3 (10.0%)	0 (0.0%)	1 (3.3%)	0 (0.0%)
Pain	RHA® Redensity™ Mepi	3 (10.0%)	2 (6.7%)	0 (0.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	RHA® Redensity™	4 (13.3%)	3 (10.0%)	0 (0.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Redness	RHA® Redensity™ Mepi	16 (53.3%)	11 (36.7%)	2 (6.7%)	3 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	RHA® Redensity™	15 (50.0%)	9 (30.0%)	5 (16.7%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Swelling	RHA® Redensity™ Mepi	21 (70.0%)	17 (56.7%)	2 (6.7%)	2 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	RHA® Redensity™	19 (63.3%)	14 (46.7%)	3 (10.0%)	2 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Tenderness	RHA® Redensity™ Mepi	13 (43.3%)	11 (36.7%)	2 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	RHA® Redensity™	12 (40.0%)	10 (33.3%)	2 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	RHA® Redensity™ Mepi	1 (3.3%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
(Needle track marks) †	RHA® Redensity™	1 (3.3%)	0 (0.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	RHA® Redensity™ Mepi	1 (3.3%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
(Injection site Soreness) ††	RHA® Redensity™	1 (3.3%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

† *As these events were **written** into the CTR diary as "other" it was processed as AEs and was not subject to CTR reporting rules for AEs (i.e., elevation to AEs if present on the last day of the diary).*

Out of the 226 reported CTRs, severity was reported as "Mild" or "Moderate" for 218 (96.5%), with 8 (3.5%) CTRs rated by subjects as "Severe". For most of those, the subjects reported those CTRs to be severe on both sides. None of the CTRs reported "Severe" by the subject were considered to be an Adverse Event by the Investigator and they all resolved within 30-days. The CTRs that were still present on the last day of the diary were all reported mild by the subject.

Table 6: CTRs by Severity

			Maximum Severity within 30 Days			
CTR	**Group**	**≥1 CTR**	**None**	**Mild**	**Moderate**	**Severe**
At least 1 CTR	**RHA® Redensity™ Mepi**	**24 (80.0%)**	**6 (20.0%)**	**14 (46.7%)**	**9 (30.0%)**	**1 (3.3%)**
	RHA® Redensity™	**25 (83.3%)**	**5 (16.7%)**	**13 (43.3%)**	**10 (33.3%)**	**2 (6.7%)**
Bruising	RHA® Redensity™ Mepi	12 (40.0%)	18 (60.0%)	9 (30.0%)	3 (10.0%)	0 (0.0%)
	RHA® Redensity™	16 (53.3%)	14 (46.7%)	9 (30.0%)	6 (20.0%)	1 (3.3%)
Discoloration	RHA® Redensity™ Mepi	10 (33.3%)	20 (66.7%)	8 (26.7%)	2 (6.7%)	0 (0.0%)
	RHA® Redensity™	10 (33.3%)	20 (66.7%)	9 (30.0%)	1 (3.3%)	0 (0.0%)
Firmness	RHA® Redensity™ Mepi	14 (46.7%)	16 (53.3%)	11 (36.7%)	3 (10.0%)	0 (0.0%)
	RHA® Redensity™	19 (63.3%)	11 (36.7%)	16 (53.3%)	3 (10.0%)	0 (0.0%)
Itching	RHA® Redensity™ Mepi	4 (13.3%)	26 (86.7%)	4 (13.3%)	0 (0.0%)	0 (0.0%)
	RHA® Redensity™	2 (6.7%)	28 (93.3%)	2 (6.7%)	0 (0.0%)	0 (0.0%)
Lumps/Bumps	RHA® Redensity™ Mepi	15 (50.0%)	15 (50.0%)	12 (40.0%)	3 (10.0%)	0 (0.0%)
	RHA® Redensity™	17 (56.7%)	13 (43.3%)	10 (33.3%)	7 (23.3%)	0 (0.0%)
Pain	RHA® Redensity™ Mepi	3 (10.0%)	27 (90.0%)	2 (6.7%)	0 (0.0%)	1 (3.3%)
	RHA® Redensity™	4 (13.3%)	26 (86.7%)	3 (10.0%)	0 (0.0%)	1 (3.3%)
Redness	RHA® Redensity™ Mepi	16 (53.3%)	14 (46.7%)	12 (40.0%)	3 (10.0%)	1 (3.3%)
	RHA® Redensity™	15 (50.0%)	15 (50.0%)	9 (30.0%)	5 (16.7%)	1 (3.3%)
Swelling	RHA® Redensity™ Mepi	21 (70.0%)	9 (30.0%)	16 (53.3%)	4 (13.3%)	1 (3.3%)
	RHA® Redensity™	19 (63.3%)	11 (36.7%)	11 (36.7%)	7 (23.3%)	1 (3.3%)
Tenderness	RHA® Redensity™ Mepi	13 (43.3%)	17 (56.7%)	11 (36.7%)	1 (3.3%)	1 (3.3%)
	RHA® Redensity™	12 (40.0%)	18 (60.0%)	10 (33.3%)	2 (6.7%)	0 (0.0%)
Other	RHA® Redensity™ Mepi	1 (3.3%)	0 (0.0%)	0 (0.0%)	1 (3.3%)	0 (0.0%)
(Needle track marks)	RHA® Redensity™	1 (3.3%)	0 (0.0%)	0 (0.0%)	1 (3.3%)	0 (0.0%)
Other	RHA® Redensity™ Mepi	1 (3.3%)	0 (0.0%)	0 (0.0%)	1 (3.3%)	0 (0.0%)
(Injection Site Soreness)	RHA® Redensity™	1 (3.3%)	0 (0.0%)	0 (0.0%)	1 (3.3%)	0 (0.0%)

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 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, 100% of them were based on CTR diary entries (Table 7).

TRAEs were reported for 4 (4/30, 13.3%) subjects in the RHA® Redensity™ Mepi group and for 3 (10%) subjects in the RHA® Redensity™ group. The most common event was injection site induration which was experienced by 2 (2/30, 6.7%) subjects in each group. There were a total of 9 TRAEs as follows:

- One subject reported injection site induration with RHA® Redensity™ Mepi and RHA® Redensity™ (i.e., two (2) TRAEs);
- One subject reported injection site induration and injection site pain with RHA® Redensity™ Mepi and RHA® Redensity™ (i.e., four (4) TRAEs);
- One subject reported needle track marks with RHA® Redensity™ Mepi and RHA® Redensity™ (i.e., two (2) TRAEs);
- One subject reported injection site mass with RHA® Redensity™ Mepi (i.e., one (1) TRAE).

Study Investigators deemed all TRAEs to be mild or moderate in severity and none were considered by Investigators to be clinically significant. All TRAEs resolved spontaneously without the need for medical therapy within 77 days. Importantly, except for injection site mass, all TRAEs occurred on both were bilateral, occurring on both sides of the subjects' mouth.

Table 7: Treatment-Related AEs Sorted by SOC and PT

TRAEs		**RHA® Redensity™ Mepi**		**RHA® Redensity™**		**All**	
SOC	**PT**	n=30		n=30		n=30	
		Subjects	**Events**	**Subjects**	**Events**	**Subjects**	**Events**
Any TRAE		**4 (13.3%) [4.4, 31.6]**	**5**	**3 (10%) [2.6, 27.7]**	**4**	**4 (13.3%) [4.4, 31.6]**	**9**
Gen. disorders and admin. site conditions		**3 (10%) [2.6, 27.7]**	**4**	**2 (6.7%) [1.2, 23.5]**	**3**	**3 (10%) [2.6, 27.7]**	**7**
	Injection site induration	2 (6.7%) [1.2, 23.5]	2	2 (6.7%) [1.2, 23.5]	2	2 (6.7%) [1.2, 23.5]	4
	Injection site mass	1 (3.3%) [0.2, 19.1]	1	0 (0%) [--, --]	0	1 (3.3%) [0.2, 19.1]	1
	Injection site pain	1 (3.3%) [0.2, 19.1]	1	1 (3.3%) [0.2, 19.1]	1	1 (3.3%) [0.2, 19.1]	2
Injury, poisoning and proc. complications		**1 (3.3%) [0.2, 19.1]**	**1**	**1 (3.3%) [0.2, 19.1]**	**1**	**1 (3.3%) [0.2, 19.1]**	**2**
	Needle track marks	1 (3.3%) [0.2, 19.1]	1	1 (3.3%) [0.2, 19.1]%]	1	1 (3.3%) [0.2, 19.1]	2

SAFT population

95% CI [xx.x, xx.x] Number of Participants (% in parenthesis). SOC=System Organ Class, PT=Preferred Term

There were no AEs reported directly by the TI.

