

TEOXANE RHA® Redensity

CAUTION: FEDERAL LAW RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A PHYSICIAN OR LICENSED PRACTITIONER.

BEFORE USING RHA® Redensity, PLEASE READ THE FOLLOWING INFORMATION THOROUGHLY

DEVICE DESCRIPTION

RHA® Redensity is a viscoelastic, sterile, non-pyrogenic, clear, colorless, homogeneous and biodegradable gel implant of both crosslinked and non-crosslinked hyaluronic acid. It is produced with sodium Hyaluronic Acid (NaHA) with a concentration of 15 mg/g obtained from bacterial fermentation using the *streptococcus equi* bacterial strain, crosslinked with 1,4-butanediol diglycidyl ether (BDDE) and reconstituted in a physiological buffer (pH 7.3). RHA® Redensity also contains 0.3% lidocaine hydrochloride monohydrate to reduce pain on injection.

INTENDED USE / INDICATIONS

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

CONTRAINDICATIONS

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

WARNINGS

RHA® Redensity must not be injected into blood vessels. Introduction of product into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction. Take extra care when injecting soft tissue fillers, for example, inject the product slowly and apply the least amount of pressure necessary. 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. Immediately stop the injection if a patient exhibits any of the following symptoms: changes in vision, signs of a stroke, blanching of the skin, or unusual pain during or shortly after the procedure. Patients should receive prompt medical attention and possibly evaluation by an appropriate health care practitioner specialist should an intravascular injection occur.

Product use at specific sites in which an active inflammatory process (skin eruptions such as cysts, pimples, rashes, or hives), infection or skin injury is present should be deferred until the underlying process has been controlled.

- Treatment site reactions consist mainly of short-term inflammatory symptoms (e.g., swelling, redness, tenderness, or pain) and generally resolve within 14 days. Refer to the ADVERSE EXPERIENCES section for details.
- Inflammatory reaction, anaphylactic reaction, edema, implant migration, acne, blisters, scarring, papules and delayed onset of granulomas have been reported following the use of dermal fillers.

PRECAUTIONS

- In order to minimize the risks of potential complications, this product should only be used by experienced health care practitioners who have appropriate training in filler injection techniques, and who are knowledgeable about the anatomy of and around the site of injection.
- Health care practitioners are encouraged to discuss all potential risks of soft tissue injection with their patients prior to treatment and ensure that patients are aware of signs and symptoms of potential complications.
- The safety and effectiveness for the treatment of anatomic regions other than those described in the INTENDED USE / INDICATIONS section have not been established in controlled clinical studies.
- As with all transcutaneous procedures, dermal filler implantation carries a risk of infection. Standard precautions associated with injectable materials should be followed.
- The safety in patients with known susceptibility to keloid formation, hypertrophic scarring, and pigmentation disorders has not been studied.
- The safety for use in sites in the presence of other implants (including permanent implants) has not been studied.
- The safety for use during pregnancy, in breastfeeding females, and in patients under 22 years of age has not been established.
- RHA® Redensity should be used with caution in patients on immunosuppressive therapy.
- Bruising or bleeding may occur at RHA® Redensity injection sites. RHA® Redensity should be used with caution in patients who are using substances that can prolong bleeding (such as thrombolytics, anticoagulants, or inhibitors of platelet aggregation).
- Injection of RHA® Redensity into patients with a history of previous herpetic eruption may be associated with reactivation of the herpes.
- If laser treatment, chemical peeling or any other procedure based on active dermal response is considered after treatment with RHA® Redensity, there is a possible risk of eliciting an inflammatory reaction at the implant site. This also applies if RHA® Redensity is administered before the skin has healed completely after such a procedure.
- RHA® Redensity is to be used as supplied. Modification or use of the product outside the Instructions for Use may adversely impact the sterility, safety, homogeneity, or performance of the product.
- RHA® Redensity is packaged for single-use. Do not reuse a syringe after treatment. Do not re-sterilize.
- Do not use if package is opened or damaged. The sterility of the product is not guaranteed in the case of failure to comply with this precaution. Failure to comply with the needle attachment instructions could result in needle disengagement and/or product leakage at the Luer-lock and needle hub connection.
- RHA® Redensity is a clear, colorless gel without particulates. In the event the contents of a syringe show signs of separation and/or appears cloudy, do not use the syringe; contact Revance Therapeutics, Inc. 877-3REVNOW (877-373-8669).

ADVERSE EXPERIENCES

1. Clinical Evaluation of RHA® Redensity

A multicenter, controlled, randomized, blinded, No-Treatment control, prospective clinical study compared the safety and effectiveness of RHA® Redensity versus a No-Treatment control for the treatment of moderate to severe dynamic perioral rhytids. The expected signs and symptoms that occur following the injection of a hyaluronic acid-based dermal filler (i.e., Common Treatment Responses; CTR) were individually assessed by subjects in a preprinted 14-day diary after each injection.

CTRs are commonly expected injection site responses which are temporally associated with injection of a dermal filler. Events like redness, swelling, pain, bruising, tenderness, and lumps and bumps are examples of expected CTRs. Severe CTRs, or those lasting longer than 14 days or present on the last day of the subject diary, were evaluated for conversion to an adverse event.

Subjects were asked to rate each CTR as None, Mild, Moderate or Severe:

- Mild: Little discomfort, no effect on daily activities, no medication or make-up required
 - Moderate: some discomfort, some effect on daily activities, possibly medication or make-up required
 - Severe: Great discomfort, daily activities compromised, very likely medication or make-up required
- CTRs by severity and duration are presented respectively, in Table 1 and Table 2.

- The most frequent CTRs were bruising, swelling, redness, firmness, lumps/bumps and tenderness.
- More than 76% of the CTRs had resolved by Day 7.
- Nearly 90% of CTRs had resolved by Day 14 without treatment.
- Other than lumps/bumps, each type of CTR that was present on the last day of the 14-Day diary was present in less than 10% of subjects.
- For nearly all CTRs (more than 92%), the maximal severity reported was "Mild" or "Moderate".
- Less than 6% of each CTR was reported as "Severe" by the subjects except for bruising (12%).
- When bruising persisted to the last day of the diary, all were deemed "Mild" by the treating investigator except 3 that were rated at "Moderate". None were "Severe". More than 90% of Bruises had resolved by end of 14-day diary.

Table 1. Common Treatment Responses by maximum severity after initial treatment with RHA® Redensity (pooled analysis) – Safety Population

Common Treatment Responses	RHA® Redensity (N=199)				
	# of subjects with ≥1 CTR n %	Mild n %	Mod ^a n %	Sev ^c n %	# of subjects with no CTR n %
Redness	131 (65.8%)	84 (42.2%)	42 (21.1%)	5 (2.5%)	68 (34.2%)
Pain	54 (27.1%)	39 (19.6%)	13 (6.5%)	2 (1.0%)	145 (72.9%)
Tenderness	105 (52.8%)	83 (41.7%)	19 (9.5%)	3 (1.5%)	94 (47.2%)
Firmness	115 (57.8%)	79 (39.7%)	33 (16.6%)	3 (1.5%)	84 (42.2%)
Swelling	146 (73.4%)	85 (42.7%)	49 (24.6%)	12 (6.0%)	53 (26.6%)
Lumps/Bumps	115 (57.8%)	71 (35.7%)	34 (17.1%)	10 (5.0%)	84 (42.2%)
Bruising	154 (77.4%)	65 (32.7%)	65 (32.7%)	24 (12.1%)	45 (22.6%)
Itching	31 (15.6%)	26 (13.1%)	3 (1.5%)	2 (1.0%)	168 (84.4%)
Discoloration	94 (47.2%)	49 (24.6%)	34 (17.1%)	11 (5.5%)	105 (52.8%)

^a Number of subjects' who provided diary answers after V1/1b

^b Mod = Moderate

^c Sev = Severe

Table 2. Duration of Common Treatment Responses after initial treatment with RHA® Redensity (pooled analysis) – Safety Population

Common Treatment Responses	RHA® Redensity (N=199)			
	1-3 Days	4-7 Days	8-14 Days	Last Day ^d
Redness	78 (39.2%)	35 (17.6%)	18 (9.0%)	8 (4.0%)
Pain	38 (19.1%)	10 (5.0%)	6 (3.0%)	1 (0.5%)
Tenderness	55 (27.6%)	29 (14.6%)	21 (10.6%)	10 (5.0%)
Firmness	63 (31.7%)	24 (12.1%)	28 (14.1%)	18 (9.0%)
Swelling	72 (36.2%)	40 (20.1%)	34 (17.1%)	10 (5.0%)
Lumps/Bumps	53 (26.6%)	29 (14.6%)	33 (16.6%)	26 (13.1%)
Bruising	30 (15.1%)	64 (32.2%)	60 (30.2%)	15 (7.5%)
Itching	21 (10.6%)	8 (4.0%)	2 (1.0%)	3 (1.5%)
Discoloration	39 (19.6%)	34 (17.1%)	21 (10.6%)	5 (2.5%)

^a Number of subjects' who provided diary answers after V1/1b

^b Number of events by maximum duration

^c Duration refers to number of days cited in the patient diary, irrespective of date of injection

^d The CTR numbers indicated in the «Last Day» column are also included in the «8-14 Days» column.

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

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

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

An adverse event (AE) was defined as a treatment-related event that was not considered typical in type and/or duration and/or severity. Also, CTRs from the patient's diary that were recorded on the last day of diary were automatically elevated to the status of adverse event, regardless of severity.

- All treatment-related AEs were mild or moderate in severity.
- Most of treatment-related AEs experienced were typical events following an injection of a hyaluronic acid-based dermal filler, such as: bruising, discoloration, erythema, injection site induration, irritation, swelling or pain. Other reported treatment-related AEs such as headache, muscle contraction or paresthesia are less typical but not unexpected following a dermal filler injection.
- All treatment-related AEs were temporally associated with a recent injection (no late onset).
- All treatment-related AEs were based on subjects' diary entries (CTRs or reported as "other") except three events at injection site assessed by the Treating Investigator during visit questioning (1 discoloration "Tyndall Effect", 1 headache, 1 oral herpes) that were reported by the Treating Investigator at time of initial injection. The "Tyndall Effect", headache and oral herpes resolved without sequelae in 384, 7 and 10 days respectively.
- The duration of treatment related adverse events varied from 1 to 90 days except for two: the "Tyndall Effect" described above and there was an involuntary muscle contraction (fasciculation, left upper lip)

which appeared after re-treatment at visit 9. It was mild in severity and no treatment was provided. It was persistent and had not improved at the study exit. The investigator followed up three months later and the subject stated it resolved 2 months prior.

- No events were deemed to be a granuloma or delayed inflammatory response.
- There were no events of vascular occlusion.
- There were no late onset treatment-related AEs.
- There were no treatment-related serious AEs.

The incidence of treatment-related AE incidence rates was not different in subjects with higher Fitzpatrick skin types. There were no reported cases of scarring, keloid formation or hyperpigmentation.

2. Post-marketing Surveillance

The following adverse events were reported as part of post-marketing surveillance on the use of RHA® Redensity outside the United States with a prevalence equal or superior to 1 occurrence for 100,000 syringes: edema, injection site masses (lumps and bumps), inflammatory nodules (papules), skin swelling, skin induration, vascular skin disorder (such as vessel compression/occlusion), pain, ecchymosis, and inflammatory reaction. Additionally, other less frequent adverse reactions have also been reported, and include dermal filler overcorrection, allergic reaction, product misplacement, skin discoloration, skin necrosis, erythema, granuloma, injection site movement impairment/paraesthesia, skin atrophy and tenderness. Delayed-onset inflammation near the site of dermal filler injections is one of the known adverse events associated with dermal fillers. Cases of delayed-onset inflammation have been reported to occur at the dermal filler treatment site following viral or bacterial illnesses or infections, vaccinations, or dental procedures. Typically, the reported inflammation was responsive to treatment or resolved on its own.

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.

CLINICAL STUDY

The safety and effectiveness of RHA® Redensity in the correction of moderate to severe dynamic perioral rhytids, was evaluated in a US/ Canadian pivotal clinical study described hereafter.

1. Pivotal Study Design

A randomized, blinded, No-Treatment control, multicenter, prospective pivotal clinical study was conducted to evaluate the clinical safety and effectiveness of RHA® Redensity in the US and in Canada. Subjects were randomly assigned to the RHA® Redensity treatment group or to the "No-Treatment" control group. The Treating Investigator administered the study device to the upper and lower perioral area, including as necessary, into the vermilion border of the lip. Subjects could receive a touch-up treatment 2 weeks after the initial treatment to optimize the results.

The follow-up period consisted of safety and effectiveness follow-up visits at 4, 8, 12, 16, 24, 36, and 52 weeks after the last treatment and 4 weeks after repeat treatment. The primary endpoint was at Week 8 after last treatment (initial treatment or touch-up).

Subjects were eligible for optional retreatment if necessary at Weeks 12, 16, 24 or 36. Subjects were also offered retreatment at Week 52, and were then followed for 1 month after retreatment or until all Adverse Events (AEs) resolved.

Subjects randomized to the "No-Treatment" control group received their first treatment after the primary endpoint evaluation (Week 8 after randomization) and then followed the same schedule as the initial treatment group until 52 weeks after repeat treatment.

2. Study Endpoints

The primary effectiveness endpoint was the analysis of superiority of RHA® Redensity versus the No-Treatment control, in terms of rate of responders (≥ 1 grade difference from pre-treatment on the PR-SRS) at 8 weeks after injection, as measured by the Blinded Live Evaluator (BLE) using a proprietary and validated 4-grade scale for scoring the severity of perioral rhytids, PR-SRS score.

Secondary effectiveness endpoints included Global Aesthetic Improvement (GAI), as assessed by the subject, TI and the BLE, impact and effectiveness of study treatment procedures from the subjects' perspective as assessed by the perioral rhytids domain of the FACE-Q®, subject satisfaction and an 11-point scale for Natural Look and Feel as assessed by the subjects.

Safety endpoints were evaluated throughout the study, with a 14-day subject diary capturing post-injection signs/symptoms following every study injection, and AE assessments at each visit. Injection site pain was self-assessed by the subject using a 100mm Visual Analog Scale

3. Demographics

A total of 202 subjects (38 to 81 years old) were allocated to RHA® Redensity and No-treatment control groups. 163 subjects were in the US and 39 in Canada. 199 subjects were included in the ITT population (pooled population).

Subject's demographics are presented in Table 3.

Table 3. Demographics

Number / % of subjects	RHA® Redensity N=150		No-Treatment N=52	
Age				
Mean (SD)	61.6	(7.2)	60.7	(7.6)
min max	38	81	46	77
Gender				
Female	147	98.0%	51	98.1%
Male	3	2.0%	1	1.9%
Race				
White	143	95.3%	52	100%
Black or African American	4	2.7%	0	0.0%
Am. Indian/N. Alask.	1	0.7%	0	0.0%
N. Hawaiian/P. Isl.	0	0.0%	0	0.0%
Asian	2	1.3%	0	0.0%
Other	0	0.0%	0	0.0%
Ethnicity				
Hispanic/Latino	25	16.7%	10	19.2%
Not Hispanic/Latino	125	83.3%	42	80.8%
Fitzpatrick Skin Phototype				
I-III		147 (72.8%)		
I	18	12.0%	6	11.5%
II	37	24.7%	13	25.0%
III	55	36.7%	18	34.6%
IV-VI		55 (27.2%)		
IV	29	19.3%	12	23.1%
V	8	5.3%	3	5.8%
VI	3	2.0%	0	0.0%

^a All randomized subjects

4. Treatment Characteristics

The overall total mean volume of RHA® Redensity injected to achieve optimal correction results was 2.8 mL. The study protocol allowed a maximum of 6.0 mL per treatment session. The proportion of subjects who received touch-up treatment with RHA® Redensity at Week 2 was 68.1%.

RHA® Redensity was administered into the dermis and superficial dermis using different injection techniques to ensure a satisfactory result of the treatment of dynamic perioral rhytids. In general, a linear threading technique combined with multiple punctures was used for 91.0% of the subjects treated with RHA® Redensity.

5. Effectiveness Results

The primary effectiveness endpoint was met for RHA® Redensity. The primary effectiveness endpoint was based on the responder rate as assessed (using the PR-SRS) by the BLE at 8 weeks after baseline. A subject was considered to be a PR-SRS responder if he/she presented with a ≥1-point improvement from pre-treatment (baseline). To successfully achieve the co-primary endpoint: 1) the responder rate for subjects with RHA® Redensity must be statistically superior to the responder rate for the No-Treatment control, and; 2) the responder rate for subjects treated with RHA® Redensity must be ≥70% and; 3) the difference between the responder rate for subjects treated with RHA® Redensity and the No-Treatment group must be ≥ 50 points. The proportion of responders, showing ≥1-grade improvement on the PR-SRS was 80.7% in the treatment group and 7.8% in the No-Treatment group. Results are presented in Table 4.

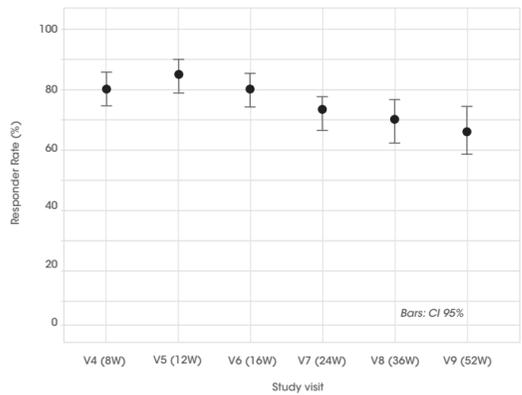
Table 4. Responder rate assessed by a Blinded Live Evaluator at primary endpoint

PR-SRS Responder Rate (BLE)	RHA® Redensity	No-Treatment	P-value ^b
Week 8	N^a	150	51
	Responder	121 (80.7%)	4 (7.8%)
	Not responder	29 (19.3%)	47 (92.2%)
	Missing values	0	0

^a ITT population – BLE assessment – Last Observation Carried Forward (LOCF)
^b Responder = at least 1-point improvement from Baseline. P-value from Fisher's Exact Test

The results demonstrated superiority of RHA® Redensity against No-Treatment control at 8 weeks for the treatment of perioral rhytids. In analyses of the pooled population, RHA® Redensity demonstrated durability with PR-SRS (BLE assessment) responder rates of 80.4%, 72.9% and 66.5% at Weeks 8, 24 and 52, respectively. Throughout the follow-up period, the aesthetic improvement of the perioral rhytids treated with RHA® Redensity continued to be clinically significant (≥ 1 grade difference from pre-treatment on the PR-SRS) for more than 66% of the subjects at 52 weeks after initial treatment (Figure 1).

Figure 1. Proportion of responders on the Perioral Rhytids Severity Rating Scale (PR-SRS) measured by a Blinded Live Evaluator for RHA® Redensity



RHA® Redensity No-Treatment Control (pooled)	Week 8	Week 12	Week 16	Week 24	Week 36	Week 52
N	194	184	183	188	188	188
Responder (BLE assessment)	156 (80.4%)	156 (84.8%)	147 (80.3%)	137 (72.9%)	131 (69.7%)	125 (66.5%)
Not Responder (BLE assessment)	38 (19.6%)	28 (15.2%)	36 (19.7%)	51 (27.1%)	57 (30.3%)	63 (33.5%)

ITT populations at the respective follow-up visits

Rate of responders: ≥ 1 grade difference from pre-treatment on the PR-SRS

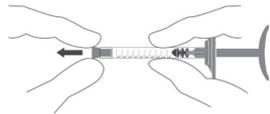
On the Global Aesthetic Improvement (GAI) scale, more than 92% of the subjects, TIs and BLEs reported that the perioral rhytids treated with RHA® Redensity were improved or very much improved at 8 weeks and this proportion remained greater than 80% up to week 52. In addition, based on the Perioral Rhytids domain of the FACE-Q® questionnaire, the subjects consistently reported improvement up to 52 weeks with a mean score change of more than 36 points from baseline throughout the follow-up period. Subjects were asked six questions within the FACE-Q® Perioral Rhytids Domain and reported being less bothered by the number and depth of lines, how noticeable lines were after treatment with RHA® Redensity. Further, based on the FACE-Q® questionnaire, subjects reported being less bothered by how perioral lines looked compared to other people their age, how old the lines made them look, and how their lines appeared when their lips are puckered.