There were no late onset of TRAEs, and no events were deemed to be granuloma.

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

Of the 9 reported TRAEs, the majority (8 events; 88.9%) occurred in 3 subjects where a linear threading injection technique was employed, while 1 (11.1%) TRAE was associated with a fan-like injection technique.

Linear threading injection technique was used for only 10 (33.3%) subjects, yet was associated with 88.9% of TRAEs. However, the small sample size for this study (i.e., n=30) does not provide sufficient power to determine the association between injection technique and TRAEs.

Lip Functionality

Lip functionality was assessed by evaluation of lip movements and lip sensation.
The mean proportion of words pronounced correctly at Visit 1 pre- and post-injection and at Visit 2 was 100%. Lip sensation (monofilament test) was assessed as per the proportion of touch-points that the subject could feel (based on a total of 3 touch-points per quadrant, subject blindfolded). The proportion of touch-points that subjects could feel at Visit 1 pre-injection and post-injection, and at Visit 2 was 100% for both treatment groups and in all quadrants. Lip sensation (cotton wisp test) was assessed as per the proportion of touch-points that the subject could feel (based on a total of 3 points per quadrant, subject blindfolded). The proportion of touch-points that subjects could feel at Visit 1 pre-injection and post-injection, and at Visit 2 was 100% for both treatment groups and in all quadrants

2. Effectiveness Results for Study G190055

Primary endpoint

The analysis of effectiveness was based on the PP population. To achieve non-inferiority, the observed p-value must be ≤0.05 (taking account of the non-inferiority margin). In case of non-inferiority, for achieving superiority of RHA® Redensity™ Mepi with mepivacaine over RHA® Redensity™ with lidocaine in terms of reducing pain, the observed p-value must be ≤0.05.
The level of pain during injection was 25.0±25.68 and 22.4±23.21 in the RHA® Redensity™ Mepi and RHA® Redensity™ group, respectively. This resulted in a difference between groups of –2.6±10.33 (Table 8). As the p-value (non-inferiority δ = 10mm) was <0.0001, non-inferiority was achieved.

Table 8: Injection Site Pain – Non-Inferiority – Primary Outcome*

	RHA® Redensity™ Mepi n=30	RHA® Redensity™ Mepi n=30	Difference** n=30
N	30	30	30
Mean ± SD	25.0 (25.63)	22.4 (23.21)	-2.6 (10.33)
Median (P25, P75)	20.0 (1.0, 39.0)	18.0 (0.0, 31.0)	0.0 (-4.0, 2.0)
Min, Max	0, 100	0, 86	-27, 10
95.0% CI	14.4, 34.5	13.7, 31.1	-6.4, 1.3
P-value (non-inferiority δ 10mm)	**<0.0002**		
P-value(superiority)	N/A***		

PP and ITT populations were identical

* During injection, upper perioral quadrants.

** If RHA® Redensity™ - RHA® Redensity™ Mepi<0, RHA® Redensity™ less painful than RHA® Redensity™ Mepi. If RHA® Redensity™ - RHA® Redensity™ Mepi>0, RHA® Redensity™ more painful than RHA® Redensity™ Mepi.

*** Superiority not tested.

Pain at injection

Other timepoints for injection pain were measured and compared for up to 60 minutes post-injection; however, they were not tested for non-inferiority.

By 15 minutes post-injection, injection pain was markedly reduced at 6.8±13.72 mm and 6.3±12.29 mm in the RHA® Redensity™ Mepi and RHA® Redensity™ group, respectively, and was totally absent by 60 minutes. There were no significant differences between treatment groups at any timepoint (Table 9).

The duration of anesthetic effect was also similar between treatment groups. The duration of anesthetic effect was 3.6±3.62 hours and 3.0±2.10 in the RHA® Redensity™ Mepi and RHA® Redensity™ group, respectively (Table 10).

Similar injection pain levels were reported between FST, ethnicity and age subgroups following RHA® Redensity™ Mepi and RHA® Redensity™ treatments.

Table 9: Injection Site Pain – Mean Pain

Pain VAS (mm)*	RHA® Redensity™ Mepi n=30	RHA® Redensity™ n=30	Difference** n=30
N	30	30	30
15 Min	6.8 (13.72)	6.3 (12.29)	-0.6 (2.16)
30 Min	1.0 (4.19)	1.0 (4.03)	-0.0 (0.18)
45 Min	0.4 (2.37)	0.3 (1.83)	-0.1 (0.55)
60 Min	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)

ITT Population (identical to PP population)
Mean (Standard Deviation)

* During injection, upper perioral quadrants.

** If RHA® Redensity™ - RHA® Redensity™ Mepi<0, RHA® Redensity™ less painful than RHA® Redensity™ Mepi. If RHA® Redensity™ - RHA® Redensity™ Mepi >0, RHA® Redensity™ more painful than RHA® Redensity™ Mepi.

Table 10: Duration of Anesthetic Effect

	RHA® Redensity™ Mepi n=30	RHA® Redensity™ n=30
N	29	29
Mean (SD)	3.59 (3.62)	3.01 (2.10)
Median (P25, P75)	2.28 (1.88, 4.05)	2.28 (1.93, 4.03)
Min, Max	0.9, 19.0*	0.3, 10.1
95% CI	2.21, 4.97	2.21, 3.81
Missing values	1 (3.3%)	1 (3.3%)

ITT Population (identical to PP population)
Mean (Standard Deviation)

** Subject 02-1801-003 was an outlier with an anesthetic duration of 19 hour for the RHA®1-M treatment group*

Secondary effectiveness analysis

Secondary endpoints included PR-SRS grade by the TI, the assessment of Global Aesthetic Improvement (GAI) by the TI and the subject. Effectiveness endpoints included two patient reported outcome measures as Subject Satisfaction and FACE-Q.

At Visit 1, the PR-SRS post-injection change from pre-injection was nearly the same between treatment groups with the RHA® Redensity™ Mepi and RHA® Redensity™ treatment groups posting reductions of -1.5±0.63 and -1.5±0.57, respectively. Similarly, at Visit 2 the RHA® Redensity™ Mepi and RHA® Redensity™ treatment groups posting reductions of -1.4±0.56 and -1.4±0.57, respectively, indicating no loss of effect at Month 1 post-injection. Responder rates were identical between treatment groups reaching 96.7%. No difference was observed in term of improvement on the PR-SRS between FST, ethnicity and age subgroups following RHA® Redensity™ Mepi and RHA® Redensity™ treatments.

The assessment of aesthetic improvement (GAI) by the TI and the subjects were identical between RHA® Redensity™ Mepi and RHA® Redensity™. The proportion of subjects demonstrating improvement (improved or much improved) at Visit 2 was 100% in both treatment groups as assessed by the TI and the subjects.

The FACE-Q score for the Perioral Rhytids domain on a scale of 0 to 100 was 12.5 and 13.0 at Visit 1 pre-injection for RHA® Redensity™ Mepi and RHA® Redensity™ respectively and 90.5 and 88.0 at Visit 2. Scores were similar between RHA® Redensity™ Mepi and RHA® Redensity™ before injection, after injection and at the last visit.

The proportion of subjects who were Satisfied or Very Satisfied with study treatment at Visit 2 was 96.7% (29/30) in both treatment groups. One subject was "Neither Satisfied nor Dissatisfied" with study treatment on either side of the face.

3. Subgroup Analyses for Study G190055

Treatment cohorts were stratified based on Fitzpatrick Skin Type (I-III vs IV), ethnicity (Hispanic vs Non-Hispanic) and age (≤59 and >59 years old).

Table 11: Subgroup analysis for RHA® Redensity™ Mepi for subjects who experienced at least 1 Treatment-Related AE

Subgroups		RHA® Redensity™ Mepi N=30	RHA® Redensity™ N=30
Fitzpatrick Skin Type (FST)	FST I-III (n=23)	2 (8.7%)	1 (4.3%)
	FST IV (n=7)	2 (28.6%)	2 (28.6%)
	FST V-VI (n=0)	NA*	NA*
Ethnicity	Hispanic (n=11)	2 (18.2%)	2 (18.2%)
	Non-Hispanic (n=19)	2 (10.5%)	1 (5.3%)
Age	≤ 59 year old (n=10)	1 (10%)	1 (10%)
	>59 year old (n=20)	3 (15%)	2 (10%)

*: there were no subjects enrolled with FST V-VI.

Common Treatment Reactions and Treatment-Related AE incidence rates were not negatively correlated with Fitzpatrick skin type IV, ethnicity and age.

4. Pediatric Extrapolation for Study G190055

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

G. Study Design for RHA® 4 Mepi for Study G190118 to Evaluate Effectiveness of RHA®4 Mepi in Reducing Pain

RHA®2 Mepi, RHA®3 Mepi and RHA®4 Mepi are identical gels except for their level of crosslinking: RHA®2 Mepi is the least crosslinked and RHA®4 Mepi is the most crosslinked. All three dermal fillers are indicated to be injected into the dynamic wrinkles and folds such as nasolabial folds. An analysis of the data of the subject's self-assessment of pain at time of injection in the long-term studies with approved RHA®2, RHA®3 and RHA®4 containing lidocaine (G140028 and G140106) showed that pain was slightly higher with the most crosslinked dermal filler RHA®4. As RHA®2 Mepi, RHA®3 Mepi and RHA®4 Mepi are identical to RHA®2, RHA®3 and RHA®4 except for their anesthetic agent (RHA® Mepi family of products containing mepivacaine and RHA® family of products containing lidocaine), the pain results of the RHA® family of products are applicable to RHA® Mepi family of products. The clinical study was performed with the worst-case representative of the three levels of crosslinked dermal fillers: RHA®4 Mepi. RHA®4 Mepi is the most crosslinked of RHA®2 Mepi, RHA®3 Mepi and RHA®4 Mepi, it is injected into the deeper layers of the dermis and subject reported pain assessment was slightly higher. The results of the study performed with RHA®4 Mepi are applicable to RHA®2 Mepi and RHA®3 Mepi.

The applicant performed this additional clinical study to demonstrate the safety and effectiveness of RHA®4 Mepi under IDE G190118. The purpose of this short term clinical study was to compare RHA®4 Mepi containing mepivacaine with RHA®4 containing lidocaine in terms of reducing pain during injection into the nasolabial folds. The goal was to show that RHA®4 Mepi was non inferior to RHA®4 in reducing pain as felt by the subject during injection assessed immediate after injection

of each side using a 100 mm Visual Analog Scale (VAS). The duration of the effectiveness of the anesthetic agent (mepivacaine or lidocaine) is less than a day.

Subjects were treated between October 30, 2019 and January 14, 2020. The database reflected data collected through February 18, 2020 and included 30 subjects who were randomized and completed the study. There were three U.S. investigational sites.

The clinical study was a randomized, double blinded, within-subject (split-face) study with the nasolabial fold of one side of the face injected with RHA®4 Mepi and the nasolabial fold (NLFs) of the other side injected with the approved control device RHA®4 (with lidocaine). The primary effectiveness objective was to demonstrate the non-inferiority of RHA®4 Mepi (with mepivacaine) versus the control (RHA®4 with lidocaine) in terms of reducing pain during device injection into the NLFs. Primary endpoint was injection site pain felt during injection of one NLF assessed by the subject immediately following injection with RHA®4 Mepi (with mepivacaine) compared to the injection site pain felt during injection into the contralateral NLF assessed immediately following injection with RHA®4 with lidocaine. RHA®4 Mepi and RHA®4 are completely identical except for 0.3% mepivacaine replacing 0.3% lidocaine. The clinical study was performed with RHA®4 Mepi as the representative product of the range of RHA®2 Mepi, RHA®3 Mepi and RHA®4 Mepi. Results are applicable to all 3 products. The study duration was 4 weeks and could be extended to 8 weeks for subjects who presented with an unresolved clinically significant device related Adverse Event.

Subjects received treatment of their NLFs with RHA®4 Mepi on one side and RHA®4 (the control) on the other side of the face. Subjects assessed their pain at time of injection and several times up to 60 minutes post injection using a 100 mm Visual Analog Scale (VAS). Subjects reported their Common Treatment Responses on a 30-day diary and the duration of the anesthetic effect and returned 30 days later for a final Visit 2. The treating investigator performed effectiveness and safety assessments at each visit, including during a call 3 days after treatment. Subjects performed effectiveness and satisfaction assessments when compared to Baseline, prior to injection.

The control group was the NLF of the same subject injected with RHA®4 which has been approved for the same indication and is identical to RHA®4 Mepi except for the anesthetic in the formulation, wherein RHA® 4 includes lidocaine and RHA®4 Mepi includes mepivacaine for pain reduction. RHA®4 is legally marketed in the United States.

1. Key Clinical Inclusion and Exclusion Criteria

Enrollment in pivotal study G190118 was limited to patients who met the following key 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.
- Moderate to severe bilateral aging defects in the nasolabial area, with wrinkles classified as NLF-WSRS grade 3 or 4 (ranging from 1 to 5)
- NLFs of the same NLF-WSRS grade on the left and right sides of the face (i.e., approximate bilateral symmetry);

- 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 not 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 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;
- Known susceptibility to keloid formation, hypertrophic scarring or skin pigmentation disorders;
- Clinically significant (Investigator discretion) active skin disease within 6 months prior to study entry;
- History of active chronic debilitating systemic disease, including insulin or non-insulin dependent diabetes;
- History of connective tissue disease (rheumatoid arthritis, scleroderma, systemic lupus erythematosus);
- History of malignancy, excluding non-melanoma skin cancer, within the past 5 years;
- 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;
- Exhibit a physical attribute(s) that may prevent assessment or treatment of NLFs such as excessive facial hair, traumatic or surgical facial scars, and/or excessive hyperpigmentation in the treatment areas;
- Elective, clinically significant facial procedures that may confound the interpretation of the results in the NLF area (TI discretion), prior to study enrollment;
- Herpes simplex lesion flare-ups greater than 6 per year;
- Clinically active disease or infection in the NLF area;
- Subjects with known prolonged bleeding times because of disease or medication. If on a drug or supplement that prolongs bleeding times (e.g., non-steroidal anti-inflammatory, anticoagulant, high-dose vitamin E, fish oil, corticosteroids), wait 14 days or until bleeding times return to normal before injecting. (Note: low dose 81mg/day acetylsalicyclic acid (ASA) is permitted).
- 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, in the judgment of the Investigator, would make the subject inappropriate for entry into this study;
- Clinically significant alcohol or drug abuse, or history of poor cooperation or unreliability;
- Exposure to any other investigational drug/device within 90 days of entering the study;
- 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.

2. Follow-up Schedule

At Visit 1, RHA®4 Mepi with mepivacaine was administered in a randomly selected sequence (first or second injection) and side of the face, and RHA®4 with lidocaine was administered to the other side. Immediately after injection of each side, subjects rated injection site pain experienced **during injection** using a 100 mm Visual Analog Scale (VAS). Injection site pain was also assessed at 15, 30, 45 and 60 minutes post-injection.
Additionally, subjects assessed anesthetic sensation on each side of the face every hour until normal sensation returned; the time for return to normal sensation was recorded.