More than 90% of the subjects reported to be satisfied or very satisfied 8 weeks after initial treatment and the rate of satisfaction remained at more than 88% at 52 weeks (the scale grades were: very satisfied, satisfied, neither satisfied nor dissatisfied, dissatisfied or very dissatisfied).

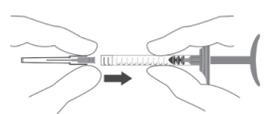
More than 78% of the subjects received repeat treatment. The effectiveness and safety profiles after repeat treatment were similar to that after initial treatment.

DIRECTIONS FOR ASSEMBLY OF THE NEEDLE TO THE SYRINGE

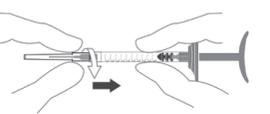
1. Remove the stopper from the syringe by pulling it off.



2. Insert the screw thread of the needle firmly into the syringe end-piece.



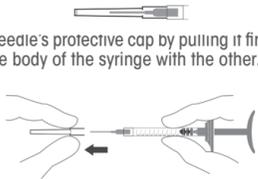
3. Screw the needle clockwise, while maintaining slight pressure between the needle and the syringe.



4. Continue screwing until the edge of the cap of the needle contacts the body of the syringe. There must be no space between these two parts. Failure to follow this instruction means that the needle could be ejected and/or leak at the Luer-lock.



5. Remove the needle's protective cap by pulling it firmly with one hand while holding the body of the syringe with the other.



DIRECTION FOR INJECTIONS

Before and after treatment, health care practitioners are encouraged to conduct vision assessments, including visual acuity, extraocular motility, and visual field testing. Health care practitioners are encouraged to be prepared with the following in the event of an intravascular injection:

- ensuring supplies are immediately available, as recommended by the American Society for Dermatologic Surgery guidelines
- identifying a local ophthalmologist or ophthalmology subspecialist to be available in the event of an ophthalmic adverse event related to a dermal filler injection
- conducting a basic neurologic examination in the event of an ophthalmic adverse event due to the association of such events with central nervous system deficits.

PRE-TREATMENT GUIDELINES

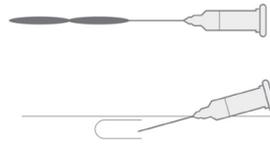
- Prior to treatment, the patient should avoid taking medications or supplements which thin the blood (e.g., aspirin, nonsteroidal anti-inflammatory medications, St. John's Wort, high doses of Vitamin E supplements, anti-coagulants) as these agents may increase bruising and bleeding at the injection site.
- Before starting treatment, a complete medical history should be taken from the patient and the patient should be counseled on appropriate indications, risks, and should be informed about the expected treatment results, and expected responses. The patient should be advised of the necessary precautions before commencing the procedure.
- Prior to treatment with RHA® Redensity the patient should be assessed for appropriate anesthetic treatment for managing comfort (e.g., topical anesthetic, local or nerve block). The patient's face should be washed with soap and water and dried with a clean towel. Cleanse the area to be treated with alcohol or another suitable antiseptic solution.
- Sterile gloves are recommended while injecting RHA® Redensity.
- Before injecting, prime the needle by carefully pressing the syringe plunger until a small droplet of the gel is visible at the tip of the needle.

INJECTION TECHNIQUES

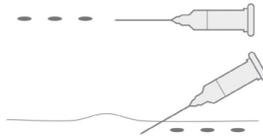
RHA® Redensity can be administered by using a thin gauge needle (30 G x ½") and with a number of different techniques that depend on the injector's experience and preference, and patient characteristics.

A. Preclinical testing between the following needles brands (TSK HPC, TSK PRC, Terumo TW, Terumo ETW) and the syringe has confirmed that the interoperability and compatibility is reliable and safe. **Serial puncture:** consists of multiple injections, evenly and closely spaced perpendicular to the lines. This technique is considered to be more precise, but may

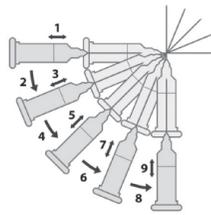
result in more discomfort for the patient due to the number of punctures.



B. Linear threading: the needle is fully introduced in the wrinkle or the fold, and the product is injected along the line, as a "thread", while withdrawing (retrograde) or pushing (antegrade) the needle.



C. Fanning technique: the needle is introduced as for the Linear threading technique, and the product is injected along several closely spaced lines, by changing the direction of the needle, all using the same puncture site (the needle is not withdrawn).



- RHA® Redensity is injected slowly into the dermis. If the injection is made too deeply, i.e. into subcutaneous tissue, the correction may not be as expected. It is possible to tell when an injection is being made too deeply because subcutaneous tissue, unlike the dermis, does not offer any resistance to product injection, the injected product may not be visible as a raised elevation on the skin and correction of the lines may not be achieved.
- The injection should be stopped before withdrawing the needle from the skin, to prevent product from leaking out, or product misplacement (too superficially in the skin).
- The volume to be injected depends on the correction to be performed, but it is important to not overcorrect. Based on the US clinical study, patients should be limited to 6.0 mL per patient per treatment session in perioral rhytids. The safety of injecting greater amounts has not been established.
- Any blanching appearing through the vascular flow may represent a vessel occlusion. If normal skin coloring does not return, do not continue with the injection. Treat in accordance with American Society for Dermatologic Surgery guidelines, which include hyaluronidase injection.
- If the perioral lines need further treatment with RHA® Redensity, the same procedure should be repeated until a satisfactory result is obtained.

POST-TREATMENT GUIDELINES

- When the injection is completed, the treated site may be gently massaged so that it conforms to the contour of the surrounding tissues. If an overcorrection has occurred, massage the area firmly between your fingers or against an underlying area to obtain optimal results.
- If the treated area is swollen immediately after the injection, an ice pack can be applied to the site for a short period (e.g., 5-10 minutes). Ice should be used with caution if the area is still numb from anesthetic to avoid thermal injury.

After use, syringes may be potential biohazards. Follow national, local, or institutional guidelines for use and disposal of medical biohazard devices. Obtain prompt medical attention if injury occurs.

STERILE NEEDLES

- After use, needles are potential biohazards. Follow national, local, or institutional guidelines for use and disposal of medical sharp devices (e.g. discard uncapped needles in approved sharps containers).
- Obtain prompt medical attention if injury with used needle occurs.
- To help avoid needle breakage, do not attempt to straighten a bent needle. Discard it and complete the procedure with a replacement needle.
- Do not recap needles. Recapping by hand is a hazardous practice and should be avoided.
- RHA® Redensity is provided with 2 needles that do not contain engineered injury protection. Administration of RHA® Redensity requires direct visualization and complete and gradual insertion of the needle making engineered protection devices not feasible. Care should be taken to avoid sharps exposure by proper environmental controls.

PATIENT INSTRUCTIONS

A patient information brochure is available on request, or via the website www.revance.com. It is recommended that the following information be shared with patients:

- Patients should be advised not to wear make-up during 12 hours following injection.
- Patient should be advised not to take high-dose Vitamin E, aspirin, anti-inflammatories or anti-coagulants during the week prior to the injection. Patients must not discontinue such treatment without talking with their prescribing physician.
- Patients should minimize exposure of the treated area to excessive sun, UV lamp exposure and extreme temperatures (e.g. cold weather, sauna) at least within the first 24 hours, or until initial swelling and redness has resolved. Exposure to any of the above may cause/exacerbate and/or extend the duration of temporary redness, swelling, and/or itching at the treatment sites.
- Patients should notify the injector if any of the following occurs:
 - Changes in vision
 - Unusual pain during or shortly after treatment
 - Significant pain away from the injection site
 - Signs of a stroke
 - Any redness and/or visible swelling that lasts for more than a week
 - Any side effect other than those described above or that occur weeks or months after injection
- Adverse reactions should be reported to Revance Therapeutics, Inc at 877-3REV-NOW (877-373-8669) and to Medical-us@teoxane.com.

HOW SUPPLIED

RHA® Redensity is supplied in individual blisters containing a 1 mL treatment syringe with two 30 G x ½" needles as indicated on the carton. The content of the syringe is sterile and non-pyrogenic. Do not re-sterilize. Do not use if package is opened or damaged. Each syringe is packaged into a blister with two unique device identifier traceability labels.

SHELF-LIFE AND STORAGE

RHA® Redensity must be used prior to the expiration date printed on the package. Store at room temperature (up to 25°C/77°F). Do not expose to direct sunlight. DO NOT FREEZE. Do not store partially used syringes.

RxOnly

Manufactured by:
TEOXANE S.A.
Rue de Lyon 105
CH 1203 Geneva
(Switzerland)

Distributed by:
Revance Therapeutics, Inc.
1222 Demonbreun Street,
Suite 2000
Nashville, Tennessee 37203

RHA® is a registered trademark of TEOXANE SA.
RHA Redensity is a trademark filed by TEOXANE SA.

Under license U.S. Pat. Nos. 8, 450, 475 ; 8,822, 676 ;
9,089, 517 ; 9,089, 518 ; 9, 089, 519 ; 9, 238,013 ; 9,358, 322.

SYMBOLS

- Manufacturer's name and address
- REF Catalog number
- LOT Lot / batch number
- Expiration date (YYYY-MM-DD)
- Consult Instructions for use
- Single use only
- Sterilized using steam
- Do not use if the package is damaged

RxOnly Caution: Federal law restricts this device to sale by or on the order of a physician or license practitioner



RHA® 2

CAUTION: FEDERAL LAW RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A PHYSICIAN OR LICENSED PRACTITIONER.

BEFORE USING RHA® 2, PLEASE READ THE FOLLOWING INFORMATION THOROUGHLY

DEVICE DESCRIPTION

RHA® 2 is a viscoelastic, sterile, non-pyrogenic, clear, colorless, homogeneous and biodegradable gel implant. It is produced with sodium Hyaluronic Acid (NaHA) with a concentration of 23 mg/g obtained from bacterial fermentation using the *Streptococcus equi* bacterial strain, crosslinked with 1,4-butanediol diglycidyl ether (BDDE) and reconstituted in a physiological buffer (pH 7.3). RHA® 2 also contains 0.3% lidocaine hydrochloride monohydrate to reduce pain on injection.

INTENDED USE / INDICATIONS

RHA® 2 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.

CONTRAINDICATIONS

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

WARNINGS

- RHA® 2 must not be injected into blood vessels. Introduction of product into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction. Take extra care when injecting soft tissue fillers, for example, inject the product slowly and apply the least amount of pressure necessary. 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. Immediately stop the injection if a patient exhibits any of the following symptoms: changes in vision, signs of a stroke, blanching of the skin, or unusual pain during or shortly after the procedure. Patients should receive prompt medical attention and possibly evaluation by an appropriate health care practitioner specialist should an intravascular injection occur.

- Product use at specific sites in which an active inflammatory process (skin eruptions such as cysts, pimples, rashes, or hives), infection or skin injury is present should be deferred until the underlying process has been controlled.
- Treatment site reactions consist mainly of short-term inflammatory symptoms (e.g., swelling, redness, tenderness, or pain) and generally resolve within 14 days. Refer to the ADVERSE EXPERIENCES section for details.
- Inflammatory reaction, anaphylactic reaction, edema, implant migration, acne, blisters, scarring, papules and delayed onset of granulomas have been reported following the use of dermal fillers.

PRECAUTIONS

- In order to minimize the risks of potential complications, this product should only be used by experienced health care practitioners who have appropriate training in filler injection techniques, and who are knowledgeable about the anatomy at and around the site of injection.
- Health care practitioners are encouraged to discuss all potential risks of soft tissue injection with their patients prior to treatment and ensure that patients are aware of signs and symptoms of potential complications.
- The safety and effectiveness for the treatment of anatomic regions other than those described in the INTENDED USE / INDICATIONS section have not been established in controlled clinical studies.
- As with all transcutaneous procedures, dermal filler implantation carries a risk of infection. Standard precautions associated with injectable materials should be followed.
- The safety in patients with known susceptibility to keloid formation, hypertrophic scarring, and pigmentation disorders has not been studied.
- The safety for use in sites in the presence of other implants (including permanent implants) has not been studied.
- The safety for use during pregnancy, in breastfeeding females, and in patients under 22 years of age has not been established.
- RHA® 2 should be used with caution in patients on immunosuppressive therapy.
- Bruising or bleeding may occur at RHA® 2 injection sites. RHA® 2 should be used with caution in patients who are using substances that can prolong bleeding (such as thrombolytics, anticoagulants, or inhibitors of platelet aggregation).
- Injection of RHA® 2 into patients with a history of previous herpetic eruption may be associated with reactivation of the herpes.
- If laser treatment, chemical peeling or any other procedure based on active dermal response is considered after treatment with RHA® 2, there is a possible risk of eliciting an inflammatory reaction at the implant site. This also applies if RHA® 2 is administered before the skin has healed completely after such a procedure.
- RHA® 2 is to be used as supplied. Modification or use of the product outside the Instructions for Use may adversely impact the sterility, safety, homogeneity, or performance of the product.
- RHA® 2 is packaged for single-patient use. Do not reuse a syringe between two treatments and/or between two patients. Do not resterilize.
- Do not use if package is opened or damaged. The sterility of the product is not guaranteed in the case of failure to comply with this precaution. Failure to comply with the needle attachment instructions could result in needle disengagement and/or product leakage at the Luer-lock and needle hub connection.
- RHA® 2 is a clear, colorless gel without particulates. In the event the contents of a syringe show signs of separation and/or appears cloudy, do not use the syringe; contact Revance Therapeutics, Inc. 877-3REV-NOW (877-373-8669).

ADVERSE EXPERIENCES

1. Clinical Evaluation of RHA® 2

A multicenter, controlled, randomized, double-blinded, within-subject (split-face), prospective US clinical study compared the safety of RHA® 2 versus a control treatment for the treatment of moderate to severe nasolabial folds, and demonstrated similar safety profiles. The expected signs and symptoms that occur following the injection of a hyaluronic acid-based dermal filler (i.e., Common Treatment Responses; CTR) were individually assessed by subjects in a preprinted 14-day diary after each injection.

Subjects were asked to rate each CTR as None, Mild, Moderate or Severe:

- Mild: Little discomfort, no effect on daily activities, no medication or make-up required
 - Moderate: some discomfort, some effect on daily activities, possibly medication or make-up required
 - Severe: Great discomfort, daily activities compromised, very likely medication or make-up required
- CTRs by severity and duration are presented respectively, in Table 1 and Table 2.

- The most frequent CTRs were firmness, redness, tenderness, swelling, lumps/bumps, and bruising.
- Proportions of subjects experiencing at least one CTR of each category were similar between RHA® 2 and control treatment.
- More than 70% of the CTRs had resolved by Day 7.
- The vast majority (more than 85%) of CTRs had resolved by Day 14.
- There were no notable differences between RHA® 2 and control treatment with regard to the small proportion of subjects who reported a severe CTR.
- For nearly all CTRs (more than 93%) experienced by any treatment group (initial treatment or touch-up treatment), the maximal severity reported was "Mild" or "Moderate".
- On the last day of the diary, nearly all ongoing CTRs had improved to mild.

Table 1. Common Treatment Responses by maximum severity after initial treatment with RHA® 2 and the Control Device – Safety Population

Common Treatment Responses	TOTALS		RHA® 2 (N=72 NLF)			Control Device (N=72 NLF)		
	RHA® 2 n° %	CTRL n° %	Mild n° %	Mod ^a n° %	Sev ^a n° %	Mild n° %	Mod ^a n° %	Sev ^a n° %
Bruising	36 50.0%	41 56.9%	15 20.8%	16 22.2%	5 6.9%	23 31.9%	9 12.5%	9 12.5%
Discoloration	24 33.3%	27 37.5%	12 16.7%	7 9.7%	5 6.9%	14 19.4%	8 11.1%	5 6.9%
Firmness	46 63.9%	48 66.7%	23 31.9%	20 27.8%	3 4.2%	27 37.5%	20 27.8%	1 1.4%
Itching	12 16.7%	15 20.8%	9 12.5%	3 4.2%	0 0.0%	10 13.9%	4 5.6%	1 1.4%
Lumps/Bumps	38 52.8%	37 51.4%	21 29.2%	14 19.4%	3 4.2%	22 30.6%	13 18.1%	2 2.8%
Pain	19 26.4%	16 22.2%	13 18.1%	6 8.3%	0 0.0%	11 15.3%	5 6.9%	0 0.0%
Redness	45 62.5%	49 68.1%	31 43.1%	13 18.1%	1 1.4%	36 50.0%	11 15.3%	2 2.8%
Swelling	42 58.3%	45 62.5%	27 37.5%	13 18.1%	2 2.8%	31 43.1%	13 18.1%	1 1.4%
Tenderness	44 61.1%	40 55.6%	34 47.2%	10 13.9%	0 0.0%	31 43.1%	9 12.5%	0 0.0%

^a Number of subjects' NLF treated with the respective device

^b Number of subjects' NLF with any specific Common Treatment Response

^c CTRL = Control treatment

^d Mod = Moderate

^e Sev = Severe

Table 2. Duration of Common Treatment Responses after initial treatment with RHA® 2 and the Control Device – Safety Population

Common Treatment Responses	RHA® 2 (N=72 NLF) N° %				Control Device (N=72 NLF) N° %			
	1-3 Days	4-7 Days	8-14 Days	Last Day ^f	1-3 Days	4-7 Days	8-14 Days	Last Day ^f
Bruising	7 9.7%	13 18.1%	16 22.2%	4 5.6%	10 13.9%	16 22.2%	15 20.8%	3 4.2%
Discoloration	11 15.3%	4 5.6%	9 12.5%	3 4.2%	8 11.1%	10 13.9%	9 12.5%	3 4.2%
Firmness	13 18.1%	11 15.3%	22 30.6%	14 19.4%	16 22.2%	13 18.1%	19 26.4%	12 16.7%
Itching	5 6.9%	4 5.6%	3 4.2%	3 4.2%	9 12.5%	2 2.8%	4 5.6%	3 4.2%
Lumps/Bumps	11 15.3%	13 18.1%	14 19.4%	12 16.7%	14 19.4%	11 15.3%	12 16.7%	6 8.3%
Pain	11 15.3%	4 5.6%	4 5.6%	3 4.2%	7 9.7%	5 6.9%	4 5.6%	2 2.8%
Redness	28 38.9%	13 18.1%	4 5.6%	1 1.4%	29 40.3%	14 19.4%	6 8.3%	3 4.2%
Swelling	19 26.4%	11 15.3%	12 16.7%	5 6.9%	22 30.6%	15 20.8%	8 11.1%	3 4.2%
Tenderness	23 31.9%	9 12.5%	12 16.7%	6 8.3%	21 29.2%	10 13.9%	9 12.5%	1 1.4%

^a Number of subject NLF treated with the respective device

^b Number of subject NLF with each specific CTR by maximum duration

^c Duration refers to number of days cited in the patient diary, irrespective of date of injection

^d The CTR numbers indicated in the "Last Day" column are also included in the "8-14 Days" column.

An adverse event (AE) was defined as a treatment-related event that was not considered typical in type and/or duration and/or severity. Also, CTRs from the patient's diary that were recorded on the last day of diary were automatically elevated to the status of adverse event, regardless of severity.

- All treatment-related AEs were mild or moderate in severity.
- All treatment-related AEs experienced by both treatment groups were typical of the expected signs and symptoms observed following an injection of a hyaluronic acid-based dermal filler.
- All treatment-related AEs were temporally associated with a recent device (RHA® 2 or control treatment) injection.
- All treatment-related AEs were based on subjects' diary entries (CTRs) except one (injection site bruising; mild) that was reported by the Treating Investigator at time of initial injection and which resolved in 12 days.
- No events were deemed to be a granuloma.
- There were no late onset treatment-related AEs.
- There were no treatment-related serious AEs.