Subjects attended Visit 2 (30 days post-injection) where efficacy and safety assessments were conducted. Subjects who presented with an unresolved clinically significant device related Adverse Event (AE) at Visit 2 received the optional follow-up phone call no later than 30 days after Visit 2. If the clinically significant AE remained unresolved, the Investigator requested that the subject attend the optional in-clinic follow-up visit (i.e., Visit 3) within 5 working days. Follow-up of the clinically significant AE continued until the AE was resolved or the TI determined that additional follow-up was not necessary.

3. Clinical Endpoints

Injection site pain was measured on each side of the face during the injection (primary endpoint) as well as at 15, 30, 45 and 60 minutes post-injection. The duration of the anesthetic effect on each side of the face was also followed on the patient diary. For safety evaluations, post-injection Common Treatment Responses (CTRs) including visual disturbances were assessed on a 30-Day patient CTR diary. Assessment of visual disturbances (Snellen visual acuity, confrontational visual fields test and ocular) motility were assessed by the TI at each visit.
CTRs that were present on the last day of diary entry, regardless of severity and duration, were automatically recorded as AEs. Adverse Events (AEs) were assessed by the TI at each visit and during a call 3 days after treatment. 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.

The primary effectiveness objective was to demonstrate the non-inferiority of RHA®4 Mepi with mepivacaine versus the control (RHA®4 with lidocaine) in terms of reducing pain during device injection into the NLFs. Pain during injection was based on the 100 mm Visual Analog Scale (VAS), as assessed by subjects immediately after injection of each side. The primary effectiveness assessment consisted in comparing the injection site pain felt during injection of one NLF assessed by the subject immediately following injection with RHA®4 Mepi (with mepivacaine) with the injection site pain felt during injection into the contralateral NLF assessed immediately following injection with RHA®4 (with lidocaine). Statistical analysis of the primary endpoint was performed using paired one-sided tests, with a significance level of 0.05, either parametric or non-parametric as appropriate.

Secondary effectiveness endpoints included the comparison of the Nasolabial Fold Wrinkle Severity Rating Scale (NLF-WSRS) severity on each side of the face and comparing them to Baseline using Teoxane validated 5-grade photonumeric scale measuring the severity of the NLFs (Wrinkles Severity Rating Scale) (see Table 12 and Figure 2 below). Other secondary effectiveness endpoints included the Subject FACE-Q Assessment (NLF domain) at Baseline and Visit 2, patient satisfaction assessment at Visit 1 after treatment and at Visit 2 and the Global Aesthetic Improvement (GAI) assessment by the subject and the TI at Visit 1 after treatment and at Visit 2. The total volume required to achieve Optimal Cosmetic Result (OCR) was also reported for each device.

Teoxane validated a proprietary Nasolabial Fold Wrinkle Severity Rating Scale (NLF-WSRS).

Table 12: Teoxane Nasolabial Fold Wrinkle Severity Rating Scale (NLF-WSRS)

Grade	Name	Description
1	Absent	No nasolabial fold, continuous skin line
2	Mild	Shallow but visible fold, slight indentation
3	Moderate	Moderately deep nasolabial fold, clear facial feature visible
4	Severe	Very deep nasolabial fold, prominent 3 dimensional feature
5	Extreme	Extremely deep and long nasolabial fold, skin redundancy

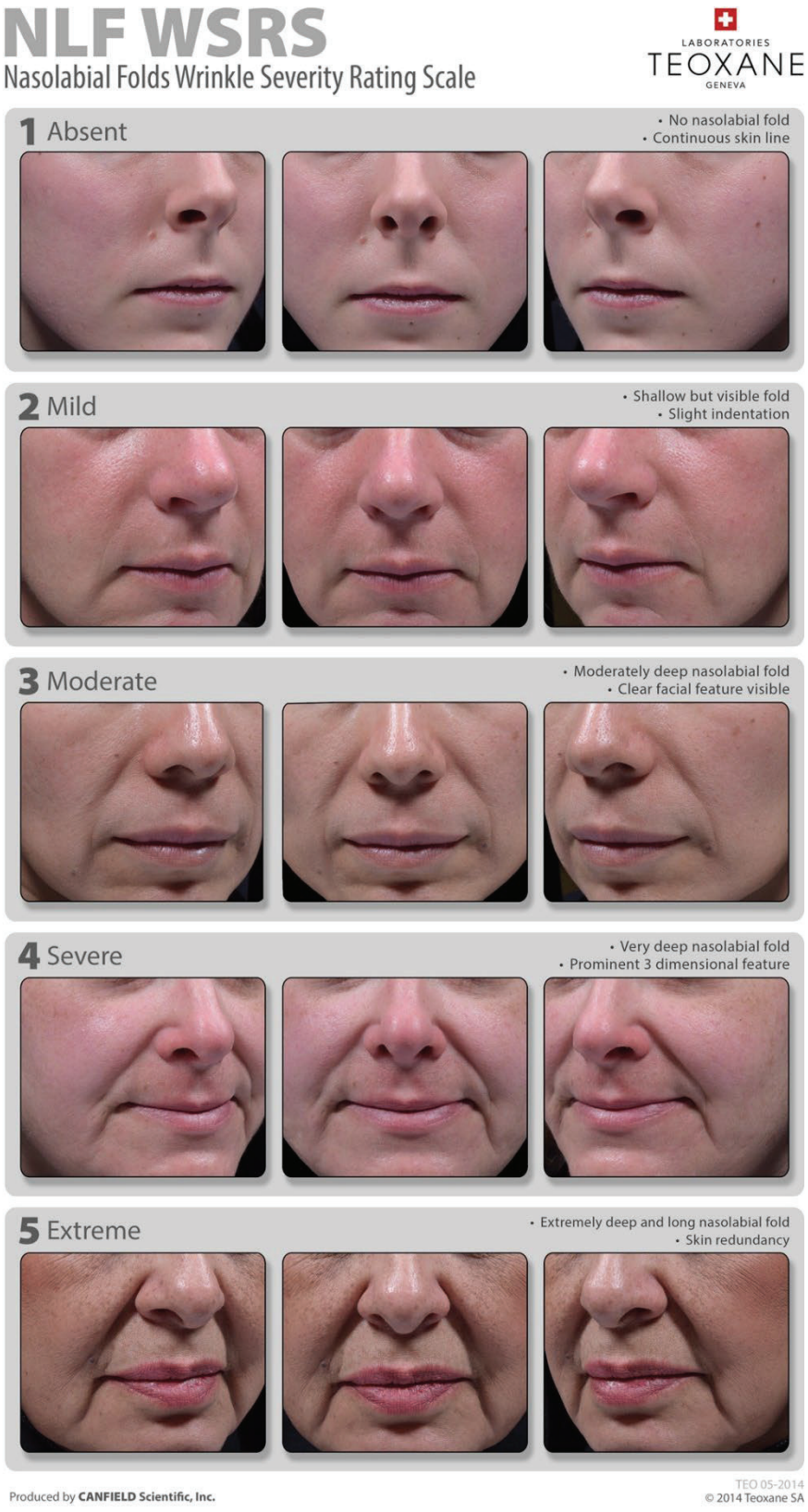

Figure 2: Teoxane NLF-WSRS

H. Accountability of PMA Cohort for RHA® 4 Mepi for Study G190118

At the time of the database lock, the 30 subjects who were randomized and enrolled, all (100%) completed the study. Each subject was injected with RHA®4 Mepi in one NLF and RHA®4 in the other NLF. There were no subjects who dropped out or were lost to follow-up prior to the final study visit.

There were no major protocol deviations reported in the study. As such, the ITT and PP populations consisted of all randomized/enrolled subjects (i.e. n=30). The Safety (SAFT) population consisted of all study subjects that were randomized and received treatment with at least one of study device, i.e. n=30.

I. Study Population Demographics and Baseline Parameters for Study G190118

Subjects had a mean age of 57.0 years and an average BMI of 28.1. The majority of subjects were female (90.0%). The majority of subjects identified as Caucasian (90.0%), with 10% of subjects identifying as Black or African American. Fitzpatrick skin types were well represented with 63.3% of subjects having skin types I-III, and 36.7% of subjects having skin types IV to VI (with 10% of subjects having skin types V/VI). Fitzpatrick skin type is a classification intended to reflect individual sun sensitivity and not race or phenotypic features.
More than 36% of subjects in the study presented Fitzpatrick skin type IV to VI which is well 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 13: Demographic characteristics at Baseline

Demographic Variable	*n=30*
Age (years)	
N	30
Mean (SD) [95% CIs]	**57.0 ± 9.7 [53.4, 60.6]**
Median (P25, P75)	**55.5 (52.0, 61.8)**
Min, Max	**33.0 – 79.0**
Missing values	0
BMI (kg/m²)	
N	30
Mean (SD) [95% CIs]	28.1 ± 4.5 [26.5, 29.8)
Median (P25, P75)	27.6 (25.3, 29.5)
Min, Max	20.7 – 37.8
Missing values	0
Gender	
N	30
Male	3 (10.0%)
Female	27 (90.0%)
Missing values	0
Race	
N	30

Demographic Variable	*n=30*
Caucasian	27 (90.0%)
Black or African American	3 (10.0%)
American Indian, Alaska Native	0 (0.0%)
Asian	0 (0.0%)
Nat. Hawaiian, Pacific Islander	0 (0.0%)
Other	0 (0.0%)
Missing values	0
Ethnicity	
N	30
Hispanic or Latino	12 (40.0%)
Not-Hispanic or Latino	18 (60.0%)
Missing values	0
Fitzpatrick Skin Type	
N	30
I-III	**19 (63.3%)**
I	1 (3.3%)
II	8 (26.7%)
III	10 (33.3%)
IV-VI	**11 (36.7%)**
IV	8 (26.7%)
V	0 (0.0%)
VI	3 (10.0%)
Missing values	0

The overall total mean volume of RHA®4 Mepi injected to achieve optimal correction results was 1.09 ± 0.31 ml. It was 1.08 ± 0.32 ml for RHA®4.

J. Safety and Effectiveness Results for Study G190118

1. Safety Results for Study G190118

The analysis of safety was based on the Safety cohort of 30 subjects who were randomized and all completed the study. The Common Treatment Responses for this study are presented below in Table 14 and Table 15.

Safety of RHA®4 Mepi was evaluated through a 30-day patient Common Treatment Response (CTR) diary which was completed after the injection individually for each side of the face, AE assessments at each visit, visual disturbances before and after injection and at each visit and measurement of injection site pain at time of injection and up to 60 minutes after injection for each side of the face.

Common Treatment Responses (CTR)

In both treatment groups, 29 of the 30 subjects (96.7%) experienced at least one CTR. The proportions of subjects experiencing at least one CTR of each category (e.g., Bruising, Lumps/Bumps, etc.) was similar between treatment groups with the majority of CTRs (292/320, 91.3%) resolving in 14 days or fewer.

Of the 320 CTRs that occurred following study treatments (including the CTRs reported in the "other" category by the subjects), 292 (91.3%) had a cumulative duration of 14 days or less (i.e., 142 [44.4%] 1-3 days, 88 [27.5%] 4-7 days, and 62 [19.4%] 8-14 days). There were 28 (8.8%) CTRs which had a cumulative duration of 15-30 days (i.e., 17 [5.3%] 15-21 days and 11 [3.4%] 22-30 days).

Ten CTRs from 5 subjects were recorded on the last day of the diary, and each was automatically elevated to a Treatment-Related AE. In total, 5 (16.7%) and 4 (13.3%) subjects in the RHA®4 Mepi and RHA®4 groups recorded CTRs on the last day of the diary.
Specifically, on the last day of the CTR diary:

- One subject reported itching with RHA®4 Mepi and RHA®4, and firmness with RHA®4
- Three subjects reported firmness with RHA®4 Mepi and RHA®4
- One subject reported lumps/bumps with RHA®4 Mepi

On the last day of diary when they were automatically elevated to Treatment-Related AEs (TRAEs), all CTRs were mild in severity. All TRAEs had resolved by the time of the study exit except the lumps/bumps for one subject. This event resolved spontaneously by day 46 post-injection without intervention.

One subject recorded a symptom in the "other" category. Specifically, on subject experienced paresthesia on the corner of the mouth (on the side treated with RHA®4 Mepi) that was elevated to a Treatment-Related AE (i.e., paresthesia oral) that was of mild severity and which resolved in 2 days.

Table 14: CTRs by Duration

			Cumulative Duration (days)					
CTR	**Group**	**≥1 CTR**	**1-3**	**4-7**	**8-14**	**15-21**	**22-30**	**CTR Last Day Diary**
At least 1 CTR	**RHA®4 Mepi**	**29 (96.7%)**	**-**	**-**	**-**	**-**	**-**	**5 (16.7%)**
	RHA®4	**29 (96.7%)**	**-**	**-**	**-**	**-**	**-**	**4 (13.3%)**
Bruising	RHA®4 Mepi	19 (63.3%)	8 (26.7%)	5 (16.7%)	5 (16.7%)	1 (3.3%)	0 (0.0%)	0 (0.0%)
	RHA®4	21 (70.0%)	9 (30.0%)	8 (26.7%)	4 (13.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Discoloration	RHA®4 Mepi	11 (36.7%)	6 (20.0%)	5 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	RHA®4	12 (40.0%)	7 (23.3%)	3 (10.0%)	2 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Firmness	RHA®4 Mepi	24 (80.0%)	5 (16.7%)	4 (13.3%)	9 (30.0%)	1 (3.3%)	5 (16.7%)	3 (10.0%)
	RHA®4	22 (73.3%)	2 (6.7%)	6 (20.0%)	6 (20.0%)	6 (20.0%)	2 (6.7%)	4 (13.3%)
Itching	RHA®4 Mepi	7 (23.3%)	5 (16.7%)	1 (3.3%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	1 (3.3%)
	RHA®4	6 (20.0%)	4 (13.3%)	1 (3.3%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	1 (3.3%)
Lumps/Bumps	RHA®4 Mepi	22 (73.3%)	8 (26.7%)	2 (6.7%)	9 (30.0%)	1 (3.3%)	2 (6.7%)	1 (3.3%)
	RHA®4	21 (70.0%)	5 (16.7%)	4 (13.3%)	6 (20.0%)	5 (16.7%)	1 (3.3%)	0 (0.0%)
Pain†	RHA®4 Mepi	12 (40.0%)	9 (30.0%)	3 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	RHA®4	9 (30.0%)	7 (23.3%)	2 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Redness	RHA®4 Mepi	21 (70.0%)	12 (40.0%)	7 (23.3%)	2 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	RHA®4	20 (66.7%)	13 (43.3%)	6 (20.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Swelling	RHA®4 Mepi	21 (70.0%)	9 (30.0%)	7 (23.3%)	5 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	RHA®4	23 (76.7%)	10 (33.3%)	8 (26.7%)	4 (13.3%)	1 (3.3%)	0 (0.0%)	0 (0.0%)
Tenderness	RHA®4 Mepi	24 (80.0%)	10 (33.3%)	8 (26.7%)	4 (13.3%)	1 (3.3%)	1 (3.3%)	0 (0.0%)
	RHA®4	24 (80.0%)	12 (40.0%)	8 (26.7%)	3 (10.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)
Other (Paresthesia) ††	RHA®4 Mepi	1 (3.3%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	RHA®4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

† *A total of 14 subjects reported pain as a CTR. Of these, 7 subjects reported pain on both sides of their face, 5 subjects reported pain on the RHA4 Mepi side only, and 2 subjects report pain on the RHA4 side only. Based on the small sample, these differences between groups are not considered to be clinically significant.*

†† *As this event was **written** into the CTR diary as "other" it was immediately processed as AEs and was not subject to CTR reporting rules for AEs (i.e., elevation to AEs if present on the last day of the diary).*

Out of the 320 reported CTRs, severity was reported as "Mild" or "Moderate" for 308 (96.3%), with 12 (3.8%) CTRs rated by subjects as "Severe". The most common severe CTRs were Firmness (2 CTRs in each treatment group) and Redness (3 and 2 CTRs in the RHA®4 Mepi and RHA®4 treatment group, respectively).