2. Post-marketing Surveillance

The following adverse events were reported as part of post-marketing surveillance on the use of RHA® 2 worldwide with a prevalence equal or superior to 1 occurrence for 100,000 syringes: injection site masses (lumps and bumps), edema, skin swelling, vascular complication, bruising, redness, inflammatory reaction, pain and firmness. Additionally, other less frequent adverse reactions have also been reported, and included dermatitis, granuloma, allergic reaction, skin necrosis, implant migration, skin discoloration/Tyndall effect, skin infection, herpes breakout, pruritus, paresthesia, abscess, acne, angioedema, blister, fainting, product misplacement, pustules and telangiectasia. Delayed-onset inflammation near the site of dermal filler injections is one of the known adverse events associated with dermal fillers. Cases of delayed-onset inflammation have been reported to occur at

the dermal filler treatment site following viral or bacterial illnesses or infections, vaccinations, or dental procedures. Typically, the reported inflammation was responsive to treatment or resolved on its own.

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, drainage, excision, implant dissolution (hyaluronidase), incision, massage and vasodilators. Adequate treatment leads to a complete resolution without sequelae.

CLINICAL STUDY

The safety and effectiveness of RHA® 2 in the correction of moderate to severe facial wrinkles and folds was evaluated in a US pivotal clinical study described hereafter.

1. Pivotal Study Design

A controlled, randomized, double-blinded, within-subject, multicenter, prospective pivotal clinical study was conducted to evaluate the clinical safety and efficacy of RHA® 2.

Subjects were randomly assigned to receive RHA® 2 and a control treatment in mid-to-deep dermis for the treatment of moderate to severe nasolabial folds, or to a non-treatment group. The side of the face for each device injected was assigned randomly.

If deemed necessary by the Treating Investigator, additional NLF correction was performed after 2 weeks (touch-up), with the same study device used for initial treatment.

The follow-up period consisted of safety and effectiveness follow-up visits at 4, 12, 24, 36, 52, and 64 weeks after the last treatment. Subjects were eligible for optional retreatment if necessary at Weeks 24 or 36. Subjects were also offered retreatment at Week 52 or Week 64, and were then followed for 1 month after retreatment or until all Adverse Events (AEs) resolved. Retreatments on either side was provided using RHA® 2 (the control treatment was not used). Subjects randomized to the "no treatment" control group did not receive treatment.

2. Study Endpoints

The primary effectiveness endpoint was the analysis of non-inferiority of RHA® 2 versus the control treatment, in terms of change from pre-injection to 24 weeks after injection, as measured by the Blinded Live Evaluator (BLE) using a proprietary and validated 5-grade scale for scoring the severity of nasolabial folds, NLF-SRS (which for the purposes of this document will be referred to as Wrinkle Severity Rating Scale (WSRS) score.

Secondary effectiveness endpoints included rates of responders (\geq 1 grade difference from pre-treatment on the WSRS), as measured by the BLE (see data in Figure 1), Global Aesthetic Improvement (GAI), as assessed by the subject and by the BLE, impact and effectiveness of study treatment procedures from the subjects' perspective as assessed by the nasolabial fold domain of the FACE-Q®, and subject satisfaction. Safety endpoints were evaluated throughout the study, with a 14-day subject diary capturing post-injection signs/symptoms following every study injection, and AE assessments at each visit. Injection site pain was self-assessed by the subject using a 100mm Visual Analog Scale.

3. Demographics

A total of 74 subjects (34 to 79 years old) were allocated to RHA® 2

and control treatment, and 26 were allocated to untreated controls. 73 subjects were included in the ITT population.

Subjects' demographics are presented in Table 3.

Table 3. Demographics

Number / % of subjects	RHA® 2 versus Control device N=73
Age	
Mean (SD)	55.5 (10.9)
min max	34 79
Gender	
Female	62 84.9%
Male	11 15.1%
Race	
Caucasian	59 80.8%
Black	9 12.3%
Am. Indian/N. Alask.	0 0.0%
N. Hawaiian/P. Isl.	0 0.0%
Asian	2 2.7%
Other	3 4.1%
Ethnicity	
Hispanic/Latino	21 28.8%
Not Hispanic/Latino	52 71.2%
Fitzpatrick Skin Phototype	
I	1 1.4%
II	24 32.9%
III	20 27.4%
IV	17 23.3%
V	7 9.6%
VI	4 5.5%

^a Number of subjects in the ITT populations

4. Treatment Characteristics

The study protocol allowed a maximum of 3.0 ml in a single NLF per treatment session. The overall total median volume of RHA® 2 injected to achieve optimal correction results was 1.4 ml. The proportion of subjects who received touch-up treatment with RHA® 2 at Week 2 was 64.4%.

In general, a linear threading or fan-like technique, or combination, was used for 91.0% of the subjects treated with RHA® 2.

5. Effectiveness Results

The primary effectiveness endpoint was met for RHA® 2. The primary effectiveness endpoint was the aesthetic improvement from pre-injection of the NLF treated with RHA® 2 compared to the improvement from pre-injection of the NLF treated with the control treatment, as assessed (using the WSRS) by the BLE at 24 weeks after baseline; results are presented in Table 4.

Table 4. Wrinkle Severity Rating Scale scores assessed by a Blinded Live Evaluator throughout the study

	n ^a	RHA® 2		Control Device	
		WSRS score ^b	WSRS Improvement ^c	WSRS score ^b	WSRS Improvement ^c
Pre-treatment	67	3.45	-	3.45	-
Week 24 ^d	67	2.28	1.16	2.31	1.13
Week 36	65	2.32	1.12	2.32	1.12
Week 52	62	2.37	1.06	2.37	1.06
Week 64	47	2.45	0.94	2.38	1.00

^a Number of subjects in the PP populations at the respective follow-up visits

^b Mean Wrinkle Severity Rating Scale score (higher scores mean deepest wrinkles)

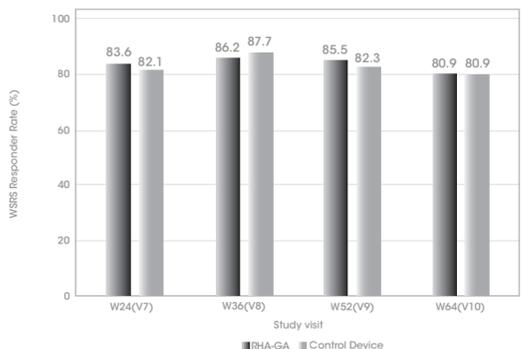
^c Mean Wrinkle Severity Rating Scale improvement from pre-treatment (higher scores mean more improvement from pre-treatment)

^d Primary effectiveness endpoint

The results demonstrated that non-inferiority to the control was achieved for RHA® 2 at 24 weeks for the treatment of NLFs. Results also showed that RHA® 2 was non-inferior to the control treatment at all study visits.

Throughout the follow-up period, the aesthetic improvement of the RHA®2 treated NLF continued to be clinically significant (≥ 1 grade difference from pre-treatment on the WSRS) for more than 80% of the subjects at 64 weeks after initial treatment (Figure 1).

Figure 1. Proportion of responders on the Wrinkle Severity Rating Scale measured by a Blinded Live Evaluator for RHA® 2 and the Control Device



	Week 24	Week 36	Week 52	Week 64
■ RHA® 2	83.6%	86.2%	85.5%	80.9%
■ Control Device	82.1%	87.7%	82.3%	80.9%

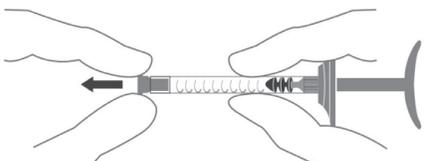
PP populations at the respective follow-up visits
Rate of responders: ≥ 1 grade difference from pre-treatment on the WSRS

On the Global Aesthetic Improvement (GAI) scale, more than 84% of the subjects and the BLEs reported that the NLF treated with RHA® 2 was improved or very much improved from week 24 to week 64. The subjects consistently reported improvement up to 64 weeks based on the NLF module of the FACE-Q® questionnaire with the mean score improving from 24 to more than 60 throughout the follow-up period. More than 90% of the subjects reported to be satisfied or very satisfied 24 weeks after initial treatment and the rate of satisfaction remained at more than 86% at 64 weeks.

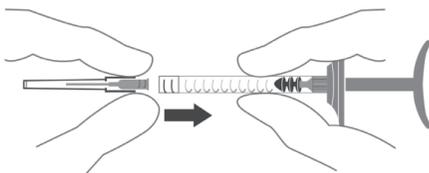
More than 78% of the subjects received repeat treatment. The effectiveness and safety profiles after repeat treatment were similar to that after initial treatment.

DIRECTIONS FOR ASSEMBLY OF THE NEEDLE TO THE SYRINGE

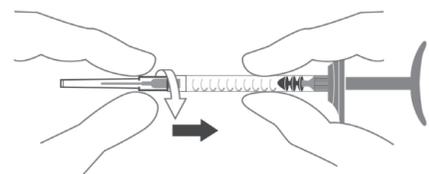
1. Remove the stopper from the syringe by pulling it off.



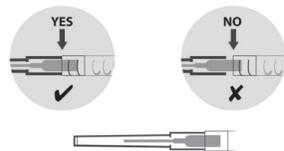
2. Insert the screw thread of the needle firmly into the syringe end-piece.



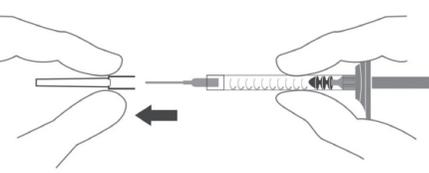
3. Screw the needle clockwise, while maintaining slight pressure between the needle and the syringe.



4. Continue screwing until the edge of the cap of the needle contacts the body of the syringe. There must be no space between these two parts. Failure to follow this instruction means that the needle could be ejected and/or leak at the Luer-lock.



5. Remove the needle's protective cap by pulling it firmly with one hand while holding the body of the syringe with the other.



PRE-TREATMENT GUIDELINES

- Prior to treatment, the patient should avoid taking medications or supplements which thin the blood (e.g., aspirin, nonsteroidal anti-inflammatory medications, St. John's Wort, or high doses of Vitamin E supplements) as these agents may increase bruising and bleeding at the injection site.
- Before starting treatment, a complete medical history should be taken from the patient and the patient should be counseled on appropriate indications, risks, and should be informed about the expected treatment results, and expected responses. The patient should be advised of the necessary precautions before commencing the procedure.
- Prior to treatment with RHA® 2 the patient should be assessed for

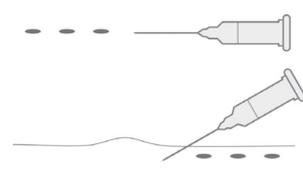
appropriate anesthetic treatment for managing comfort (e.g., topical anesthetic, local or nerve block). The patient's face should be washed with soap and water and dried with a clean towel. Cleanse the area to be treated with alcohol or another suitable antiseptic solution.

- Sterile gloves are recommended while injecting RHA® 2.
- Before injecting, prime the needle by carefully pressing the syringe plunger until a small droplet of the gel is visible at the tip of the needle.

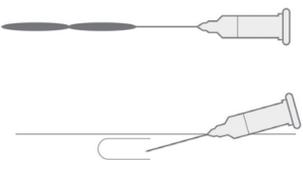
INJECTION TECHNIQUES

- RHA® 2 is administered by using a thin gauge needle (30 G x ½"). The needle is inserted into the mid-to-deep dermis at an approximate angle of 15° to 30° parallel to the length of the wrinkle or fold.
- RHA® 2 can be injected by a number of different techniques that depend on the injector's experience and preference, and patient characteristics.

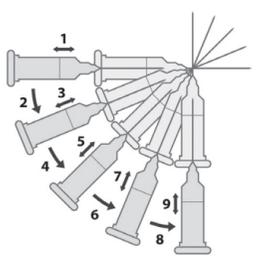
A. Serial puncture: consists of multiple injections, evenly and closely spaced all along wrinkles or folds. This technique is considered to be more precise, but may result in more discomfort for the patient due to the number of punctures.



B. Linear threading: the needle is fully introduced in the wrinkle or the fold, and the product is injected along the line, as a "thread", while withdrawing (retrograde) or pushing (antegrade) the needle.



C. Fanning technique: the needle is introduced as for the *Linear threading technique*, and the product is injected along several closely spaced lines, by changing the direction of the needle, all using the same puncture site (the needle is not withdrawn).



• RHA® 2 is injected slowly into the mid-to-deep dermis. If the injection is made too deeply, i.e. into subcutaneous tissue, the correction may not be as expected. It is possible to tell when an injection is being made too deeply because subcutaneous tissue does not offer any resistance to product injection, unlike the dermis.

- If the color of the needle can be seen through the skin during injection, this means that the injection is too superficial. This should be avoided as the results of the correction could be irregular.
- The injection should be stopped before pulling the syringe out of the skin, to prevent product from leaking out, or product misplacement (too superficially in the skin).
- The volume to be injected depends on the corrections to be performed, but it is important to not overcorrect. Based on the US clinical study, patients should be limited to 6.0 ml per patient per treatment session in wrinkles and folds such as NLFs. The safety of injecting greater amounts has not been established.
- If blanching is observed (e.g., the overlying skin turns a whitish color), the injection should be stopped immediately and the area massaged until it returns to a normal color. Blanching may represent a vessel occlusion. If normal skin coloring does not return, do not continue with the injection. Treat in accordance with American Society for Dermatologic Surgery guidelines, which include hyaluronidase injection.
- If the wrinkles need further treatment with RHA® 2, the same procedure should be repeated until a satisfactory result is obtained.

POST-TREATMENT GUIDELINES

- When the injection is completed, the treated site should be gently massaged so that it conforms to the contour of the surrounding tissues. If an overcorrection has occurred, massage the area firmly between your fingers or against an underlying area to obtain optimal results.
- If the treated area is swollen immediately after the injection, an ice pack can be applied to the site for a short period (e.g., 5-10 minutes). Ice should be used with caution if the area is still numb from anesthetic to avoid thermal injury.
- After use, syringes may be potential biohazards. Follow national, local, or institutional guidelines for use and disposal of medical biohazard devices. Obtain prompt medical attention if injury occurs.

STERILE NEEDLES

- After use, needles are potential biohazards. Follow national, local, or institutional guidelines for use and disposal of medical sharp devices (e.g. discard uncapped needles in approved sharps containers).
- Obtain prompt medical attention if injury with used needle occurs.
- To help avoid needle breakage, do not attempt to straighten a bent needle. Discard it and complete the procedure with a replacement needle.
- Do not recap needles. Recapping by hand is a hazardous practice and should be avoided.
- RHA® 2 is provided with 2 needles that do not contain engineered injury protection. Administration of RHA® 2 requires direct visualization and complete and gradual insertion of the needle making engineered protection devices not feasible. Care should be taken to avoid sharps exposure by proper environmental controls.

PATIENT INSTRUCTIONS

Patient information brochure is available on request, or via the website www.revance.com.

It is recommended that the following information be shared with patients:

- Patients should be advised not to wear make-up during 12 hours following injection.
- Patient should be advised not to take high-dose Vitamin E, aspirin, anti-inflammatories or anti-coagulants during the week prior to the injection. Patients must not discontinue such treatment without talking with their prescribing physician.
- Patients should minimize exposure of the treated area to excessive sun, UV lamp exposure and extreme temperatures (e.g. cold weather, sauna) at least within the first 24 hours, or until initial swelling and redness has resolved. Exposure to any of the above may cause/exacerbate and/or extend the duration of temporary redness, swelling, and/or itching at the treatment sites.
- Patients should notify the injector if any of the following occurs:
 - Changes in vision
 - Unusual pain during or shortly after treatment
 - Significant pain away from the injection site
 - Signs of a stroke
 - Any redness and/or visible swelling that lasts for more than a week
 - Any side effect other than those described above or that occur weeks or months after injection
- Adverse reactions should be reported to Revance Therapeutics, Inc at 877-3REV-NOW (877-373-8669) and to Medical-us@teoxane.com

HOW SUPPLIED

RHA® 2 is supplied in individual blisters containing a 1ml treatment syringe with two 30 G x ½" needles as indicated on the carton. The content of the syringe is sterile and non-pyrogenic. Do not resterilize. Do not use if package is opened or damaged. Each syringe is packaged into a blister with two unique device identifier traceability labels.

SHELF-LIFE AND STORAGE

RHA® 2 must be used prior to the expiration date printed on the package. Store at room temperature (up to 25°C/77°F). Do not expose to direct sunlight. DO NOT FREEZE.

RxOnly

Manufactured by:

TEOXANE S.A.
Rue de Lyon 105
CH 1203 Geneva
(Switzerland)

Distributed by:

Revance Therapeutics, Inc.
1222 Demonbreun Street,
Suite 2000
Nashville, Tennessee 37203

RHA® is a registered trademark of TEOXANE SA.

Under license U.S. Pat. Nos. 8,357,795 ; 8,450,475 ; 8,822,676 ; 9,089,517 ; 9,089,518 ; 9,089,519 ; 9,238,013 ; 9,358,322.

SYMBOLS

Manufacturer's name and address

Catalog number

Lot / batch number

Expiration date (YYYY-MM-DD)

Consult Instructions for use

Single use only

Sterilized using steam

Do not use if the package is damaged

RxOnly Caution: Federal law restricts this device to sale by or on the order of a physician or licensed practitioner

TEOXANE

RHA® 3

CAUTION: FEDERAL LAW RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A PHYSICIAN OR LICENSED PRACTITIONER.

BEFORE USING RHA® 3, PLEASE READ THE FOLLOWING INFORMATION THOROUGHLY

DEVICE DESCRIPTION

RHA® 3 is a viscoelastic, sterile, non-pyrogenic, clear, colorless, homogeneous and biodegradable gel implant. It is produced with sodium Hyaluronic Acid (NaHA) with a concentration of 23 mg/g obtained from bacterial fermentation using the *Streptococcus equi* bacterial strain, crosslinked with 1,4-butanediol diglycidyl ether (BDDE) and reconstituted in a physiological buffer (pH 7.3). RHA® 3 also contains 0.3% lidocaine hydrochloride monohydrate to reduce pain on injection.

INTENDED USE / INDICATIONS

RHA® 3 is indicated for injection into the mid-to-deep dermis for the correction of moderate to severe dynamic facial wrinkles and folds, such as nasolabial folds (NLFs), in adults aged 22 years or older.

RHA® 3 is indicated for injection into the vermilion body, vermilion border and oral commissure to achieve lip augmentation and lip fullness, in adults aged 22 years or older.

CONTRAINDICATIONS

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

WARNINGS

- Introduction of product into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction. To avoid this:
 - Do not inject into blood vessels
 - Take extra care when injecting soft tissue fillers, inject the product slowly and apply the least amount of pressure necessary.

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. If a patient exhibits any of the following symptoms: changes in vision, signs of a stroke, blanching of the skin, or unusual pain during or shortly after the procedure, immediately stop the injection. Patients should receive prompt medical attention and possibly evolution by an appropriate health care practitioner specialist should an intravascular injection occur.

- Product use of specific sites in which an active inflammatory process (skin eruptions such as cysts, pimples, rashes, or hives), infection or skin injury is present should be deferred until the underlying process has been controlled.
- Treatment site reactions consist mainly of short-term inflammatory symptoms (e.g., swelling, redness, tenderness, or pain) and generally resolve within 14 days. Refer to the ADVERSE EXPERIENCES section for details.
- Inflammatory reaction, anaphylactic reaction, edema, implant migration, acne, blisters, scarring, papules and delayed onset of granulomas have been reported following the use of dermal fillers.

PRECAUTIONS

- In order to minimize the risks of potential complications, this product should only be used by experienced health care practitioners who have appropriate training in filler injection techniques, and who are knowledgeable about the anatomy at and around the site of injection.
- Health care practitioners are encouraged to discuss all potential risks of soft tissue injection with their patients prior to treatment and ensure that patients are aware of signs and symptoms of potential complications.
- The safety and effectiveness for the treatment of anatomic regions other than those described in the INTENDED USE / INDICATIONS section have not been established in controlled clinical studies.
- As with all transcutaneous procedures, dermal filler implantation carries a risk of infection. Standard precautions associated with injectable materials should be followed.
- The safety in patients with known susceptibility to keloid formation, hypertrophic scarring, and pigmentation disorders has not been studied.
- The safety for use in sites in the presence of other implants (including permanent implants) has not been studied.
- The safety for use during pregnancy, in breastfeeding females, and in patients under 22 years of age has not been established.
- RHA® 3 should be used with caution in patients on immunosuppressive therapy.
- Bruising or bleeding may occur at RHA® 3 injection sites. RHA® 3 should be used with caution in patients who are using substances that can prolong bleeding (such as thrombolytics, anticoagulants, or inhibitors of platelet aggregation).

- Injection of RHA® 3 into patients with a history of previous herpetic eruption may be associated with reactivation of the herpes.
- If laser treatment, chemical peeling or any other procedure based on active dermal response is considered after treatment with RHA® 3, there is a possible risk of eliciting an inflammatory reaction at the implant site. This also applies if RHA® 3 is administered before the skin has healed completely after such a procedure.
- RHA® 3 is to be used as supplied. Modification or use of the product outside the Instructions for Use may adversely impact the sterility, safety, homogeneity, or performance of the product.
- RHA® 3 is packaged for single-patient use. Do not reuse a syringe between two treatments and/or between two patients. Do not derolize.
- Do not use if package is opened or damaged. The sterility of the product is not guaranteed in the case of failure to comply with this precaution. RHA® 3 is a clear, colorless gel without particulates. In the event the contents of a syringe show signs of separation and/or appears cloudy, do not use the syringe; contact Revance Therapeutics, Inc. 877-3REV-NOW (877-373-8669).
- Failure to comply with the needle attachment instructions could result in needle disengagement and/or product leakage at the Luer-lock and needle hub connection.

ADVERSE EXPERIENCES

There were two U.S. studies from which safety is summarized. One study was conducted in support of the indication for correction of moderate to severe dynamic wrinkles and folds, such as NLFs using RHA® 3, and one study was conducted in support of the indication for lip augmentation using RHA® 3.

1. Clinical Evaluation of RHA® 3 into the NLFs

Clinical study TEO-RHA-1302 was a multicenter, controlled, randomized, double-blinded, within-subject (split-face), prospective US study designed to compare the safety of RHA® 3 versus a control treatment for the treatment of moderate to severe nasolabial folds, and demonstrated similar safety profiles. The expected signs and symptoms that occur following the injection of a hyaluronic acid-based dermal filler (i.e., Common Treatment Responses; CTR) were individually assessed by subjects in a preprinted 14-day diary after each injection. Subjects were asked to rate each CTR as None, Mild, Moderate or Severe.

- Mild: Little discomfort, no effect on daily activities, no medication or make-up required.
- Moderate: some discomfort, some effect on daily activities, possibly medication or make-up required.
- Severe: Great discomfort, daily activities compromised, very likely medication or make-up required.

- CTR by severity and duration are presented respectively, in Table 1 and Table 2.
- The most frequent CTRs were firmness, redness, tenderness, swelling, lumps/bumps, and bruising.
- Proportions of subjects experiencing at least one CTR of each category was similar between RHA® 3 and control treatment.
- More than 60% of the CTRs had resolved by Day 7.
- The majority (more than 88%) of CTRs had resolved by Day 14.
- There were no notable differences between RHA® 3 and control treatment with regard to the small proportion of subjects who reported a severe CTR.
- For the majority of CTRs (more than 84%) experienced by any treatment group (initial treatment or touch-up treatment), the maximal severity reported was "Mild" or "Moderate".
- On the last day of the diary, nearly all ongoing CTR had improved to mild.

Table 1. Common Treatment Responses by maximum severity after initial treatment with RHA® 3 and the control device reported in subject 14-day-diary – Safety Population

Common Treatment Responses	TOTALS			RHA® 3 (N=75 NLF)			Control Device (N=75 NLF)		
	RHA® 3 n° n° %	CTR ¹ n° n° %	Mild n° n° %	Mod ² n° n° %	Sev ³ n° n° %	Mild n° n° %	Mod ⁴ n° n° %	Sev ³ n° n° %	
Bruising	42	38	20	15	7	12	20	6	
	56.0%	50.7%	26.7%	(20.0%)	9.3%	16.0%	26.7%	8.0%	
Discoloration	22	22	7	11	4	10	8	4	
	29.3%	29.3%	9.3%	14.7%	5.3%	13.3%	10.7%	5.3%	
Firmness	48	45	21	21	6	22	21	2	
	64.0%	60.0%	28.0%	28.0%	8.0%	29.3%	28.0%	2.7%	
Itching	13	11	7	4	2	5	4	2	
	17.3%	14.7%	9.3%	5.3%	2.7%	6.7%	5.3%	2.7%	
Lumps/Bumps	49	40	21	21	7	22	14	4	
	65.3%	53.3%	28.0%	28.0%	9.3%	29.3%	18.7%	5.3%	
Pain	30	23	21	6	3	18	4	1	
	40.0%	30.7%	28.0%	8.0%	4.0%	24.0%	5.3%	1.3%	
Redness	43	42	26	14	3	26	15	1	
	57.3%	56.0%	34.7%	18.7%	4.0%	34.7%	20.0%	1.3%	
Swelling	41	38	22	15	4	22	15	1	
	54.7%	50.7%	29.3%	20.0%	5.3%	29.3%	20.0%	1.3%	
Tenderness	44	37	29	12	3	26	10	1	
	58.7%	49.3%	38.7%	16.0%	4.0%	34.7%	13.3%	1.3%	

- ¹ Number of subjects' NLF treated with the respective device
- ² Number of subjects' NLF with any specific Common Treatment Response
- ³ CTRL = Control treatment
- ⁴ Mod = Moderate
- ⁵ Sev = Severe

Table 2. Duration of Common Treatment Responses after initial treatment with RHA® 3 and the control device reported in subject 14-day-diary – Safety Population

Common Treatment Responses	RHA® 3 (N=75 NLF) n° n° %				Control Device (N=75 NLF) n° n° %			
	1-3 Days	4-7 Days	8-14 Days	Last Day ¹	1-3 Days	4-7 Days	8-14 Days	Last Day ¹
Bruising	11	19	12	4	11	16	11	1
	14.7%	25.3%	16.0%	5.3%	14.7%	21.3%	14.7%	1.3%

Discoloration	10	6	6	4	13	5	4	3
	13.3%	8.0%	8.0%	5.3%	17.3%	6.7%	5.3%	4.0%
Firmness	18	7	23	9	16	14	15	3
	24.0%	9.3%	30.7%	12.0%	21.3%	18.7%	20.0%	4.0%
Itching	9	4	0	0	8	3	0	0
	12.0%	5.3%	0.0%	0.0%	10.7%	4.0%	0.0%	0.0%
Lumps/Bumps	17	11	21	12	15	13	12	6
	22.7%	14.7%	28.0%	16.0%	20.0%	17.3%	16.0%	8.0%
Pain	21	7	2	0	18	3	2	1
	28.0%	9.3%	2.7%	0.0%	24.0%	4.0%	2.7%	1.3%
Redness	27	9	7	2	27	10	5	2
	36.0%	12.0%	9.3%	2.7%	36.0%	13.3%	6.7%	2.7%
Swelling	18	12	11	5	19	11	8	4
	24.0%	16.0%	14.7%	6.7%	25.3%	14.7%	10.7%	5.3%
Tenderness	17	13	14	5	17	13	7	3
	22.7%	17.3%	18.7%	6.7%	22.7%	17.3%	9.3%	4.0%

- ¹ Number of subject NLF treated with the respective device
- ² Number of subject NLF with each specific CTR by maximum duration
- ³ Duration refers to number of days cited in the patient diary, irrespective of date of injection
- ⁴ The CTR numbers indicated in the "Last Day" column are also included in the "8-14 Days" column

An adverse event (AE) was defined as a treatment-related event that was not considered typical in type and/or duration and/or severity. Also, CTRs from the patient's diary that were recorded on the last day of diary were automatically elevated to the status of adverse event, regardless of severity.

- All treatment-related AEs were mild or moderate in severity.
- All treatment-related AEs experienced by both treatment groups were typical of the expected signs and symptoms observed following an injection of a hyaluronic acid-based dermal filler.
- All treatment-related AEs were temporally associated with a recent device (RHA® 3 or control treatment) injection (no late onset).
- All treatment-related AEs were based on subjects' diary entries.
- No events were deemed to be a granuloma.
- There were no late onset treatment-related AEs.
- There were no treatment-related serious AEs.

2. Clinical Evaluation of RHA® 3 into the lips

The safety of the RHA® 3 indicated for lip augmentation was studied against a control treatment in a multicenter, controlled, randomized, double-blinded, between-subject, prospective U.S. clinical study. Similar safety profiles between RHA® 3 and its comparator were demonstrated. The expected signs/symptoms that occur following the injection (i.e., CTRs) were captured by subjects in a 30-day diary. Injection sites on each side of the face were individually assessed by subjects over 30 days following study injections.

- CTR by severity and duration are presented respectively, in Table 3 and Table 4.
- The most frequent CTRs were swelling, lumps/bumps, firmness, tenderness, bruising and redness.
- Proportions of subjects with at least one CTR were similar between RHA® 3 and control treatment.
- The majority (84%, 278/329) of CTRs resolved within 14 days.
- There were no notable differences between RHA® 3 and control treatment with regard to the proportion of subjects with at least one severe CTR: 22% (31/140) for RHA® 3 against 23% (11/47) for the control. The most common CTR reported as severe was swelling. All severe CTRs did not last more than 8 days, except for 1 RHA® 3 subject who experienced severe Tenderness and severe Firmness which had a maximum duration of 14 days.

- For most of the diaries with a least one CTR reported, the maximal severity was "Mild" or "Moderate" in both treatment groups (78%, 109/140 for RHA® 3 and 77%, 36/47 for the control).
- 19% of the retrieved diaries (37/195) contained at least one CTR on the last day of the 30-day diary: 20% in the RHA® 3 group (30/147) against 15% in the control group (7/48). All were mild in severity and not clinically significant. They were all elevated to Treatment-related AEs.

Similar safety profiles were observed after touch-up and retreatment, with no difference between RHA® 3 and control groups.

Table 3. Common Treatment Responses by maximum severity after initial treatment with RHA® 3 and the control device reported in subject 30-day diary – Safety Population

Common Treatment Responses	TOTALS			RHA® 3 (N=153)			Control (N=49)		
	RHA® 3 n° n° %	Control n° n° %	Mild n° n° %	Mod ² n° n° %	Sev ³ n° n° %	Mild n° n° %	Mod ⁴ n° n° %	Sev ³ n° n° %	
At least 1 CTR	140	47	58	51	31	17	19	11	
	95.2%	97.9%	41.4%	36.4%	22.1%	36.2%	40.4%	23.4%	
Bruising	102	25	51	34	17	18	6	1	
	69.4%	52.1%	50.0%	33.3%	16.7%	72.0%	24.0%	4.0%	
Discoloration	65	20	39	19	7	12	7	1	
	44.2%	41.7%	60.0%	29.2%	10.8%	60.0%	35.0%	5.0%	
Firmness	115	38	56	47	12	17	18	3	
	78.2%	79.2%	48.7%	40.9%	10.4%	44.7%	47.4%	7.9%	
Itching	39	9	31	6	2	7	1	1	
	26.5%	18.8%	79.5%	15.4%	5.1%	77.8%	11.1%	11.1%	
Lumps/Bumps	115	38	58	46	11	24	10	4	
	78.2%	79.2%	50.4%	40.0%	9.6%	63.2%	26.3%	10.5%	
Pain	77	31	53	21	3	15	14	1	
	52.4%	64.6%	68.8%	27.3%	3.9%	48.4%	45.2%	6.5%	
Redness	81	28	49	23	9	17	9	2	
	55.1%	58.3%	60.5%	28.4%	11.1%	60.7%	32.1%	7.1%	
Swelling	134	47	61	45	28	21	17	9	
	91.2%	97.9%	45.5%	33.6%	20.9%	44.7%	36.2%	19.1%	
Tenderness	114	38	69	35	10	17	20	1	
	77.6%	79.2%	60.5%	30.7%	8.8%	44.7%	52.6%	2.6%	

- ¹ Number of subjects' Lips treated with the respective device
- ² Number of subjects' Lips with any specific Common Treatment Response
- ³ Mod = Moderate
- ⁴ Sev = Severe

Table 4. Duration of Common Treatment Responses after initial treatment with RHA® 3 and the control device reported in subject 30-day diary – Safety Population

CTR Duration ¹	Group (N= subjects)	1-3 Days	4-7 Days	8-14 Days	15-30 Days	Last Day ²
		n° n° %	n° n° %	n° n° %	n° n° %	n° n° %
At least 1 CTR	RHA® 3 (N=153)	111	100	67	51	30
	Control (N=49)	40	33	11	10	7
Bruising	RHA® 3 (N=153)	29	34	33	6	1
	Control (N=49)	12	10	2	1	0
Discoloration	RHA® 3 (N=153)	25	18	15	7	3
	Control (N=49)	13	5	2	0	0
Firmness	RHA® 3 (N=153)	32	26	27	30	11
	Control (N=49)	12	18	4	4	3
Itching	RHA® 3 (N=153)	22	8	4	5	1
	Control (N=49)	10	4	0	0	0
Lumps/Bumps	RHA® 3 (N=153)	30	23	17	45	27
	Control (N=49)	13	14	2	9	7
Pain	RHA® 3 (N=153)	40	19	10	8	0
	Control (N=49)	20	9	2	0	0
Redness	RHA® 3 (N=153)	42	18	15	6	0
	Control (N=49)	19	6	3	0	0
Swelling	RHA® 3 (N=153)	45	43	32	14	1
	Control (N=49)	25	17	2	3	0
Tenderness	RHA® 3 (N=153)	37	32	27	18	3
	Control (N=49)	16	13	6	3	1

- ¹ Number of subjects' Lips treated with the respective device
- ² Number of subjects' Lips with any specific CTR by maximum duration
- ³ Duration refers to number of days cited in the patient diary, irrespective of date of injection

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

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

All subjects were able to perform the tests successfully pre-injection and at every visit thereafter. Less than 10% of subjects had difficulty sucking through a straw, feeling the mono-filament and cotton wisp, or pronouncing certain words, right after injection. All those subjects successfully completed the tests at subsequent visits.

An adverse event (AE) was defined as a treatment-related event that was not considered typical in type and/or duration and/or severity. Also, CTRs from the patient's diary that were recorded on the last day of diary were automatically elevated to the status of adverse event, regardless of severity.

- Both RHA® 3 and control treatment groups presented with similar adverse event (AE) profiles with an overall of 64 subjects experiencing a total of 146 treatment-related AEs after initial treatment and touch-up injections.
- All treatment-related AEs were mild or moderate in severity. No severe treatment-related AEs were reported.
- Most of treatment-related AEs experienced in both treatment groups were typical of the expected signs and symptoms observed following an injection of a hyaluronic acid-based dermal filler, such as: injection site mass, injection site swelling and injection site induration. Other reported treatment-related AEs such as headache, or pruritus are less typical but not unexpected following a dermal filler injection.
- Most of treatment-related AEs were based on subjects' diary entries (CTR): 75% (81/108) were either a CTR, or listed as Others, or from the list of pre-identified AEs on the diary and 25% (27/108) were identified by the TI.
- Most treatment-related AEs (79%, 85/108) resolved within 30 days and the proportion of subjects with reported treatment related AE was similar across the 2 treatment groups. The duration of treatment-related AEs varied from 1 to 90 days, except for 11 treatment-related AEs (with 9 of them started during the retreatment period) that were still ongoing at the end of the study (i.e., one month after retreatment). These 11 treatment-related AEs were all the typical and expected signs and symptoms observed following the injection of a dermal filler (8 Lumps/Bumps, 1 swelling, 2 firmness). All of them were mild in severity, except one moderate Lumps/Bumps, that resolved one month after injection.
- There were no treatment-related serious AEs.
- One AE of Special Interest (AESI) was reported. The subject received RHA® 3 and developed an event of Vision blurred with mild severity, the same day of the injection. The event was assessed as Unlikely related to the study treatment or the study procedure and did not

More than 77% of the subjects received repeat treatment. The effectiveness and safety profiles after repeat treatment were similar to that after initial treatment.

TEO-RHA-1806 – RHA® 3 into the lips – CLINICAL STUDY

The safety and effectiveness of the RHA® 3 indicated for lip augmentation were evaluated in comparison to a control in a U.S. pivotal clinical study described hereafter.

1. Pivotal Study Design

A prospective, double-blinded, randomized, controlled, between-subject, multicenter clinical study was conducted to evaluate the clinical safety and effectiveness of RHA® 3 versus control for injection into the lips (vermillion body, vermillion border, and oral commissures) for lip augmentation. A total of 202 subjects were randomized and underwent treatment with either RHA® 3 (N = 153) or control (N = 49) in the vermillion border, vermillion body and oral commissure for the lip augmentation and lip fullness. If deemed necessary to achieve optimal correction, additional lip correction was performed after 4 weeks (touch-up), with the same study device used for initial treatment. The follow-up period consisted of safety and effectiveness follow-up visits at 4, 8, 12, 24, 36, and 52 weeks after the last treatment.

Subjects were eligible for optional retreatment if necessary at Weeks 36 or 52, and were then followed for 1 month after retreatment or until all Adverse Events (AEs) resolved or TI determines that follow-up is no longer necessary. Retreatments were provided using RHA® 3 (the control device was not used).

2. Study Endpoints

The primary effectiveness endpoint was the analysis of non-inferiority of RHA® 3 versus control in terms of change from Baseline (pre-injection) 12 weeks after injection, as measured by a Blinded Live Evaluator (BLE) using the proprietary and validated 5-grade Teoxane Lip Fullness Scale (TLFS). The co-primary endpoint was the proportion of responders with a ≥1-grade point increase on the TLFS at 12 weeks when compared to pretreatment, which should be ≥ 70%.

Secondary effectiveness endpoints included TLFS change from Baseline and rates of responders, as assessed by the BLE at each study visits (see data in Table 8 and Figure 2), Global Aesthetic Improvement (GAI), as assessed by the subject, and by the BLE, impact and effectiveness of study treatment procedures from the subjects' perspective as assessed by the lip domain and satisfaction of the outcome module of the FACE-Q®, and subject satisfaction.

Safety endpoints was evaluated throughout the study, with a 30-day subject diary capturing post-injection signs/symptoms following every study injection, and AE assessments and lip functionality at each visit, and included self-assessment of injection site pain by the subject using a 100mm Visual Analog Scale. Safety endpoints also included assessment of visual disturbances before and after injection and at each visit.

3. Demographics

A total of 202 subjects (22 to 76 years old) were enrolled and included in the Safety population with 153 subjects allocated to RHA® 3 treatment, and 49 allocated to the control treatment. Subjects' demographics are presented in Table 7. A total of 181 subjects were enrolled and included in the mITT population, with 137 subjects allocated to RHA® 3 treatment, and 44 allocated to the control treatment. The mITT population consisted of all enrolled subjects who received treatment and had at least one post-Baseline primary effectiveness visit, excluding subjects with high TLFS grades at Baseline TLFS (a few subjects with FS1 V and VI to be followed for safety only).

Table 7. Demographics

Number / % of subjects	RHA® 3 N=153	Control N=49	Total N=202
Age Mean (SD) min max	48.8 (13.19) 22, 76	48.5 (11.69) 22, 68	48.7 (12.82) 22, 76
Gender Female Male	151 (98.7%) 2 (1.3%)	48 (98.0%) 1 (2.0%)	199 (98.5%) 3 (1.5%)
Race Am. Indian/N. Alask. Asian Black or African American N. Hawaiian/P. Isl. White	2 (1.3%) 4 (2.6%) 15 (9.8%) 2 (1.3%) 130 (85.0%)	1 (2.0%) 1 (2.0%) 2 (4.1%) 0 45 (91.8%)	3 (1.5%) 5 (2.5%) 17 (8.4%) 2 (1.0%) 175 (86.6%)
Ethnicity Hispanic/Latino Not Hispanic/Latino Not available	32 (20.9%) 118 (77.1%) 3 (2.0%)	13 (26.5%) 35 (71.4%) 1 (2.0%)	45 (22.3%) 153 (75.7%) 4 (2.0%)
Fitzpatrick Skin Phototype I-III I II III IV-VI IV V VI	114 (74.5%) 10 (6.5%) 46 (30.1%) 58 (37.9%) 39 (25.5%) 22 (14.4%) 10 (6.5%) 7 (4.6%)	35 (71.5%) 7 (14.3%) 9 (18.4%) 19 (38.8%) 14 (28.6%) 10 (20.4%) 3 (6.1%) 1 (2.0%)	149 (73.8%) 17 (8.4%) 55 (27.2%) 77 (38.2%) 53 (26.2%) 32 (15.8%) 13 (6.4%) 8 (4.0%)

* Number of subjects in the safety populations

4. Treatment Characteristics

The study protocol allowed a maximum of 1.5 ml per lip at each treatment session. The overall total mean volume of RHA® 3 injected to achieve optimal correction (OCR) (initial + touch-up) was 1.78±0.64 ml. Injection volumes into the lips tended to be lower after retreatment, with total mean injection volume being 1.03±0.45 ml after retreatment. Similar mean injection volumes were used in subjects treated with the control device: 1.95±0.73 ml to achieve OCR and 1.03±0.41 ml after retreatment. The proportion of subjects who received touch-up treatment at Week 4 was lower with RHA® 3 (58.2%, 89/153) than with control (73.5%, 36/49).