Table 15: CTRs by severity

			Maximum Severity within 30 Days			
CTR	**Group**	**≥1 CTR**	**None**	**Mild**	**Moderate**	**Severe**
At least 1 CTR	**RHA®4 Mepi**	**29 (96.7%)**	**1 (3.3%)**	**8 (26.7%)**	**18 (60.0%)**	**3 (10.0%)**
	RHA®4	**29 (96.7%)**	**1 (3.3%)**	**8 (26.7%)**	**19 (63.3%)**	**2 (6.7%)**
Bruising	RHA®4 Mepi	19 (63.3%)	11 (36.7%)	7 (23.3%)	12 (40.0%)	0 (0.0%)
	RHA®4	21 (70.0%)	9 (30.0%)	10 (33.3%)	11 (36.7%)	0 (0.0%)
Discoloration	RHA®4 Mepi	11 (36.7%)	19 (63.3%)	8 (26.7%)	2 (6.7%)	1 (3.3%)
	RHA®4	12 (40.0%)	18 (60.0%)	8 (26.7%)	4 (13.3%)	0 (0.0%)
Firmness	RHA®4 Mepi	24 (80.0%)	6 (20.0%)	12 (40.0%)	10 (33.3%)	2 (6.7%)
	RHA®4	22 (73.3%)	8 (26.7%)	9 (30.0%)	11 (36.7%)	2 (6.7%)

			Maximum Severity within 30 Days			
CTR	**Group**	**≥1 CTR**	**None**	**Mild**	**Moderate**	**Severe**
Itching	RHA®4 Mepi	7 (23.3%)	23 (76.7%)	7 (23.3%)	0 (0.0%)	0 (0.0%)
	RHA®4	6 (20.0%)	24 (80.0%)	6 (20.0%)	0 (0.0%)	0 (0.0%)
Lumps/Bumps	RHA®4 Mepi	22 (73.3%)	8 (26.7%)	10 (33.3%)	11 (36.7%)	1 (3.3%)
	RHA®4	21 (70.0%)	9 (30.0%)	10 (33.3%)	11 (36.7%)	0 (0.0%)
Pain	RHA®4 Mepi	12 (40.0%)	18 (60.0%)	10 (33.3%)	2 (6.7%)	0 (0.0%)
	RHA®4	9 (30.0%)	21 (70.0%)	6 (20.0%)	3 (10.0%)	0 (0.0%)
Redness	RHA®4 Mepi	21 (70.0%)	9 (30.0%)	12 (40.0%)	6 (20.0%)	3 (10.0%)
	RHA®4	20 (66.7%)	10 (33.3%)	14 (46.7%)	4 (13.3%)	2 (6.7%)
Swelling	RHA®4 Mepi	21 (70.0%)	9 (30.0%)	11 (36.7%)	9 (30.0%)	1 (3.3%)
	RHA®4	23 (76.7%)	7 (23.3%)	14 (46.7%)	9 (30.0%)	0 (0.0%)
Tenderness	RHA®4 Mepi	24 (80.0%)	6 (20.0%)	16 (53.3%)	8 (26.7%)	0 (0.0%)
	RHA®4	24 (80.0%)	6 (20.0%)	18 (60.0%)	6 (20.0%)	0 (0.0%)
Other (Paresthesia)	RHA®4 Mepi	1 (3.3%)	0 (0.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)
	RHA®4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

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 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, 100% of them were based on CTR diary entries (Table 16).

The 10 CTRs (5 from RHA®4 Mepi and 5 from RHA®4) that lasted until the last day of the diary were automatically elevated to the status of a device-related AE. They were all considered to be mild by the subject and by the TI.
In addition Paresthesia, the only "non-CTR" event that was reported in the diary, was also automatically elevated to the status of an AE; and considered to be mild by the subject and by the TI. It lasted for 2 days.

Of the eleven (11) AEs, all were Treatment-Related (Table 16).

Table 16: Treatment-Related AEs Sorted by SOC and PT

TRAEs		**RHA®4 Mepi**		**RHA®4**		**All**	
SOC	**PT**	n=30		n=30		n=30	
		Subjects	**Events**	**Subjects**	**Events**	**Subjects**	**Events**
Any TRAE		**5 (16.7%) [6.3, 35.5]**	**6**	**4 (13.3%) [4.4, 31.6]**	**5**	**5 (16.7%) [6.3, 35.5]**	**11**
Gen. disorders and admin. site conditions		**5 (16.7%) [6.3, 35.5]**	**5**	**4 (13.3%) [4.4, 31.6]**	**5**	**5 (16.7%) [6.3, 35.5]**	**10**

TRAEs		RHA®4 Mepi		RHA®4		All	
SOC	PT	n=30		n=30		n=30	
		Subjects	Events	Subjects	Events	Subjects	Events
	Injection site induration	3 (10%) [2.6, 27.7]	3	4 (13.3%) [4.4, 31.6]	4	4 (13.3%) [4.4, 31.6]	7
	Injection site mass	1 (3.3%) [0.2, 19.1]	1	0 (0%) [--, --]	0	1 (3.3%) [0.2, 19.1]	1
	Injection site pruritus	1 (3.3%) [0.2, 19.1]	1	1 (3.3%) [0.2, 19.1]	1	1 (3.3%) [0.2, 19.1]	2
Nervous system disorders		**1 (3.3%) [0.2, 19.1]**	**1**	**0 (0%) [--, --]**	**0**	**1 (3.3%) [0.2, 19.1]**	**1**
	*Paresthesia oral	1 (3.3%) [0.2, 19.1]	1	0 (0%) [--, --]	0	1 (3.3%) [0.2, 19.1]	1

SAFT population

95% CI [xx.x, xx.x] Number of Participants (% in parenthesis). SOC=System Organ Class, PT=Preferred Term

There were no AEs reported directly by the TI.

There was no late onset of TRAEs, and no events were deemed to be a granuloma.

All eleven (11) AEs that were Treatment-Related were reported by five (5) subjects (5/30, 16.7%).

- One subject reported intermittent Firmness on the side of RHA®4 and Itching on both sides with RHA®4 Mepi and RHA®4
- One subject reported Firmness on both sides with RHA®4 Mepi and RHA®4 and Paresthesia on the side of RHA®4 Mepi
- One subject reported Lump/Bump on the side of RHA®4 Mepi that lasted to the last day of the diary
- Two subjects reported Firmness on both sides with RHA®4 Mepi and RHA®4

All AEs were Treatment-Related and deemed to be mild by the TI. All AEs had resolved by the time of the study exit except lump/bump for one subject (on side of RHA®4 Mepi) that lasted 46 days post-injection, and the TI deemed that no additional follow-up was necessary as it is a Common Treatment Response.

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

Of the 11 reported TRAEs, the majority (8 events; 72.7%) occurred in 3 subjects where a fan-like injection technique was employed. A total of 2 (18.2%) TRAEs were associated with a linear threading/multiple punctate pools injection technique, and 1 (9.1%) TRAE was associated with a linear threading/fan-like injection technique. The small sample size for the study (i.e., n=30) does not provide sufficient power to allow for a viable interpretation of the association between injection technique and TRAEs.

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

The average volume injected into the NLF was nearly identical between treatment groups with volumes of 1.09±0.31 and 1.08±0.32 in the RHA®4 Mepi and RHA®4 groups, respectively.

2. Effectiveness Results for Study G190188

Primary endpoint

The analysis of effectiveness was based on the PP population. To achieve non-inferiority, the observed p-value must be ≤0.05 (taking account of the non-inferiority margin). In case of non-inferiority, for achieving superiority of RHA®4 Mepi with mepivacaine over RHA®4 with lidocaine in terms of reducing pain, the observed p-value must be ≤0.05.
The level of pain during injection was 17.1±18.38 and 16.3±18.89 in the RHA®4 Mepi and RHA®4 groups, respectively. This resulted in a difference between groups of -0.8±8.09 (Table 17). As the p-value (non-inferiority δ = 10mm) was <0.0001, non-inferiority was achieved.
Superiority of RHA®4 Mepi in reducing injection pain was not tested.