In general, a linear threading, either as a stand-alone technique or in combination with other techniques such as multiple punctate pools or fan like injection, was used for the vast majority of subjects in both treatment groups.

5. Effectiveness Results

The primary effectiveness endpoint was the fullness improvement from pre-injection of the lips treated with RHA® 3 compared to the improvement from pre-injection of the lip treated with the control treatment, using the TLFS, as assessed by the BLE at 12 weeks; results are presented in Table 8. Table 9 shows the number of responders and the responder rate as assessed by the BLE 12 weeks after last treatment based on the TLFS grade at Baseline 1, 2 and/or 3.

Table 8. TLFS Grade Change from Baseline as assessed by the BLE

	RHA® 3 (N=137)		Control (N=44)	
	Mean TLFS score (SD)	Mean TLFS change from Baseline (SD)	Mean TLFS score (SD)	Mean TLFS change from Baseline (SD)
Baseline	2.4 (0.62)	-	2.3 (0.60)	-
Week 12^{a,b}	3.4 (0.61)	1.0 (0.65)	3.1 (0.65)	0.8 (0.70)
Week 24	3.3 (0.75)	0.8 (0.64)	2.8 (0.69)	0.5 (0.63)
Week 36	3.1 (0.78)	0.7 (0.65)	2.8 (0.73)	0.5 (0.63)
Week 52	3.0 (0.75)	0.5 (0.64)	2.5 (0.67)	0.1 (0.63)

^a Primary effectiveness endpoint

^b Estimate of difference in means RHA3 – control is 0.19 (-0.03, -0.42) calculated by

Bootstrap estimate using 1000 samples.

mITT population

Table 9. TLFS responder rate (BLE) at Week 12 – mITT Population

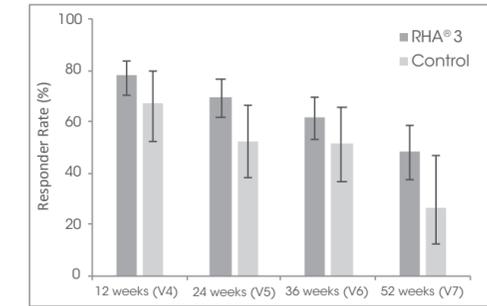
	RHA® 3	Control
Baseline TLFS grades 1, 2 & 3		
N	137	44
# of responders (%) [95% CI]	107 (78.1%) [70.5 - 84.2%]	29 (65.9%) [51.1 - 78.1%]
Baseline TLFS grades 1 & 2		
N	68	27
# of responders (%) [95% CI]	64 (94.1%) [85.8-97.7%]	24 (88.9%) [71.9-96.1%]
Baseline TLFS grade 3		
N	69	17
# of responders (%) [95% CI]	43 (62.3%) [50.5-72.8%]	5 (29.4%) [13.3-53.1%]

mITT population

The results demonstrated that non-inferiority to the control in terms of mean TLFS change from baseline was achieved for RHA® 3 at 12 weeks for lip augmentation. However, for the co-primary endpoint, the responder rate for the control group did not meet the performance goal of 70%.

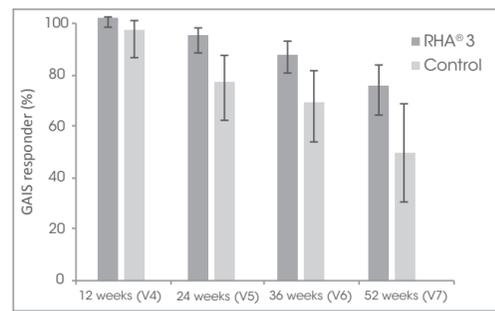
Throughout the follow-up period, the aesthetic improvement of the RHA® 3 continued to be clinically significant (≥ 1 grade difference from pre-treatment on the TLFS) for 61% (81/132) of the subjects at 36 weeks after last treatment, and for 48% (38/79) at 52 weeks after last treatment (Figure 2).

Figure 2. Proportion of responders on the TLFS measured by the BLE for RHA® 3 and the Control Device



On the Global Aesthetic Improvement (GAI) scale, more than 73% (99%, 134/135 at 12 weeks, 92%, 122/132 at 24 weeks, 86%, 113/132 at 36 weeks and 73%, 58/79 at 52 weeks) of the subjects and the BLE reported that the lips treated with RHA® 3 was improved or very much improved from week 12 to week 52. GAI responder rate was similar at Week 12 between RHA® 3 and control as assessed by BLE, and GAI responder rates in the RHA® 3 group are higher than the GAI responder rates in the control group at all subsequent visits (24, 36 and 52 weeks after last treatment; Figure 3).

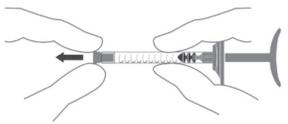
Figure 3. GAIIS through 1 year as assessed by the BLE



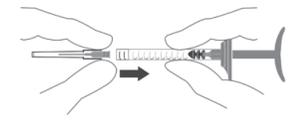
The subjects treated with RHA® 3 consistently reported improvement up to 52 weeks based on the Satisfaction with lips module of the FACE-Q® questionnaire with the mean score improving from Baseline by 51 points at Week 12, to more than 36 points throughout the follow-up period (46 at Week 24, 41 at Week 36 and 36 at Week 52). Similar results were found with the Satisfaction with outcomes module of the FACE-Q® questionnaire. 84% (113/135) of the subjects reported to be satisfied or very satisfied 12 weeks after treatment and the rate of satisfaction was 83% (67/81) at 52 weeks (the scale grades were: very satisfied, satisfied, neither satisfied nor dissatisfied, dissatisfied, or very dissatisfied). 59% (90/153) of the subjects received repeat treatment. The effectiveness and safety profiles after repeat treatment were similar to that after initial treatment and touch-up.

DIRECTIONS FOR ASSEMBLY OF THE NEEDLE TO THE SYRINGE

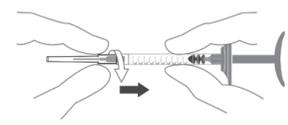
1. Remove the stopper from the syringe by pulling it off.



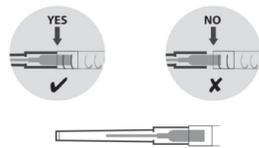
2. Insert the screw thread of the needle firmly into the syringe end-piece.



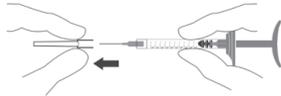
3. Screw the needle clockwise, while maintaining slight pressure between the needle and the syringe.



4. Continue screwing until the edge of the cap of the needle contacts the body of the syringe. There must be no space between these two parts. Failure to follow this instruction means that the needle could be ejected and/or leak at the Luer-lock.



5. Remove the needle's protective cap by pulling it firmly with one hand while holding the body of the syringe with the other.



PRE-TREATMENT GUIDELINES

- Prior to treatment, the patient should avoid taking medications or supplements which thin the blood (e.g., aspirin, nonsteroidal anti-inflammatory medications, St. John's Wort, or high doses of Vitamin E supplements) as these agents may increase bruising and bleeding at the injection site.
- Before starting treatment, a complete medical history should be taken from the patient and the patient should be counseled on appropriate indications, risks, and should be informed about the expected treatment results, and expected responses. The patient should be advised of the necessary precautions before commencing the procedure.
- Prior to treatment with RHA® 3 the patient should be assessed for appropriate anesthetic treatment for managing comfort (e.g., topical anesthetic, local or nerve block). The patient's face should be washed with soap and water and dried with a clean towel. Cleanse the area to be treated with alcohol or another suitable antiseptic solution.
- Sterile gloves are recommended while injecting RHA® 3.
- Before injecting, prime the needle by carefully pressing the syringe plunger until a small droplet of the gel is visible at the tip of the needle.
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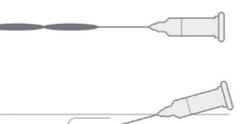
INJECTION TECHNIQUES

- RHA® 3 is administered by using a thin gauge needle (27 G x ½"). For the treatment of NLFs, the needle is inserted into the mid-to-deep dermis at an approximate angle of 15° to 30° parallel to the length of the wrinkle or fold. For lip augmentation, RHA® 3 is injected into the lip mucosa and/or mid to deep dermis as appropriate.
- RHA® 3 can be injected by a number of different techniques that depend on the injector's experience and preference, and patient characteristics. The techniques may include:

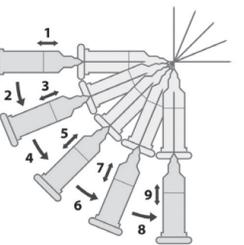
A. **Serial puncture:** consists of multiple injections, evenly and closely spaced all along wrinkles or folds. This technique is considered to be more precise, but may result in more discomfort for the patient due to the number of punctures.



B. **Linear threading:** the needle is fully introduced in the wrinkle or the fold, and the product is injected along the line, as a "thread", while withdrawing (retrograde) or pushing (antegrade) the needle.



C. **Fanning technique:** the needle is introduced as for the Linear threading technique, and the product is injected along several closely spaced lines, by changing the direction of the needle, all using the same puncture site (the needle is not withdrawn).



- RHA® 3 is injected slowly into the mid-to-deep dermis or into the lip mucosa. If the injection is made too deeply, i.e. into sub-cutaneous tissue, the correction may not be as expected. It is possible to tell when an injection is being made too deeply because subcutaneous tissue does not offer any resistance to product injection, unlike the dermis.
- If the color of the needle can be seen through the skin during injection, this means that the injection is too superficial. This should be avoided as the results of the correction could be irregular.
- The injection should be stopped before pulling the syringe out of the skin, to prevent product from leaking out, or product misplacement (too superficially in the skin).
- The volume to be injected depends on the corrections to be performed, but it is important to not overcorrect. Based on the US clinical study, patients should be limited to 6.0ml per patient per treatment session in wrinkles and folds such as NLFs, and should not exceed 1.5 ml per upper lip and 1.5 ml per lower lip per treatment session. The safety of injecting greater amounts has not been established.
- If blanching is observed (e.g., the overlying skin turns a whitish color), the injection should be stopped immediately and the area massaged until it returns to a normal color. Blanching may represent a vessel occlusion. If normal skin coloring does not return, do not continue with the injection. Treat in accordance with American Society for Dermatologic Surgery guidelines, which include hyaluronidase injection.
- If the wrinkles or lips need further treatment with RHA® 3, the same procedure should be repeated until a satisfactory result is obtained.

POST-TREATMENT GUIDELINES

- When the injection is completed, the treated site may be gently massaged so that it conforms to the contour of the surrounding tissues. If an overcorrection has occurred, massage the area firmly between your fingers or against an underlying area to obtain optimal results.
- If the treated area is swollen immediately after the injection, an ice pack may be applied to the site for a short period (e.g., 5-10 minutes). Ice should be used with caution if the area is still numb from anesthetic to avoid thermal injury.
- After use, syringes may be potential biohazards. Follow national, local, or institutional guidelines for use and disposal of medical biohazard devices. Obtain prompt medical attention if injury occurs.

STERILE NEEDLES

- After use, needles are potential biohazards. Follow national, local, or institutional guidelines for use and disposal of medical sharp devices (e.g. discard uncapped needles in approved sharps containers).
- Disposal should be in accordance with accepted medical practice and applicable local, State and Federal requirements.
- To help avoid needle breakage, do not attempt to straighten a bent needle. Discard it and complete the procedure with a replacement needle.
- Do not recap needles. Recapping by hand is a hazardous practice and should be avoided.
- RHA® 3 is provided with 2 needles that do not contain engineered injury protection. Administration of RHA® 3 requires direct visualization and complete and gradual insertion of the needle making engineered protection devices not feasible. To avoid needle stick injury and sharp exposure, take care to inject in appropriate conditions.
- Obtain prompt medical attention if injury with used needle occurs.

PATIENT INSTRUCTIONS

Patient information brochure is available on request, or via the website www.revance.com. It is recommended that the following information be shared with patients:

- Patients should be advised not to wear make-up during 12 hours following injection.
- Patient should be advised not to take high-dose Vitamin E, aspirin, anti-inflammatories or anti-coagulants during the week prior to the injection. Patients must not discontinue such treatment without talking with their prescribing physician.
- Patients should minimize exposure of the treated area to excessive sun, UV lamp exposure and extreme temperatures (e.g., cold weather, sauna) at least within the first 24 hours, or until initial swelling and redness has resolved. Exposure to any of the above may cause/exacerbate and/or extend the duration of temporary redness, swelling, and/or itching at the treatment sites.
- Patients should notify the injector if any of the following occurs:
 - Changes in vision
 - Unusual pain during or shortly after treatment
 - Significant pain away from the injection site
 - Signs of a stroke
 - Any redness and/or visible swelling that lasts for more than a week
 - Any side effect other than those described above or that occur weeks or months after injection
- Adverse reactions should be reported to Revance Therapeutics, Inc at 877-3REV-NOW (877-373-8669) and to Medical-us@teoxane.com.

RxOnly

HOW SUPPLIED

RHA® 3 is supplied in individual blisters containing a 1 ml treatment syringe with two 27 G x ½" needles as indicated on the carton. The content of the syringe is sterile and non-pyrogenic. Do not resterilize. Do not use if package is opened or damaged. Each syringe is packaged into a blister with two unique device identifier traceability labels.

SHELF-LIFE AND STORAGE

RHA® 3 must be used prior to the expiration date printed on the package. Store at room temperature (up to 25°C/77°F). Do not expose to direct sunlight. DO NOT FREEZE. Do not store partially used syringes.

Manufactured by:	Distributed by:
TEOXANE S.A. Rue de Lyon 105 CH 1203 Geneva (Switzerland)	Revance Therapeutics, Inc. 1222 Demonbreun Street, Suite 2000 Nashville, Tennessee 37203

RHA® is a registered trademark of TEOXANE SA.

Under license U.S. Pat. Nos. 8,357,795; 8,450,475; 8,822,676; 9,089,517; 9,089,518; 9,089,519; 9,238,013; 9,358,322.

SYMBOLS

- Manufacturer's name and address
- Catalog number
- Lot / batch number
- Expiration date (YYYY-MM-DD)
- Consult instructions for use
- Single use only
- Sterilized using steam
- Do not use if the package is damaged
- Caution: Federal law restricts this device to sale by or on the order of a physician or licensed practitioner



TEOXANE

RHA® 4

CAUTION: FEDERAL LAW RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A PHYSICIAN OR LICENSED PRACTITIONER.

BEFORE USING RHA® 4, PLEASE READ THE FOLLOWING INFORMATION THOROUGHLY

DEVICE DESCRIPTION

RHA® 4 is a viscoelastic, sterile, non-pyrogenic, clear, colorless, homogeneous and biodegradable gel implant. It is produced with sodium Hyaluronic Acid (NaHA) with a concentration of 23 mg/g obtained from bacterial fermentation using the *Streptococcus equi* bacterial strain, crosslinked with 1,4-butanediol diglycidyl ether (BDDE) and reconstituted in a physiological buffer (pH 7.3). RHA® 4 also contains 0.3% lidocaine hydrochloride monohydrate to reduce pain on injection.

INTENDED USE / INDICATIONS

RHA® 4 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.

CONTRAINDICATIONS

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

WARNINGS

- RHA® 4 must not be injected into blood vessels. Introduction of product into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction. Take extra care when injecting soft tissue fillers, for example, inject the product slowly and apply the least amount of pressure necessary. 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. Immediately stop the injection if a patient exhibits any of the following symptoms: changes in vision, signs of a stroke, blanching of the skin, or unusual pain during or shortly after the procedure. Patients should receive prompt medical attention and possibly evolution by an appropriate health care practitioner specialist should an intravascular injection occur.
- Product use at specific sites in which an active inflammatory process (skin eruptions such as cysts, pimples, rashes, or hives), infection or skin injury is present should be deferred until the underlying process has been controlled.
- Treatment site reactions consist mainly of short-term inflammatory symptoms (e.g., swelling, redness, tenderness, or pain) and generally resolve within 14 days. Refer to the ADVERSE EXPERIENCES section for details.
- Inflammatory reaction, anaphylactic reaction, papule, acne, blisters, scarring, papules, unsatisfactory results, scarring and delayed onset of granulomas have been reported following the use of dermal fillers.

PRECAUTIONS

- In order to minimize the risks of potential complications, this product should only be used by experienced health care practitioners who have appropriate training in filler injection techniques, and who are knowledgeable about the anatomy at and around the site of injection.
- Health care practitioners are encouraged to discuss all potential risks of soft tissue injection with their patients prior to treatment and ensure that patients are aware of signs and symptoms of potential complications.
- The safety and effectiveness for the treatment of anatomic regions other than those described in the INTENDED USE / INDICATIONS section have not been established in controlled clinical studies.
- The safety and effectiveness of cannula injection of RHA® 4 with lidocaine for the correction of moderate to severe dynamic facial wrinkles and folds, such as NLF have only been clinically evaluated with two brands of blunt-tip cannulas (Soffii® Precision and TSK STERIGLIDE™) that were 25G and 2 inches in length.
- As with all transcutaneous procedures, dermal filler implantation carries a risk of infection. Standard precautions associated with injectable materials should be followed.
- The safety in patients with known susceptibility to keloid formation, hypertrophic scarring, and pigmentation disorders has not been studied.
- The safety for use in sites in the presence of other implants (including permanent implants) has not been studied.

- The safety for use during pregnancy, in breastfeeding females, and in patients under 22 years of age has not been established.
- RHA® 4 should be used with caution in patients on immunosuppressive therapy.
- Bruising or bleeding may occur at RHA® 4 injection sites. RHA® 4 should be used with caution in patients who are using substances that can prolong bleeding (such as thrombolytics, anticoagulants, or inhibitors of platelet aggregation).
- Injection of RHA® 4 into patients with a history of previous herpetic eruption may be associated with reactivation of the herpes.
- If laser treatment, chemical peeling or any other procedure based on active dermal response is considered after treatment with RHA® 4, there is a possible risk of eliciting an inflammatory reaction at the implant site. This also applies if RHA® 4 is administered before the skin has healed completely after such a procedure.
- RHA® 4 is to be used as supplied. Modification or use of the product outside the Instructions for Use may adversely impact the sterility, safety, homogeneity, or performance of the product.
- RHA® 4 is packaged for single-patient use. Do not reuse a syringe between two treatments and/or between two patients. Do not resterilize.
- Do not use if package is opened or damaged. The sterility of the product is not guaranteed in the case of failure to comply with this precaution. Failure to comply with the needle/blunt cannula attachment instructions could result in needle/blunt cannula disengagement and/or product leakage at the Luer-lock and needle/blunt cannula hub connection.
- RHA® 4 is a clear, colorless gel without particulates. In the event the contents of a syringe show signs of separation and/or appears cloudy, do not use the syringe; contact Revance Therapeutics, Inc. 877-3REV-NOW (877-373-8669).

ADVERSE EXPERIENCES

There were two U.S. studies that reported adverse experiences. One study was conducted in support of the indication for correction moderate to severe dynamic wrinkles and folds, such as NLF, and one study was conducted in support of using a small bore, blunt-tip cannula for the same indication.

1. Clinical Evaluation of RHA® 4 Into the NLFs

Clinical study TEO-RHA-1402 was a multicenter, controlled, randomized, double-blinded, within-subject (split-face), prospective US study designed to compare the safety of RHA® 4 versus a control treatment for the treatment of moderate to severe nasolabial folds, and demonstrated similar safety profiles. The expected signs and symptoms that occur following the injection of a hyaluronic acid-based dermal filler (i.e., Common Treatment Responses; CTR) were individually assessed by subjects in a preprinted 14-day diary after each injection.

- Mild: Little discomfort, no effect on daily activities, no medication or make-up required
- Moderate: some discomfort, some effect on daily activities, possibly medication or make-up required
- Severe: Great discomfort, daily activities compromised, very likely medication or make-up required

CTR by severity and duration are presented respectively, in Table 1 and Table 2.

- The most frequent CTRs were swelling, firmness, tenderness, redness, lumps/bumps, pain, and bruising.
- Proportions of subjects experiencing at least one CTR of each category was similar between RHA® 4 and Control treatment.
- More than 67% of the CTRs had resolved by Day 7.
- The majority (80%) of CTRs had resolved by Day 14.
- There were almost 3 times less subjects who reported severe CTR with RHA® 4 than with Control treatment.
- For nearly all CTRs (more than 90%) experienced by any treatment group (initial treatment or touch-up treatment), the maximal severity reported was "Mild" or "Moderate".

Table 1. Common Treatment Responses by maximum severity after initial treatment with RHA® 4 and the Control Device – Safety Population

Common Treatment Responses	TOTALS		RHA® 4 (N=120 NLF)			Control Device (N=120 NLF)		
	RHA® 4 n ^o	CTRL ^o n ^o %	Mild n ^o %	Mod ^a n ^o %	Sev ^b n ^o %	Mild n ^o %	Mod ^a n ^o %	Sev ^b n ^o %
Bruising	70 58.3	72 60.0	35 29.2	26 21.7	9 7.5	37 30.8	25 20.8	10 8.3
Discoloration	50 41.7	56 46.7	30 25.0	16 13.3	4 3.3	30 25.0	20 16.7	6 5.0
Firmness	91 75.8	93 77.5	36 30.0	46 38.3	9 7.5	13 10.8	50 41.7	30 25.0
Itching	30 25.0	44 36.7	25 20.8	5 4.2	0	28 23.3	14 11.7	2 1.7
Lumps/Bumps	81 67.5	90 75.0	36 30.0	33 27.5	12 10.0	28 23.3	37 30.8	25 20.8
Pain	66 55.0	87 72.5	42 35.0	19 15.8	5 4.2	30 25.0	40 33.3	17 14.2
Redness	84 70.0	91 75.8	42 35.0	38 31.7	4 3.3	32 26.7	42 35.0	17 14.2
Swelling	97 80.8	104 86.7	41 34.2	44 36.7	10 8.3	21 17.5	38 31.7	45 37.5
Tenderness	90 75.0	95 79.2	53 44.2	30 25.0	7 5.8	23 19.2	45 37.5	27 22.5

- ^a Number of subjects' NLF treated with the respective device
- ^b Number of subjects' NLF with any specific Common Treatment Response
- ^c CTRL = Control treatment
- ^d Mod = Moderate
- ^e Sev = Severe

Table 2. Duration of Common Treatment Responses after initial treatment with RHA® 4 and the Control Device – Safety Population

Common Treatment Responses	RHA® 4 (N=120 NLF) N ^o %				Control Device (N=120 NLF) N ^o %			
	1-3 Days	4-7 Days	8-14 Days	Last Day ^a	1-3 Days	4-7 Days	8-14 Days	Last Day ^a
Bruising	22 18.3	28 23.3	20 16.7	6 5.0	37 30.8	28 23.3	7 5.8	4 3.3
Discoloration	28 23.3	10 8.3	12 10.0	10 8.3	34 28.3	14 11.7	8 6.7	4 3.3
Firmness	16 13.3	20 16.7	55 45.8	35 29.2	13 10.8	26 21.7	54 45.0	26 21.7
Itching	20 16.7	8 6.7	2 1.7	2 1.7	24 20.0	14 11.7	6 5.0	3 2.5
Lumps/Bumps	19 15.8	14 11.7	48 40.0	30 30.0	25 20.8	24 20.0	41 34.2	27 22.5
Pain	48 40.0	12 10.0	6 5.0	3 2.5	54 45.0	25 20.8	8 6.7	2 1.7
Redness	42 35.0	30 25.0	12 10.0	6 5.0	42 35.0	37 30.8	12 10.0	5 4.2
Swelling	36 30.0	29 24.2	32 26.7	13 13.3	27 22.5	50 41.7	20 17.5	11 9.2
Tenderness	41 34.2	22 18.3	27 22.5	14 11.7	26 21.7	39 32.5	30 25.0	8 6.7

- ^a Number of subject NLF treated with the respective device
- ^b Number of subject NLF with each specific CTR by maximum duration
- ^c Duration refers to number of days cited in the patient diary, irrespective of date of injection
- ^d The CTR numbers indicated in the «Last Day» column are also included in the «8-14 Days» column.

An adverse event (AE) was defined as a treatment-related event that was not considered typical in type and/or duration and/or severity. Also, CTRs from the patient's diary that were recorded on the last day of diary were automatically elevated to the status of adverse event, regardless of severity.

- All treatment-related AEs were mild or moderate in severity.
- The vast majority of treatment-related AEs experienced by both treatment groups were typical of the expected signs and symptoms observed following an injection of a dermal filler.
- All treatment-related AEs were temporally associated with a recent device (RHA® 4 or control treatment) injection (no late onset).
- Nearly all treatment-related AEs were based on subjects' diary entries (CTRs). Also, there were 11 treatment-related AEs (all of mild severity) in 11 subjects with RHA® 4 reported by the Treating Investigator which consisted of acne, discoloration, firmness, headache, pain, swelling, telangiectasia, and tenderness.
- No events were deemed to be a granuloma.
- There were no late onset treatment-related AEs.
- There were no treatment-related serious AEs.

2. Clinical Evaluation of RHA® 4 for the use of a small bore, blunt tip cannula into the NLFs

Clinical study TEO-RHA-2001 was a multicenter, controlled, single-blinded, within-subject (split-face), prospective study to evaluate the effectiveness and safety of using RHA® 4 injected with a blunt cannula (25G x 2") or with a sharp needle (27G x ½") for the treatment of moderate to severe nasolabial folds. The expected signs and symptoms that occur following the injection of a hyaluronic acid-based dermal filler (i.e., Common Treatment Responses; CTR) were individually assessed by subjects in a preprinted 28-day diary after each injection. Subjects were asked to rate each CTR as None, Mild, Moderate or Severe:

- Mild: Little discomfort, no effect on daily activities, no medication or make-up required
- Moderate: some discomfort, some effect on daily activities, possibly medication or make-up required
- Severe: Great discomfort, daily activities compromised, very likely medication or make-up required

CTR by severity and duration are presented respectively, in Table 3 and Table 4.

- The most frequent CTRs were firmness, swelling, tenderness, lumps/bumps, redness, pain and bruising.
- Proportions of subjects experiencing at least one CTR of each category was similar between RHA® 4 injected with a cannula and between RHA® 4 injected with a needle.
- When analyzed for each individual sign or symptom, the number of subjects who experienced at least 1 CTR was consistently and markedly lower in the RHA® 4-cannula group, with a significant difference between treatment groups for bruising, lumps/bumps, redness, itching, and pain.
- The majority (73%) of CTRs had resolved by Day 14.
- For nearly all CTRs (more than 80%) experienced by any treatment group (initial treatment or touch-up treatment), the maximal severity reported was "Mild" or "Moderate".
- There were approximately the same number of subjects who reported severe CTR with RHA® 4 injected with a cannula (10%) as RHA® 4 injected with a needle (14%).

Table 3. Common Treatment Responses by maximum severity after initial treatment with RHA® 4 injected using a cannula and RHA® 4 injected using a needle – Safety Population

Common Treatment Responses	TOTALS		RHA® 4-cannula (N=50 NLF)			RHA® 4-needle (N=50 NLF)		
	RHA® 4 -C nb	RHA® 4 -N nb %	Mild n ^o %	Mod ^a n ^o %	Sev ^b n ^o %	Mild n ^o %	Mod ^a n ^o %	Sev ^b n ^o %
Bruising	10 20%	27 54%	9 16%	1 2%	0 0%	18 36%	7 14%	2 4%
Discoloration	9 18%	16 32%	8 16%	1 2%	0 0%	10 20%	5 10%	1 2%

Firmness	40 80%	43 86%	23 46%	14 28%	3 6%	23 46%	17 34%	3 6%
Itching	10 20%	17 34%	9 16%	2 4%	0 0%	14 28%	2 4%	2 4%
Lumps/Bumps	33 66%	45 90%	24 48%	5 10%	4 8%	28 56%	12 24%	5 10%
Pain	21 42%	30 60%	13 26%	4 8%	0 0%	21 42%	9 18%	0 0%
Redness	21 42%	33 66%	17 34%	4 8%	0 0%	26 52%	7 14%	0 0%
Swelling	36 72%	41 82%	25 50%	10 20%	2 4%	36 72%	16 32%	2 4%
Tenderness	38 76%	44 88%	27 54%	9 18%	2 4%	42 84%	10 20%	4 8%

- ^a Number of subjects' NLF treated with the respective device
- ^b Number of subjects' NLF with any specific Common Treatment Response
- ^c CTRL = Control treatment
- ^d Mod = Moderate
- ^e Sev = Severe

Table 4. Duration of Common Treatment Responses after RHA® 4 injection using a cannula and using a needle – Safety Population

Common Treatment Responses	RHA® 4-cannula (N=50 NLF) N ^o %					RHA® 4-needle (N=50 NLF) N ^o %						
	1-3 d	4-7 d	8-14 d	15-21 d	22-28 d	Last Day	1-3 d	4-7 d	8-14 d	15-21 d	22-28 d	Last Day
Bruising	3 6%	4 8%	3 6%	0 0%	0 0%	0 0%	8 16%	11 22%	5 10%	2 4%	1 2%	0 0%
Discoloration	4 8%	2 4%	0 0%	1 2%	2 4%	2 4%	6 12%	5 10%	2 4%	1 2%	2 4%	2 4%
Firmness	7 14%	4 8%	8 16%	15 30%	12 24%	12 24%	7 14%	4 8%	8 16%	19 38%	13 26%	13 26%
Itching	6 12%	4 8%	0 0%	0 0%	0 0%	0 0%	14 28%	2 4%	1 2%	0 0%	0 0%	0 0%
Lumps/Bumps	10 20%	0 0%	9 18%	2 4%	12 24%	20 40%	7 14%	5 10%	8 16%	20 40%	14 28%	14 28%
Pain	15 30%	2 4%	2 4%	1 2%	1 2%	1 2%	22 44%	6 12%	1 2%	0 0%	1 2%	0 0%
Redness	12 24%	4 8%	8 16%	2 4%	2 4%	2 4%	19 38%	7 14%	3 6%	1 2%	3 6%	4 8%
Swelling	15 30%	6 12%	6 12%	4 8%	5 10%	4 8%	9 18%	14 28%	7 14%	2 4%	9 18%	6 12%
Tenderness	16 32%	7 14%	6 12%	6 12%	3 6%	3 6%	19 38%	10 20%	9 18%	2 4%	4 8%	4 8%

- ^a Number of subject NLF treated with the respective device
- ^b Number of subject NLF with each specific CTR by maximum duration
- ^c Duration refers to number of days (d) cited in the patient diary, irrespective of date of injection

An adverse event (AE) was defined as a treatment-related event that was not considered typical in type and/or duration and/or severity. Also, CTRs from the patient's diary that were recorded on the last day of diary were automatically elevated to the status of adverse event, regardless of severity.

- Most treatment-related AEs were mild or moderate in severity, except for only 1 subject with severe treatment-related AEs: severe Injection Site Induration, severe Injection Site Mass, and severe Injection Site Pain in both treatment groups, and severe Injection Site Swelling in the RHA® 4-needle group only. All severe TRAEs were experienced by this one subject.
- The vast majority of treatment-related AEs experienced by both treatment groups were typical of the expected signs and symptoms observed following an injection of a dermal filler.
- All treatment-related AEs were temporally associated with a recent device (RHA® 4 injected with a cannula or with a needle) injection (no late onset).
- Nearly all treatment-related AEs were based on subjects' diary entries (CTRs). Also, there were 5 treatment-related AEs (all of mild severity) in 3 subjects with RHA® 4 reported by the Treating Investigator which consisted of injection site mass (2 events), facial asymmetry (2 events) and neuralgia (1 event). None were clinically significant.
- The type and the severity of TRAEs were comparable between RHA® 4 injected with a cannula and RHA® 4 injected with a needle, with the exception of Injection Site Mass that were less prominent in the RHA® 4-cannula group.
- The duration of treatment related adverse events was on average 20 to 50 days lasting from 1 to 90 days period, except for three subjects for whom their TRAEs had not resolved at the time of study exit. These three subjects experienced two events of injection site mass, two events of injection site swelling and one event of injection site hemorrhage in the RHA®-needle group, and one event of injection site mass, one event of injection site swelling and one event of injection site hemorrhage in the RHA®-cannula group. There were all mild to moderate in severity and no treatment was provided. It was persistent and had not improved at the study exit. The investigator followed up one month later and the subjects stated each event as being mild at the time of interview.
- No events were deemed to be a granuloma.
- There were no late onset treatment-related AEs.
- There were no treatment-related serious AEs.

3. Post-marketing Surveillance

The following adverse events were reported as part of post-marketing surveillance on the use of RHA® 4 worldwide with a prevalence equal or superior to one occurrence for 100,000 syringes: Injection site masses (lumps and bumps), skin swelling, firmness, edema,

inflammatory reaction, erythema, pain, granuloma, vascular complication, skin infection and bruising.

Additionally, other less frequent adverse reactions have also been reported, and includes implant migration, allergic reaction, skin discoloration/flyndall effect, tenderness, abscess, overcorrection, pruritus, anaphylactic reaction, pigmentation disorder, skin necrosis, urticaria, angioedema, chopped lips, dermatitis, fibrosis, herpes breakout, influenza-like illness, numbness, pustules, telangiectasia and visual impairment.

Delayed-onset inflammation near the site of dermal filler injections is one of the known adverse events associated with dermal fillers. Cases of delayed-onset inflammation have been reported to occur at the dermal filler treatment site following viral or bacterial illnesses or infections, vaccinations, or dental procedures. Typically, the reported inflammation was responsive to treatment or resolved on its own.

In many cases the symptoms resolved without any treatment. Reported treatments included the use of (in alphabetical order): analgesics, antibiotics, anti-histamines, anti-inflammatories, anti-viral, drainage, excision, implant dissolution (hyaluronidase), incision, massage and vasodilators.

CLINICAL TRIALS

A. Pivotal STUDY for RHA® 4 into the NLFs

The safety and effectiveness of RHA® 4 in the correction of moderate to severe facial wrinkles and folds was evaluated in a US pivotal clinical study described hereafter.

1. Pivotal Study Design

A controlled, randomized, double-blinded, within-subject, multicenter, prospective pivotal clinical study was conducted to evaluate the clinical safety and effectiveness of RHA® 4. Subjects were randomly assigned to receive RHA® 4 and a control treatment in deep dermis to superficial subcutaneous for the treatment of moderate to severe nasolabial folds, or to a non-treatment group. The side of the face for each device injected was assigned randomly. If deemed necessary by the Treating Investigator, additional NLF correction was performed after 2 weeks (touch-up), with the same study device used for initial treatment. The follow-up period consisted of safety and effectiveness follow-up visits at 4, 12, 24, 36, 52, and 64 weeks after the last treatment.

Subjects were eligible for optional retreatment if necessary at Weeks 24 or 36. Subjects were also offered retreatment at Week 52 or Week 64, and were then followed for 1 month after retreatment or until all Adverse Events (AEs) resolve. Retreatments on either side was provided using RHA® 4 (the Control treatment was not used).

Subjects randomized to the "no treatment" control group did not receive treatment.

2. Study Endpoints

The primary effectiveness endpoint was the analysis of non-inferiority of RHA® 4 versus the Control treatment, in terms of change from pre-injection to 24 weeks after injection, as measured by the Blinded Live Evaluator (BLE) using a proprietary and validated 5-grade scale for scoring the severity of nasolabial folds. NLF-WSRS (which for the purposes of this document will be referred to as NLF-Wrinkle Severity Rating Scale (WSRS)) score. Secondary effectiveness endpoints included rates of responders (≥ 1 grade difference from pre-treatment on the NLF-WSRS), as measured by the BLE (see data in Figure 1), Global Aesthetic Improvement (GAI), as assessed by the subject and by the BLE, impact and effectiveness of study treatment procedures from the subjects' perspective as assessed by the nasolabial fold domain of the FACE-Q[®], and subject satisfaction.

Safety endpoints was evaluated throughout the study, with a 14-day subject diary capturing post-injection signs/symptoms following every study injection, and AE assessments at each visit, and included self-assessment of injection site pain by the subject using a Visual Analog Scale.

3. Demographics

A total of 120 subjects (27 to 86 years old) were allocated to RHA® 4 and Control treatment, and 20 were allocated to untreated controls. 118 subjects were included in the ITT population. Subject's demographics are presented in Table 5.

Table 5. Demographics

Number / % of subjects	RHA® 4 versus Control Device N=118	
Age Mean (SD) min max	57.4 27 86	(10.0)
Gender Female 		

B. Clinical Evaluation of RHA® 4 for the use of a small bore, blunt tip cannula into the NLFs

1. Clinical Study Design

A multicenter, controlled, single-blinded, within-subject (split-face), prospective study was conducted to evaluate the clinical safety and effectiveness using RHA® 4 injected with a blunt cannula (25G x 2" long) or with a sharp needle (27G x ½") for the treatment of moderate to severe nasolabial folds.

Subjects were randomized to undergo RHA® 4 treatment into their NLFs with the cannula on one side of the face, and with a sharp needle on the other side.

If deemed necessary by the Treating Investigator, additional NLF correction was performed after 4 weeks (touch-up), with the same study device used for initial treatment.

All 50 subjects received a safety follow-up call within 3-days of initial treatment, and if applicable, within 3 days of touch-up treatment. Thereafter, subjects were to return periodically for safety and effectiveness evaluations at 4, 8 and 12 weeks after the last treatment. The primary endpoint was at 12 weeks after initial or touch-up treatment, assessed by the BLE.

If a subject presented with an unresolved clinically significant device-related adverse event (AE), an optional visit or phone-call follow-up was scheduled within 4 weeks of the last study visit, and until the AE was resolved or the TI determined that additional follow-up was no longer necessary.

2. Study Endpoints

The primary effectiveness endpoint was the analysis of non-inferiority of RHA® 4 injected with a cannula versus with a needle, in terms of change from pre-injection to 12 weeks after injection, as measured by the BLE using a proprietary and validated 5-grade scale for scoring the severity of nasolabial folds, the NLF-WSRS.

Secondary effectiveness endpoints included rates of responders (≥ 1 grade difference from pre-treatment on the NLF-WSRS), as measured by the BLE, Global Aesthetic Improvement (GAI), as assessed by the subject and by the BLE, impact and effectiveness of study treatment procedures from the subjects' perspective as assessed by the nasolabial fold domain of the FACE-Q®, and subject satisfaction.

Safety endpoints were evaluated throughout the study, with a 28-day subject diary capturing post-injection signs/symptoms following every study injection, and AE assessments at each visit, and included self-assessment of injection site pain by the subject using a Visual Analog Scale.

3. Demographics

A total of 50 subjects (42 to 77 years old) were injected with RHA® 4 into their NLFs with a cannula on one side of the face, and with a sharp needle on the other side. Subject's demographics are presented in Table 7.