Table 17: Injection Site Pain – Non-Inferiority – Primary Outcome

	RHA®4 Mepi n=30	**RHA®4** n=30	**Difference**** n=30
N	30	30	30
Mean (SD)	17.1 (18.38)	16.3 (18.89)	-0.8 (8.09)
Median (P25, P75)	12.5 (0.0, 29.0)	10.0 (0.0, 28.0)	0.0 (-2.0, 1.0)
Min, Max	0, 55	0, 70	-20, 20
CI 95.0%	10.2, 23.9	9.2, 23.3	-3.8, 2.2
P-value (non-inferiority δ 10mm)	**<0.0001**		
P-value(superiority)	N/A***		

PP and ITT populations were identical
* During injection
** If RHA®4 - RHA®4 Mepi <0, RHA®4 less painful than RHA® 4-Mepi. If RHA®4 - RHA®4 Mepi >0, RHA®4 more painful than RHA®4 Mepi.
*** Superiority not tested.

Pain at injection
Other timepoints for injection pain were measured and compared statistically for up to 60 minutes post-injection; however, they were not tested for non-inferiority.

By 15 minutes post-injection, injection pain was markedly reduced at 4.9±12.33 and 5.1±15.94 in the RHA®4 Mepi and RHA®4 groups, respectively (Table 18). At 60 minutes post-injection pain was 0±0 and 1.9±10.22 in the RHA®4 Mepi and RHA®4 groups, respectively (Table 18).
The duration of anesthetic effect was also similar between treatment groups. The duration of anesthetic effect was 6.0±5.89 hours and 4.1±4.53 in the RHA®4 Mepi and RHA®4 groups, respectively (Table 19).

Similar injection pain level was reported between FST, ethnicity and age subgroups following RHA®4 Mepi and RHA®4 treatments.

Table 18: Injection Site Pain – Mean Pain

Pain VAS (mm)	**RHA®4 Mepi** n=30	**RHA®4** n=30	**Difference*** n=30
N	**30**	**30**	**30**
15 Min	4.9 (12.33)	5.1 (15.94)	0.2 (6.81)
30 Min	2.0 (5.66)	3.1 (12.30)	1.1 (10.36)
45 Min	0.0 (0.00)	2.1 (11.68)	2.1 (11.68)

Pain VAS (mm)	RHA®4 Mepi n=30	RHA®4 n=30	Difference* n=30
60 Min	0.0 (0.00)	1.9 (10.22)	1.9 (10.22)

ITT Population (identical to PP population)
Mean (Standard Deviation)
* If RHA®4 - RHA®4 Mepi <0, RHA®4 less painful than RHA®4 Mepi . If RHA®4 - RHA®4 Mepi >0, RHA®4 more painful than RHA®4 Mepi

Table 19: Duration of Anesthetic Effect

	RHA®4 Mepi n=30	RHA®4 n=30
N	29	29
Mean (SD)	5.95 (5.886)	4.11 (4.534)
Median (P25, P75)	3.08 (2.25, 6.20)	2.73 (2.02, 4.10)
Min, Max	1.0, 22.3*	1.0, 22.2*
95% CI	3.71, 8.18	2.39, 5.83
Missing values	1	1

ITT Population (identical to PP population)
Mean (Standard Deviation)
** Subject 02-1801-008 was an outlier with anesthetic duration approximately 22 hours for both treatment groups*

Secondary effectiveness analysis

Secondary endpoints included NLF-WSRS grade by the TI, the assessment of Global Aesthetic Improvement (GAI) by the TI and the subject. Effectiveness endpoints included two patient reported outcome measures as Subject Satisfaction and FACE-Q.

The NLF-WSRS post-injection change from pre-injection was identical between both treatment groups, with a 100% responder rates. At Visit 2, the RHA®4 Mepi and RHA®4 treatment groups posted reductions of -1.9±0.48 and -1.8±0.63, respectively, indicating no loss of effect at Month 1 post-injection. These results (i.e., nearly a 2-grade improvement from pre-injection) are comparable to those obtained in a previous study with RHA®4 (TEO-RHA-1402 – IDE G140106) where an NLF-WSRS change from pre-injection of -1.9±0.58 was achieved at Week 4. Responder rates were comparable in both treatment groups, reaching 100% and 96.7% for RHA®4 Mepi and RHA®4, respectively. No difference was observed in term of improvement on the NLF-WSRS between FST, ethnicity and age subgroups following RHA®4 Mepi and RHA®4 treatments.

The assessment of aesthetic improvement (GAI) by the TI and the subjects were nearly identical between RHA®4 Mepi and RHA®4. The proportion of subjects demonstrating improvement (improved or much improved) at Visit 2 was 100% and 96.7% in the RHA®4 Mepi and RHA®4 treatment groups, as assessed by the TI and 100% for both groups as assessed by the subjects.

The FACE-Q score for the NLF domain on a scale of 0 to 100 was 25.2 and 24.3 at Visit 1 pre-injection for RHA®4 Mepi and RHA®4 respectively and 89.0 and 88.5 at Visit 2. Scores were similar before injection, after injection and at the last visit.

The proportion of subjects who were Satisfied or Very Satisfied with study treatment at Visit 2 was 96.7% (29/30) in both treatment groups. One subject was “Neither Satisfied nor Dissatisfied” with study treatment on either side of the face.

3. Subgroup Analyses for Study 1802

Treatment cohorts were stratified based on Fitzpatrick Skin Type (I-III vs IV-VI), ethnicity (Hispanic vs Non-Hispanic) and age (≤59 and >59 years old).

Table 20: Subgroup analysis for RHA® 4 Mepi for subjects who experienced at least 1 Treatment Related AE

Subgroups		RHA® 4 Mepi N=30	RHA® 4 N=30
Fitzpatrick Skin Type (FST)	FST I-III (n=19)	4 (21.1%)	3 (15.8%)
	FST IV-VI (n=11)	1 (9.1%)	1 (9.1%)
Ethnicity	Hispanic (n=12)	1 (8.3%)	1 (8.3%)
	Non-Hispanic (n=19)	4 (22.2%)	3 (16.7%)
Age	≤ 59 year old (n=20)	3 (15.0%)	2 (10.0%)
	>59 year old (n=10)	2 (20.0%)	2 (20.0%)

Common Treatment Reactions and Treatment-Related AE incidence rates were not negatively correlated with higher Fitzpatrick skin type, ethnicity and age.

4. Pediatric Extrapolation for Study G190188

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

K. Financial Disclosure for Studies G190055 and G190118

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 G190055 included 3 investigators. The pivotal clinical study G190118 included 3 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 G190055

Study results clearly demonstrate that RHA® Redensity™ Mepi containing mepivacaine is non-inferior to RHA® Redensity™ containing lidocaine with regard to injection pain. There were no significant differences out to 60 minutes post-injection with pain being markedly reduced in both groups by 15 minutes post-injection. Furthermore, there were no significant differences between groups with regard to duration of anesthetic effect, PR-SRS, FACE-Q, GAI, and Patient Satisfaction.
No differences in injection site pain were found between FST, ethnicity and age subgroups. Improvement on the PR-SRS was similar between FST, ethnicity and age subgroups following RHA® Redensity™ Mepi and RHA® Redensity™ treatments.

The anesthetic profile of RHA® Redensity™ Mepi was the same as RHA® Redensity™.The lidocaine studies for RHA® Redensity™ for the perioral rhytids were leveraged to support the effectiveness of the mepivacaine products (RHA® Redensity™ Mepi). We have an understanding of the overall effectiveness of the devices based on what we learned in the lidocaine studies (presented in the SSED available on the CDRH website under approved supplement P170002/S012 on December 22, 2021). This data for the lidocaine studies was relied upon to provide certainty of benefit for the subject devices containing mepivacaine.