Table 7. Demographics

Number / % of subjects	Cannula versus Needle N=50	
Age		
Mean (SD)	55.8	(8.2)
min max	42	77
Gender		
Female	49	98.0%
Male	1	2.0%
Race		
Caucasian	39	78%
Black	6	12%
Am. Indian/N. Alask.	0	0%
N. Hawaiian/P. Isl.	0	0%
Asian	4	8%
Other	1	2%
Ethnicity		
Hispanic/Latino	5	10%
Not Hispanic/Latino	45	90%
Fitzpatrick Skin Phototype		
I	3	6%
II	14	28%
III	21	42%
IV	6	12%
V	3	6%
VI	3	6%

* Number of subjects in the ITT populations

4. Treatment Characteristics

In this study, subjects were randomized to undergo RHA® 4 treatment into their NLFs with the cannula (25G x 2" long) on one side of the face, and with a sharp needle (27G x ½") on the other side.

The study protocol allowed a maximum of 3.0 ml in a single NLF per treatment session. The overall total median volume of RHA® 4 injected to achieve optimal correction results was 1.7 ml with a cannula and 1.5 ml with a needle. The proportion of subjects who received touch-up treatment at Week 4 was 40% in the RHA® 4-cannula group, and 34% in the RHA® 4-needle group.

Linear threading or fan-like techniques were used for 80% of the subjects treated with RHA® 4 injected with a cannula. Linear threading, multiple puncture techniques, or a combination, were used for 74% of the subjects treated with RHA® 4 with a needle.

5. Effectiveness Results

The primary effectiveness endpoint was met. The study demonstrated the non-inferiority of RHA® 4 administered with a cannula versus a needle, as assessed (using the WSRS) by the BLE at 12 weeks after baseline, and results are presented in Table 8.

Table 8. NLF-Wrinkle Severity Rating Scale scores assessed by a Blinded Live Evaluator throughout the study

	n ^a	RHA® 4-cannula		RHA® 4-needle	
		NLF-WSRS score ^b	NLF-WSRS Improvement ^c	WSRS score ^b	WSRS Improvement ^c
Pre-treatment	46	3.3	-	3.3	-
Week 12 ^d	46	1.7	1.61	1.7	1.65

^a Number of subjects in the PP populations

^b Mean Wrinkle Severity Rating Scale score (higher scores mean deepest wrinkles)

^c Mean Wrinkle Severity Rating Scale improvement from pre-treatment (higher scores mean more improvement from pre-treatment)

^d Primary effectiveness endpoint

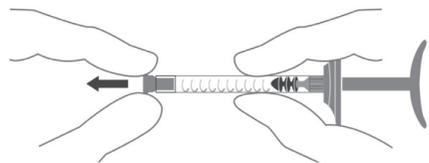
The aesthetic improvement of the RHA® 4 treated NLF with a cannula was similar to the one of the RHA® 4 treated NLF with a needle. These similar improvements were clinically significant (≥ 1 grade difference from pre-treatment on the NLF-WSRS) for 94% of the subjects at 12 weeks after initial treatment.

On the Global Aesthetic Improvement (GAI) scale, more than 90% of the subjects, TIs and BLE reported that the NLFs treated with RHA® 4 were improved or very much improved at week 12, in both cannula and needle treatment groups. In addition, based on the Nasolabial Folds domain of the FACE-Q® questionnaire, the subjects consistently reported improvement up to 12 weeks, with similar improvements in the cannula and the needle treatment groups. Comparably, more than 90% of the subjects reported to be satisfied or very satisfied in both treatment groups (the scale grades were: very satisfied, satisfied, neither satisfied nor dissatisfied, dissatisfied or very dissatisfied).

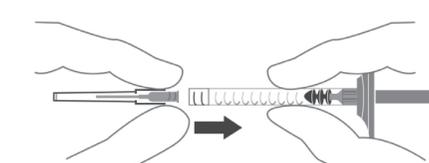
There were no differences in term of effectiveness and safety profiles between cannula brands were observed. Similar effectiveness and safety profiles were observed by age group.

DIRECTIONS FOR ASSEMBLY OF THE NEEDLE TO THE SYRINGE

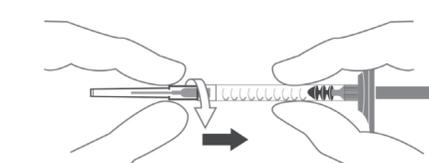
1. Remove the stopper from the syringe by pulling it off.



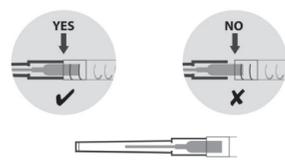
2. Insert the screw thread of the needle firmly into the syringe end-piece.



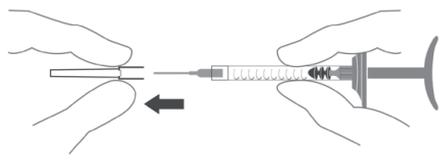
3. Screw the needle clockwise, while maintaining slight pressure between the needle and the syringe.



4. Continue screwing until the edge of the cap of the needle contacts the body of the syringe. There must be no space between these two parts. Failure to follow this instruction means that the needle could be ejected and/or leak at the Luer-lock.



5. Remove the needle's protective cap by pulling it firmly with one hand while holding the body of the syringe with the other.



PRE-TREATMENT GUIDELINES

* Prior to treatment, the patient should avoid taking medications or supplements which thin the blood (e.g., aspirin, nonsteroidal anti-inflammatory medications, St. John's Wort, or high doses of Vitamin E supplements) as these agents may increase bruising and bleeding at the injection site.

* Before starting treatment, a complete medical history should be taken from the patient and the patient should be counseled on appropriate indications, risks, and should be informed about the expected treatment results, and expected responses. The patient should be advised of the necessary precautions before commencing the procedure.

* Prior to treatment with RHA® 4 the patient should be assessed for appropriate anesthetic treatment for managing comfort (e.g., topical anesthetic, local or nerve block). The patient's face should be washed with soap and water and dried with a clean towel. Cleanse the area to be treated with alcohol or another suitable antiseptic solution.

* Sterile gloves are recommended while injecting RHA® 4.

* Before injecting, prime the needle by carefully pressing the syringe plunger until a small droplet of the gel is visible at the tip of the needle.

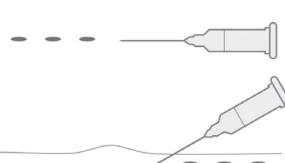
INJECTION TECHNIQUES

* RHA® 4 is administered by using a thin gauge needle (27 G x ½") or a blunt tip cannula (25 G x 2"). RHA® 4 is supplied with 27 G x ½" needles. The Soffil® Precision and TSK STERIGLIDE™ cannulas were used in the clinical trials and are recommended for use with RHA® 4.

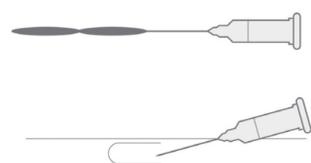
* When using a needle, the needle is inserted into the deep dermis to superficial subcutaneous at an approximate angle of 15° to 30° parallel to the length of the wrinkle or fold. When using a cannula, an entry point is made in the skin with the provided pre-hole needle.

* RHA® 4 can be injected by a number of different techniques that depend on the injector's experience and preference, and patient characteristics.

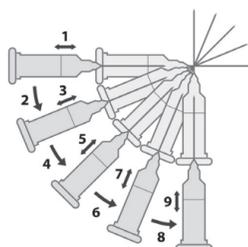
A. Serial puncture: (only recommended for needle): consists of multiple injections, evenly and closely spaced all along wrinkles or folds. This technique is considered to be more precise, but may result in more discomfort for the patient due to the number of punctures.



B. Linear threading: the needle/cannula is fully introduced in the wrinkle or the fold, and the product is injected along the line, as a "thread", while withdrawing (retrograde) or pushing (antegrade) the needle/cannula.



C. Fanning technique: the needle/cannula is introduced as for the Linear threading technique, and the product is injected along several closely spaced lines, by changing the direction of the needle/cannula, all using the same puncture site (the needle/cannula is not withdrawn).



* RHA® 4 is injected slowly into the deep dermis to superficial subcutaneous.

* If the color of the needle/cannula can be seen through the skin during injection, this means that the injection is too superficial. This should be avoided as the results of the correction could be irregular.

* The injection should be stopped before pulling the syringe out of the skin, to prevent product from leaking out, or product misplacement (too superficially in the skin).

* The volume to be injected depends on the corrections to be performed, but it is important to not overcorrect. Based on the US clinical study, patients should be limited to 6.0 ml per patient per treatment session in wrinkles and folds such as NLFs. The safety of injecting greater amounts has not been established.

* If blanching is observed (e.g., the overlying skin turns a whitish color), the injection should be stopped immediately and the area massaged until it returns to a normal color. Blanching may represent a vessel occlusion. If normal skin coloring does not return, do not continue with the injection. Treat in accordance with American Society for Dermatologic Surgery guidelines, which include hyaluronidase injection.

* If the wrinkles need further treatment with RHA® 4, the same procedure should be repeated until a satisfactory result is obtained.

POST-TREATMENT GUIDELINES

* When the injection is completed, the treated site should be gently massaged so that it conforms to the contour of the surrounding tissues. If an overcorrection has occurred, massage the area firmly between your fingers or against an underlying area to obtain optimal results.

* If the treated area is swollen immediately after the injection, an ice pack can be applied to the site for a short period (e.g., 5-10 minutes). Ice should be used with caution if the area is still numb from anesthetic to avoid thermal injury.

* After use, syringes may be potential biohazards. Follow national, local, or institutional guidelines for use and disposal of medical biohazard devices. Obtain prompt medical attention if injury occurs.

STERILE NEEDLES

* After use, needles and cannula are potential biohazards. Follow national, local, or institutional guidelines for use and disposal of medical sharp devices (e.g. discard uncapped needles and cannulas in approved sharps containers).

* Disposal should be in accordance with accepted medical practice and applicable local, State and Federal requirements.

* Obtain prompt medical attention if injury with used needles/cannulas occurs.

* To help avoid needle breakage, do not attempt to straighten a bent needle. Discard it and complete the procedure with a replacement needle.

* Do not recap needles/cannulas. Recapping by hand is a hazardous practice and should be avoided.

* RHA® 4 is provided with 2 needles that do not contain engineered injury protection. Administration of RHA® 4 requires direct visualization and complete and gradual insertion of the needle making engineered protection devices not feasible. Care should be taken to avoid sharps exposure by proper environmental controls.

PATIENT INSTRUCTIONS

Patient information brochure is available on request, or via the website www.revance.com. It is recommended that the following information be shared with patients:

* Patients should be advised not to wear make-up during 12 hours following injection.

* Patient should be advised not to take high-dose Vitamin E, aspirin, anti-inflammatories or anti-coagulants during the week prior to the injection. Patients must not discontinue such treatment without talking with their prescribing physician.

* Patients should minimize exposure of the treated area to excessive sun, UV lamp exposure and extreme temperatures (e.g. cold weather, sauna) at least within the first 24 hours, or until initial swelling and redness has resolved. Exposure to any of the above may cause/exacerbate and/or extend the duration of temporary redness, swelling, and/or itching at the treatment sites.

* Patients should notify the injector if any of the following occurs:
- Changes in vision
- Unusual pain during or shortly after treatment
- Significant pain away from the injection site
- Signs of a stroke

- Any redness and/or visible swelling that lasts for more than a week
- Any side effect other than those described above or that occur weeks or months after injection

- Adverse reactions should be reported to Revance Therapeutics, Inc at 877-3REV-NOW (877-373-8669) and to Medical-us@teoxane.com.

HOW SUPPLIED

RHA® 4 is supplied in individual blisters containing a 1.2 ml treatment syringe with two 27 G x ½" needles as indicated on the carton.

The content of the syringe is sterile and non-pyrogenic. Do not resterilize. Do not use if package is opened or damaged.

Each syringe is packaged into a blister with two unique device identifier traceability labels.

SHELF-LIFE AND STORAGE

RHA® 4 must be used prior to the expiration date printed on the package.

Store at room temperature (up to 25°C/77°F). Do not expose to direct sunlight. DO NOT FREEZE.

Manufactured by:

TEOXANE SA
Rue de Lyon, 105
CH 1203 Geneva
Switzerland

Distributed by:

Revance Therapeutics, Inc.
1222 Demonbreun Street,
Suite 2000
Nashville, Tennessee 37203

RHA® is a registered trademark of TEOXANE SA.

Under license U.S. Pat. Nos. 8,357,795 ; 8,450,475 ; 8,822,676 ; 9,089,517 ; 9,089,518 ; 9,089,519 ; 9,238,013 ; 9,358,322.

SYMBOLS

Manufacturer's name and address

Catalog number

Lot / batch number

Expiration date (YYYY-MM-DD)

Consult Instructions for use

Single use only

Sterilized using steam

Do not use if the package is damaged

RxOnly Caution: Federal law restricts this device to sale by or on the order of a physician or licensed practitioner

RxOnly





RHA® Redensity Mepi

CAUTION: FEDERAL LAW RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A PHYSICIAN OR LICENSED PRACTITIONER.

BEFORE USING RHA® Redensity Mepi, PLEASE READ THE FOLLOWING INFORMATION THOROUGHLY.

DEVICE DESCRIPTION

RHA® Redensity Mepi is a viscoelastic, sterile, non-pyrogenic, clear, colorless, homogeneous and biodegradable gel implant of both crosslinked and non-crosslinked hyaluronic acid. It is produced with sodium Hyaluronic Acid (NaHA) with a concentration of 15 mg/g obtained from bacterial fermentation using the *streptococcus equi* bacterial strain, crosslinked with 1,4-butanediol diglycidyl ether (BDDE) and reconstituted in a physiological buffer (pH 7.3). RHA® Redensity Mepi also contains 0.3% mepivacaine hydrochloride to reduce pain on injection.

INTENDED USE / INDICATIONS

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.

CONTRAINDICATIONS

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

WARNINGS

- Introduction of product into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction. To avoid this:
 - Do not inject into blood vessels.
 - Take extra care when injecting soft tissue fillers, inject the product slowly and apply the least amount of pressure necessary.
- 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. If a patient exhibits any of the following symptoms: changes in vision, signs of a stroke, blanching of the skin, or unusual pain during or shortly after the procedure, immediately stop the injection. Patients should receive prompt medical attention and possibly evaluation by an appropriate health care practitioner specialist should an intravascular injection occur.
- Product use at specific sites in which an active inflammatory process (skin eruptions such as cysts, pimples, rashes, or hives), infection or skin injury is present should be deferred until the underlying process has been controlled.
- Treatment site reactions consist mainly of short-term inflammatory symptoms (e.g., swelling, redness, tenderness, or pain) and generally resolve within 14 days. Refer to the ADVERSE EXPERIENCES section for details.
- Inflammatory reaction, anaphylactic reaction, edema, implant migration, acne, blisters, scarring, papules and delayed onset of granulomas have been reported following the use of dermal fillers.

PRECAUTIONS

- In order to minimize the risks of potential complications, this product should only be used by experienced health care practitioners who have appropriate training in filler injection techniques, and who are knowledgeable about the anatomy at and around the site of injection.
- Health care practitioners are encouraged to discuss all potential risks of soft tissue injection with their patients prior to treatment and ensure that patients are aware of signs and symptoms of potential complications.
- The safety and effectiveness for the treatment of anatomic regions other than those described in the INTENDED USE / INDICATIONS section have not been established in controlled clinical studies.
- As with all transcutaneous procedures, dermal filler implantation carries a risk of infection. Standard precautions associated with injectable materials should be followed.
- The safety in patients with known susceptibility to keloid formation, hypertrophic scarring, and pigmentation disorders has not been studied.
- The safety for use in sites in the presence of other implants (including permanent implants) has not been studied.
- The safety for use during pregnancy, in breastfeeding females, and in patients under 22 years of age has not been established.
- The safety and effectiveness of RHA® Redensity Mepi for the correction of dynamic perioral rhytids have not been clinically evaluated in patients with Fitzpatrick Skin Types V and VI.
- RHA® Redensity Mepi should be used with caution in patients on immunosuppressive therapy.

- Bruising or bleeding may occur at RHA® Redensity Mepi injection sites. RHA® Redensity Mepi should be used with caution in patients who are using substances that can prolong bleeding (such as thrombolytics, anticoagulants, or inhibitors of platelet aggregation).
- Injection of RHA® Redensity Mepi into patients with a history of previous herpetic eruption may be associated with reactivation of the herpes.
- If laser treatment, chemical peeling or any other procedure based on active dermal response is considered after treatment with RHA® Redensity Mepi, there is a possible risk of eliciting an inflammatory reaction at the implant site. This also applies if RHA® Redensity Mepi is administered before the skin has healed completely after such a procedure.
- RHA® Redensity Mepi is to be used as supplied. Modification or use of the product outside the Instructions for Use may adversely impact the sterility, safety, homogeneity, or performance of the product.
- RHA® Redensity Mepi is packaged for single-use. Do not reuse a syringe after treatment. Do not re-sterilize.
- Do not use if package is opened or damaged. The sterility of the product is not guaranteed in the case of failure to comply with this precaution.
- RHA® Redensity Mepi is a clear, colorless gel without particulates. In the event the contents of a syringe show signs of separation and/or appears cloudy, do not use the syringe; contact Revance Therapeutics, Inc. 877-3REVNOW (877-373-8669).
- Failure to comply with the needle attachment instructions could result in needle disengagement and/or product leakage at the Luer-lock and needle hub connection.

ADVERSE EXPERIENCES

RHA® Redensity Mepi and RHA® Redensity have the same formulation except for a difference in the anesthetic agent: RHA® Redensity Mepi contains mepivacaine (0.3% w/w), while RHA® Redensity contains lidocaine (0.3% w/w). Mepivacaine and lidocaine have many similar and equivalent physico-chemical characteristics and properties, they are also pharmacologically related. Due to the similarities in the formulation of RHA® Redensity Mepi and RHA® Redensity, the U.S. clinical evaluation of RHA® Redensity to support the indication for the correction of moderate to severe perioral rhytids provided safety and effectiveness information about RHA® Redensity Mepi for the indication for the correction of moderate to severe perioral rhytids. This safety information from this study apply to both RHA® Redensity Mepi and RHA® Redensity, and are summarized below under "Clinical Evaluation of RHA® Redensity in the perioral rhytids".

A second U.S. study was conducted for the indication for the correction of moderate to severe perioral rhytids to evaluate the safety of RHA® Redensity Mepi when compared to RHA® Redensity. The safety information from this clinical study is summarized below under "Clinical Evaluation of RHA® Redensity Mepi in the perioral rhytids".

1. Clinical Evaluation of RHA® Redensity in the perioral rhytids
Clinical study TEO-RHA-1402 was a multicenter, controlled, randomized, blinded, No-Treatment control, prospective clinical study designed to compare the safety and effectiveness of RHA® Redensity versus a No-Treatment control for the treatment of moderate to severe dynamic perioral rhytids. The expected signs and symptoms that occur following the injection of a hyaluronic acid-based dermal filler (i.e., Common Treatment Responses; CTR) were individually assessed by subjects in a preprinted 14-day diary after each injection. CTRs are commonly expected injection site responses which are temporally associated with injection of a dermal filler. Events like redness, swelling, pain, bruising, tenderness, and lumps and bumps are examples of expected CTRs. Severe CTRs, or those lasting longer than 14 days or present on the last day of the subject diary, were evaluated for conversion to an adverse event. Subjects were asked to rate each CTR as None, Mild, Moderate or Severe:

- Mild: Little discomfort, no effect on daily activities, no medication or make-up required.
- Moderate: some discomfort, some effect on daily activities, possibly medication or make-up required.
- Severe: Great discomfort, daily activities compromised, very likely medication or make-up required.

CTRs by severity and duration are presented respectively, in Table 1 and Table 2.

- The most frequent CTRs were bruising, swelling, redness, firmness, lumps/bumps and tenderness.
- More than 76% of the CTRs had resolved by Day 7.
- Nearly 90% of CTRs had resolved by Day 14 without treatment.
- Other than lumps/bumps, each type of CTR that was present on the last day of the 14-Day diary was present in less than 10% of subjects.
- For nearly all CTRs (more than 92%), the maximal severity reported was "Mild" or "Moderate".
- Less than 6% of each CTR was reported as "Severe" by the subjects except for bruising (12%).
- When bruising persisted to the last day of the diary, all were deemed "Mild" by the treating investigator except 3 that were rated at "Moderate". None were "Severe". More than 90% of Bruises had resolved by end of 14-day diary.