Study G190118

Study results clearly demonstrate that RHA®4 Mepi containing mepivacaine is non-inferior to RHA®4 containing lidocaine with regard to injection pain. There were no significant differences out to 60 minutes post-injection with pain being markedly reduced in both groups by 15 minutes post-injection. Furthermore, there were no significant differences between groups with regard to duration of anesthetic effect, NLF-WSRS, FACE-Q, GAI, and Patient Satisfaction.
No differences in injection site pain were found between FST, ethnicity and age subgroups. Improvement on the NLF-WSRS was similar between FST, ethnicity and age subgroups following RHA®4 Mepi and RHA®4 treatments.
The results of IDE G190118 with RHA®4 Mepi are applicable to RHA®2 Mepi and RHA®3 Mepi for the same indications, i.e. for the correction of moderate to severe dynamic facial wrinkles and folds such as nasolabial folds, in adults aged 22 years or older.

The anesthetic profile of RHA®4 Mepi was the same as RHA®4.

The lidocaine studies for RHA®2, RHA®3 and RHA®4 for the NLFs were leveraged to support the effectiveness of the mepivacaine products (RHA®2 Mepi RHA®3 Mepi and RHA®4 Mepi). We have an understanding of the overall effectiveness of the devices based on what we learned in the lidocaine studies (presented in the SSED available on CDRH website under original approval of P170002 on October 19, 2017). This data for the lidocaine studies was relied upon to provide certainty of benefit for the subject devices containing mepivacaine.

B. Safety Conclusions

Study G190055

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

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

Treatment-Related Adverse Events rates were not negatively correlated with higher Fitzpatrick skin type IV, ethnicity (Hispanic vs Non-Hispanic) and age (subjects aged ≤59 vs >59).

The Adverse Events were all anticipated and were typical of a dermal filler injected in the perioral rhytids area. There were no late onset TRAEs. All TRAEs were mild and resolved without the need for therapy. The majority of adverse events were the results of CTRs that lasted until the last day of the diary. Investigators were not required to consider that a CTR was clinically significant or clinically relevant in order for a CTR to be elevated to AE status; the CTR only needed to persist out to Day 30 of the diary (or be present on the last day of diary entry). Thus, the sensitivity for reporting Treatment-Related AEs was amplified by this method of handling CTR diary entries.

The lidocaine studies for RHA® Redensity™ for the perioral rhytids were leveraged to support the safety of mepivacaine products (RHA® Redensity™ Mepi). Overall, the type, and duration of CTRs were similar between RHA® Redensity™ Mepi and RHA® Redensity™. Similarly, the type and severity of AEs (Treatment-Related) were similar between RHA® Redensity™ Mepi and RHA® Redensity™.

Study G190118

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

Study treatment with RHA®4 Mepi as representative and worst case formulation of RHA®2 Mepi, RHA®3 Mepi, RHA®4 Mepi formulations, appeared to be safe and well tolerated. There were no reports of deaths, Treatment-Related Serious Adverse Events or Unexpected Adverse Device Effects in the study.

Treatment-Related Adverse Events rates were not negatively correlated with higher Fitzpatrick skin type, ethnicity (Hispanic vs Non-Hispanic) and age (subjects aged ≤59 vs >59).

The Adverse Events were all anticipated and were typical of a dermal filler injected in the nasolabial folds area. There were no late onset TRAEs. All TRAEs were mild and resolved without the need for therapy. The majority of adverse events were the results of CTRs that lasted until the last day of the diary. Investigators were not required to consider that a CTR was clinically significant or clinically relevant in order for a CTR to be elevated to AE status; the CTR only needed to persist out to Day 30 of the diary (or be present on the last day of diary entry). Thus, the sensitivity for reporting Treatment-Related AEs was amplified by this method of handling CTR diary entries.

The lidocaine studies for RHA®2, RHA®3 and RHA®4 for the NLFs were leveraged to support the safety of mepivacaine products (RHA®2 Mepi RHA®3 Mepi and RHA®4 Mepi). Overall, the type, and duration of CTRs were similar between RHA®4 Mepi and RHA®4. Similarly, the type and severity of AEs (Treatment-Related) were similar between RHA®4 Mepi and RHA®4.

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.

Study G190055 was a randomized, controlled, double-blinded, within subject (split-face), multicenter and prospective study using the subject assessment of pain immediately after injection using a 100 mm Visual Analog Scale to determine the effectiveness primary endpoint. This is a strong study design for determining the effect of the anesthetic agent. Non-inferiority was confirmed between RHA® Redensity™ Mepi and RHA® Redensity™. Common Treatment Responses and Treatment Related Adverse Events were typical and expected in associated with injection of a dermal fillers and the rates of events were nearly identical for RHA® Redensity™ Mepi and its control. 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 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 nasolabial fold domain of the validated FACE-Q© patient-reported outcome measurement
- Subject satisfaction survey

The sole difference between RHA® Redensity™ and RHA® Redensity™ Mepi products is the anesthetic agent, lidocaine or mepivacaine. In conclusion, given the available information above, data support that the difference in anesthetic agent of RHA® Redensity™ Mepi dermal fillers had no impact on clinical performance or safety of the devices for the correction of moderate to severe dynamic perioral rhytids in adults aged 22 years or over, and the probable benefits outweigh the probable risks.

Study G190118 (Study 1802) was a randomized, controlled, double-blinded, within subject (split-face), multicenter and prospective study using the subject assessment of pain immediately after injection using a 100 mm Visual Analog Scale to determine the effectiveness primary endpoint. This is a strong study design for determining the effect of the anesthetic agent. Non-inferiority was confirmed between RHA®4 Mepi and RHA®4 with the results extrapolating to RHA®2 Mepi and RHA®3 Mepi for the same indications. Common Treatment Responses and Treatment Related Adverse Events were typical and expected in associated with injection of a dermal fillers and the rates of events were nearly identical for RHA® Mepi and its control. No new or unanticipated risks or adverse events were identified. 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 Perspectives

Patient perspective 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 nasolabial fold domain of the validated FACE-Q© patient-reported outcome measurement
- Subject satisfaction survey

The sole difference between RHA® (RHA® 2, RHA® 3 and RHA® 4) and RHA® Mepi (RHA® 2 Mepi, RHA® 3 Mepi and RHA® 4 Mepi) families of products is the anesthetic agent, lidocaine or mepivacaine. Long term benefit and risks determinations were supported and leveraged by the prior clinical studies of RHA® with lidocaine. In conclusion, given the available information above, data support that the difference in anesthetic agent of RHA® Mepi dermal fillers had no impact on clinical performance or safety of the devices for the correction of moderate to severe dynamic facial wrinkles and folds, such as nasolabial folds (NLF) 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 RHA® Redensity™ Mepi, RHA® 2 Mepi, RHA® 3 Mepi and RHA® 4 Mepi 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 13, 2023.

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

The post approval study (TEO-PAS-2302) is a randomized, controlled, double-blinded, within-subject (split-face), multi-center, prospective study to investigate whether RHA Redensity™ Mepi with mepivacaine is non-inferior to RHA Redensity™ with lidocaine in terms of site injection pain felt by the subject during injection. The PAS will have a cohort of approximately 20 US subjects treated with RHA Redensity™ and RHA Redensity™ Mepi, at 3 US sites, specifically:

- Fitzpatick Skin Type I-IV (n=10)
- Fitzpatick Skin Type V (n=5)
- Fitzpatick Skin Type VI (n=5)

The overall study population will include a minimum of four (4) Hispanic subjects (20% of population). The PAS duration will be approximately 60 days and the primary endpoint of injection site pain felt during injection of the upper perioral quadrant will be analyzed in a non-inferiority statistical model with a non-inferiority margin of 10mm for the difference in mean pain between RHA Redensity™ Mepi and RHA Redensity™.

The primary endpoint will use a paired-design and will be analyzed using a one-sided parametric or non-parametric test for paired data, as appropriate. To achieve non-inferiority the observed p-value must be ≤0.05 (taking account of the non-inferiority margin of 10mm; Pain VAS of 0-100mm).

Adverse Events: AEs related to study device (ADEs), Unanticipated Adverse Device Effects (UADEs), Serious AEs (SAEs), Serious Adverse Device Effects (SADEs), and Adverse Events of Special Interest (AESIs) as per TI assessment. Causality, duration, and severity will be determined.

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.