Table 1. Common Treatment Responses by maximum severity after initial treatment with RHA® Redensity (pooled analysis) – Safety Population

Common Treatment Responses	RHA® Redensity (N=199)				
	# of subjects with ≥1 CTR n° (%)	Mild n° (%)	Mod ^a n° (%)	Sev ^a n° (%)	# of subjects with no CTR n° (%)
Redness	131 (65.8%)	84 (42.2%)	42 (21.1%)	5 (2.5%)	68 (34.2%)
Pain	54 (27.1%)	39 (19.6%)	13 (6.5%)	2 (1.0%)	145 (72.9%)
Tenderness	105 (52.8%)	83 (41.7%)	19 (9.5%)	3 (1.5%)	94 (47.2%)

Firmness	115 (57.8%)	79 (39.7%)	33 (16.6%)	3 (1.5%)	84 (42.2%)
Swelling	146 (73.4%)	85 (42.7%)	49 (24.6%)	12 (6.0%)	53 (26.6%)
Lumps/Bumps	115 (57.8%)	71 (35.7%)	34 (17.1%)	10 (5.0%)	84 (42.2%)
Bruising	154 (77.4%)	65 (32.7%)	65 (32.7%)	24 (12.1%)	45 (22.6%)
Itching	31 (15.6%)	26 (13.1%)	3 (1.5%)	2 (1.0%)	168 (84.4%)
Discoloration	94 (47.2%)	49 (24.6%)	34 (17.1%)	11 (5.5%)	105 (52.8%)

^a Number of subjects' who provided diary answers after V1/1b
^b Number of subjects' perioral rhytids with any specific Common Treatment Response
^c Mod = Moderate
^d Sev = Severe

Table 2. Duration of Common Treatment Responses after initial treatment with RHA® Redensity (pooled analysis) – Safety Population

Common Treatment Responses	RHA® Redensity (N=199)			
	1-3 Days n° (%)	4-7 Days n° (%)	8-14 Days n° (%)	Last Day ^d n° (%)
Redness	78 (39.2%)	35 (17.6%)	18 (9.0%)	8 (4.0%)
Pain	38 (19.1%)	10 (5.0%)	6 (3.0%)	1 (0.5%)
Tenderness	55 (27.6%)	29 (14.6%)	10 (5.0%)	10 (5.0%)
Firmness	63 (31.7%)	24 (12.1%)	28 (14.1%)	18 (9.0%)
Swelling	72 (36.2%)	40 (20.1%)	34 (17.1%)	10 (5.0%)
Lumps/Bumps	53 (26.6%)	29 (14.6%)	33 (16.6%)	26 (13.1%)
Bruising	30 (15.1%)	64 (32.2%)	60 (30.2%)	15 (7.5%)
Itching	21 (10.6%)	8 (4.0%)	2 (1.0%)	3 (1.5%)
Discoloration	39 (19.6%)	34 (17.1%)	21 (10.6%)	5 (2.5%)

^a Number of subjects' who provided diary answers after V1/1b
^b Number of events by maximum duration
^c Duration refers to number of days cited in the patient diary, irrespective of date of injection
^d The CTR numbers indicated in the "Last Day" column are also included in the "8-14 Days" column

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

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

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

An adverse event (AE) was defined as a treatment-related event that was not considered typical in type and/or duration and/or severity. Also, CTRs from the patient's diary that were recorded on the last day of diary were automatically elevated to the status of adverse event, regardless of severity.

- All treatment-related AEs were mild or moderate in severity.
- Most of treatment-related AEs experienced were typical events following an injection of a hyaluronic acid-based dermal filler, such as: bruising, discoloration, erythema, injection site induration, irritation, swelling or pain. Other reported treatment-related AEs such as headache, muscle contraction or paresthesia are less typical but not unexpected following a dermal filler injection.
- All treatment-related AEs were temporally associated with a recent injection (no late onset).
- All treatment-related AEs were based on subjects' diary entries (CTR) or reported as "other" except three events at injection site assessed by the Treating Investigator during visit questioning (1 discoloration "Tyndall Effect", 1 headache, 1 oral herpes) that were reported by the Treating Investigator at time of initial injection. The "Tyndall Effect", headache and oral herpes resolved without sequelae in 384, 7 and 10 days respectively.
- The duration of treatment related adverse events varied from 1 to 90 days except for two: the "Tyndall Effect" described above and there was an involuntary muscle contraction (fasciculation, left upper lip) which appeared after re-treatment at visit 9. It was mild in severity and no treatment was provided. It was persistent and had not improved at the study exit. The investigator followed up three months later and the subject stated it resolved 2 months prior.
- No events were deemed to be a granuloma or delayed inflammatory response.
- There were no events of vascular occlusion.
- There were no late onset treatment-related AEs.
- There were no treatment-related serious AEs.

The incidence of treatment-related AE incidence rates was not different in subjects with higher Fitzpatrick skin types.

There were no reported cases of scarring, keloid formation or hyperpigmentation.

2. Clinical Evaluation of RHA® Redensity Mepi in the perioral rhytids

The safety of the RHA® Redensity Mepi dermal filler with mepivacaine indicated for injection into the perioral rhytids was studied against the approved RHA® Redensity dermal filler family with lidocaine in the clinical study TEO-RHA-1801, a multicenter, controlled, randomized, double-blinded, within-subject (split-face), prospective U.S. clinical study for the treatment of moderate to severe perioral rhytids with RHA® Redensity Mepi versus RHA® Redensity. Similar safety profiles between RHA® Redensity and RHA® Redensity Mepi were demonstrated. The expected signs/symptoms that occur following the injection (i.e., CTRs) were captured by subjects in a 30-day diary. Injection sites on each side of the face were individually assessed by subjects over 30 days following study injections. CTRs by severity and duration are presented respectively, in Table 3 and Table 4.

- The most frequent CTRs were firmness, tenderness, lumps/bumps, redness, swelling, and bruising.
- Proportions of subjects experiencing at least one CTR of each category were similar between RHA® Redensity Mepi and RHA® Redensity treatments.
- The majority (97.4%) of CTRs resolved within 14 days.
- There were no notable differences between RHA® Redensity Mepi and RHA® Redensity with regard to the proportion of subjects (3.5%) who reported a severe CTR, the most common severe CTRs reported being swelling, tenderness, redness and pain.
- For nearly all CTRs (96.5%) experienced by any treatment group, the maximal severity reported was "Mild" or "Moderate".

Importantly, on the last day of diary all ongoing CTRs (5 CTRs from 3 subjects) were reported by the subjects mild in severity and deemed by the Investigators to be mild in severity and not clinically significant. There were all elevated to Treatment-Related AEs.

Table 3. Common Treatment Responses by maximum severity after initial treatment with RHA® Redensity Mepi and the control device RHA® Redensity reported in subject 30-day diary – Safety Population

Common Treatment Responses	TOTALS			RHA® Redensity Mepi (N=30 Perioral)			RHA® Redensity (N=30 Perioral)			
	RHA® Redensity Mepi n° (%)	RHA® Redensity n° (%)	Mod ^a n° (%)	Sev ^a n° (%)	Mild n° (%)	Mod ^a n° (%)	Sev ^a n° (%)	Mild n° (%)	Mod ^a n° (%)	Sev ^a n° (%)
Bruising	12 (40.0%)	16 (53.3%)	9 (30.0%)	3 (10.0%)	0 (0.0%)	9 (30.0%)	6 (20.0%)	1 (3.3%)		
Discoloration	10 (33.3%)	10 (33.3%)	8 (26.7%)	2 (6.7%)	0 (0.0%)	9 (30.0%)	1 (3.3%)	0 (0.0%)		
Firmness	14 (46.7%)	19 (63.3%)	11 (36.7%)	3 (10.0%)	0 (0.0%)	16 (53.3%)	3 (10.0%)	0 (0.0%)		
Itching	4 (13.3%)	2 (6.7%)	13 (43.3%)	0 (0.0%)	0 (0.0%)	2 (6.7%)	0 (0.0%)	0 (0.0%)		
Lumps/Bumps	15 (50.0%)	17 (56.7%)	12 (40.0%)	3 (10.0%)	0 (0.0%)	10 (33.3%)	7 (23.3%)	0 (0.0%)		
Pain	3 (10.0%)	4 (13.3%)	2 (6.7%)	0 (0.0%)	1 (3.3%)	3 (10.0%)	0 (0.0%)	1 (3.3%)		
Redness	16 (53.3%)	15 (50.0%)	12 (40.0%)	3 (10.0%)	1 (3.3%)	9 (30.0%)	5 (16.7%)	1 (3.3%)		
Swelling	21 (70.0%)	19 (63.3%)	16 (53.3%)	13 (43.3%)	1 (3.3%)	11 (36.7%)	7 (23.3%)	1 (3.3%)		
Tenderness	13 (43.3%)	12 (40.0%)	11 (36.7%)	3 (10.0%)	1 (3.3%)	10 (33.3%)	2 (6.7%)	0 (0.0%)		
Others ^a	1 (3.3%)	1 (3.3%)	0 (0.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		
Others ^b	1 (3.3%)	1 (3.3%)	0 (0.0%)	1 (3.3%)	0 (0.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)		

^a Number of subjects' perioral rhytids treated with the respective device
^b Number of subjects' perioral rhytids with any specific Common Treatment Response
^c Mod = Moderate
^d Sev = Severe
^e One patient reported needle track marks on the corner of the mouth treated with RHA® Redensity Mepi dermal filler and which resolved in 2 days
^f One patient reported injection site soreness on the corner of the mouth treated with RHA® Redensity Mepi dermal filler and which resolved in 2 days

Table 4. Duration of Common Treatment Responses after initial treatment with RHA® Redensity Mepi and RHA® Redensity reported in subject 30-day diary – Safety Population

CTR Duration ^c	Group (N=30)	1-3 Days n° (%)	4-7 Days n° (%)	8-14 Days n° (%)	15-21 Days n° (%)	22-30 Days n° (%)	Last Day ^d n° (%)
Bruising	RHA® Redensity Mepi	4 (13.3%)	7 (23.3%)	3 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	RHA® Redensity	3 (10.0%)	11 (36.7%)	2 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Discoloration	RHA® Redensity Mepi	7 (23.3%)	3 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	RHA® Redensity	7 (23.3%)	10 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Firmness	RHA® Redensity Mepi	9 (30.0%)	2 (6.7%)	1 (3.3%)	1 (3.3%)	1 (3.3%)	2 (6.7%)
	RHA® Redensity	11 (36.7%)	4 (13.3%)	2 (6.7%)	3 (10.0%)	1 (3.3%)	2 (6.7%)
Itching	RHA® Redensity Mepi	3 (10.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	RHA® Redensity	1 (3.3%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Lumps/Bumps	RHA® Redensity Mepi	11 (36.7%)	3 (10.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)	1 (3.3%)
	RHA® Redensity	5 (16.7%)	8 (26.7%)	3 (10.0%)	0 (0.0%)	1 (3.3%)	0 (0.0%)
Pain	RHA® Redensity Mepi	2 (6.7%)	0 (0.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	RHA® Redensity	3 (10.0%)	0 (0.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Redness	RHA® Redensity Mepi	11 (36.7%)	2 (6.7%)	3 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	RHA® Redensity	9 (30.0%)	5 (16.7%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Swelling	RHA® Redensity Mepi	17 (56.7%)	2 (6.7%)	2 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	RHA® Redensity	14 (46.7%)	3 (10.0%)	2 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Tenderness	RHA® Redensity Mepi	11 (36.7%)	2 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	RHA® Redensity	10 (33.3%)	2 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Others ^{e,f}	RHA® Redensity Mepi	2 (6.6%) ^a	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	RHA® Redensity	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

^a Number of subjects' perioral rhytids treated with the respective device
^b Number of subjects' perioral rhytids with each specific CTR by maximum duration
^c Duration refers to number of days cited in the patient diary, irrespective of date of injection
^d The CTR numbers indicated in the "Last Day" column are also included in the "22-30 Days" column
^e One patient reported needle track marks on the corner of the mouth treated with RHA® Redensity Mepi dermal filler and which resolved in 2 days
^f One patient reported injection site soreness on the corner of the mouth treated with RHA® Redensity Mepi dermal filler and which resolved in 2 days

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

- Lip function: ability to suck liquid through a straw.
 - Lip sensation: ability to feel change of lip sensation with a monofilament and cotton wisp at different locations.
 - Lip movement: ability to pronounce specific letters and words.
- All subjects from both groups were able to perform the tests successfully pre and post-injection and at every visit thereafter.
- Both RHA® Redensity Mepi and RHA® Redensity treatment groups presented with very similar adverse event profiles with 4 (13.3%) subjects experiencing a total of 9 treatment-related AEs. A total of 3 (10.0%) subjects in the RHA® Redensity treatment group experienced 4 treatment-related AEs, and 4 (13.3%) subjects in the RHA® Redensity Mepi treatment group experienced 5 treatment-related AEs.
 - All treatment-related AEs were based on subjects' diary entries (CTR)
 - All treatment-related AEs were mild in severity and none were considered by Investigators to be clinically significant. All events resolved spontaneously without the need for medical therapy.
 - All treatment-related AEs experienced by both treatment groups were typical of the expected signs and symptoms observed following an injection of a hyaluronic acid-based dermal filler except one (needle track marks) that was reported by the subject in the "other" category of the 30-day diary and which resolved in 3.5 days.
 - The average duration of a treatment related adverse event was 1-3.5 days except for two: an injection site mass experienced by 1 subject with only RHA® Redensity Mepi which resolved spontaneously after 35 days, and an injection site induration which was experienced by 2 (6.7%) subjects in each group. It was persistent and had not improved at the study exit for the 2 subjects. The site conducted post-exit telephone interviews with these subjects who both confirmed that the events had resolved spontaneously without intervention within 77 days post-injection.
 - No events were deemed to be a granuloma.
 - There were no events of vascular occlusion.
 - There were no late onset treatment-related AEs.
 - There were no treatment-related serious AEs.
 - There were no subjects who withdrew from the study due to AEs.
- Safety profile by Fitzpatrick skin type (I to IV), ethnicity, and age was not different. There were no reported cases of scarring, keloid formation or hyperpigmentation.

3. Post-marketing Surveillance

Post-marketing surveillance data are based on RHA® Redensity containing lidocaine, these data are representative and applicable to RHA® Redensity Mepi. The following adverse events were reported as part of post-marketing surveillance on the use of RHA® Redensity outside the United States 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 complication (such as vessel compression/occlusion), pain, ecchymosis, erythema, skin discoloration and inflammatory reaction. Additionally, other less frequent adverse reactions have also been reported, and include dermal filler overcorrection, allergic reaction, product misplacement, inflammatory nodules (papules), skin necrosis, granuloma, injection site movement impairment, paresthesia, skin atrophy, injection site fibrosis, urticaria and device dislocation. Delayed-onset inflammation near the site of dermal filler injections is one of the known adverse events associated with dermal fillers. Cases of delayed-onset inflammation have been reported to occur at the dermal filler treatment site following viral or bacterial illnesses or infections, vaccinations, or dental procedures. Typically, the reported inflammation was responsive to treatment or resolved on its own. In many cases the symptoms resolved without any treatment. Reported treatments included the use of (in alphabetical order): analgesics, antibiotics, antihistamines, anti-inflammatories, anti-viral, corticosteroids, implant dissolution (hyaluronidase), massage, and vasodilators. Final resolution varies from ongoing to total resolution of the symptoms with or without sequelae.

CLINICAL STUDIES

CLINICAL STUDY OF RHA® REDENSITY™

RHA® Redensity Mepi is strictly identical to RHA® Redensity except for the small amount of anesthetic medicine: RHA® Redensity Mepi contains mepivacaine and RHA® Redensity contains lidocaine. Both anesthetics agents are of the same family with the same mechanisms of effect. RHA® Redensity Mepi and RHA® Redensity have the same indication. The long-term safety and effectiveness of RHA® Redensity M

RHA® Redensity was administered into the dermis and superficial dermis using different injection techniques to ensure a satisfactory result of the treatment of dynamic perioral rhytids. In general, a linear threading technique combined with multiple punctures was used for 91.0% of the subjects treated with RHA® Redensity.

5. Effectiveness Results

The primary effectiveness endpoint was met for RHA® Redensity. The primary effectiveness endpoint was based on the responder rate as assessed (using the Perioral Rhytids Severity Rating Scale - PR-SRS) by the BLE at 8 weeks after baseline. A subject was considered to be a PR-SRS responder if he/she presented with a ≥1-point improvement from pre-treatment (baseline). To successfully achieve the co-primary endpoint: 1) the responder rate for subjects with RHA® Redensity must be statistically superior to the responder rate for the No-Treatment control, and; 2) the responder rate for subjects treated with RHA® Redensity must be ≥70% and; 3) the difference between the responder rate for subjects treated with RHA® Redensity and the No-Treatment group must be ≥50 points.

The proportion of responders, showing ≥1-grade improvement on the PR-SRS was 80.7% in the treatment group and 7.8% in the No-Treatment group. Results are presented in Table 6.

Table 6. Responder rate assessed by a Blinded Live Evaluator at primary endpoint

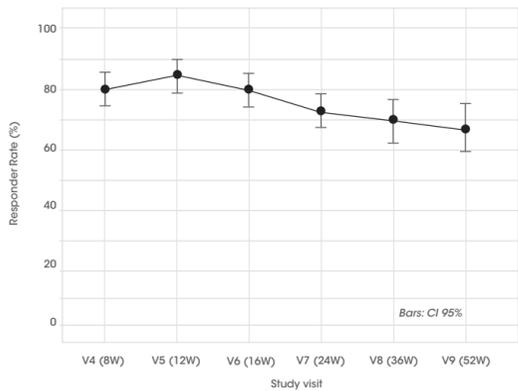
PR-SRS Responder Rate (BLE)	RHA® Redensity	No-Treatment	P-value ^a
Week 8	N^b 150	51	
Responder	121 (80.7%)	4 (7.8%)	< 0.0001
Not responder	29 (19.3%)	47 (92.2%)	
Missing values	0	0	

^a ITT population – BLE assessment – Last Observation Carried Forward (LOCF)

^b Responder = at least 1-point improvement from Baseline. P-value from Fisher's Exact Test

The results demonstrated superiority of RHA® Redensity against No-Treatment control at 8 weeks for the treatment of perioral rhytids. In analyses of the pooled population, RHA® Redensity demonstrated marked durability with PR-SRS (BLE assessment) responder rates of 80.4%, 72.9% and 66.5% at Weeks 8, 24 and 52, respectively. Throughout the follow-up period, the aesthetic improvement of the perioral rhytids treated with RHA® Redensity continued to be clinically significant (≥ 1 grade difference from pre-treatment on the PR-SRS) for more than 66% of the subjects at 52 weeks after initial treatment (Figure 1).

Figure 1. Proportion of responders on the Perioral Rhytids Severity Rating Scale (PR-SRS) measured by a Blinded Live Evaluator for RHA® Redensity



RHA® Redensity No-Treatment Control (pooled)	Week 8	Week 12	Week 16	Week 24	Week 36	Week 52
N	194	184	183	188	188	188
Responder (BLE assessment)	156 (80.4%)	156 (84.8%)	147 (80.3%)	137 (72.9%)	131 (69.7%)	125 (66.5%)
Not Responder (BLE assessment)	38 (19.6%)	28 (15.2%)	36 (19.7%)	51 (27.1%)	57 (30.3%)	63 (33.5%)

ITT populations at the respective follow-up visits

Rate of responders: ≥ 1 grade difference from pre-treatment on the PR-SRS

On the Global Aesthetic Improvement (GAI) scale, more than 92% of the subjects, TIs and BLEs reported that the perioral rhytids treated with RHA® Redensity were improved or very much improved at 8 weeks and this proportion remained greater than 80% up to week 52. In addition, based on the Perioral Rhytids domain of the FACE-Q® questionnaire, the subjects consistently reported improvement up to 52 weeks with a mean score change of more than 36 points from baseline throughout the follow-up period. Subjects were asked six questions within the FACE-Q® Perioral Rhytids Domain and reported being less bothered by the number and depth of lines, how noticeable lines were after treatment with RHA® Redensity. Further, based on the

FACE-Q® questionnaire, subjects reported being less bothered by how perioral lines looked compared to other people their age, how old the lines made them look, and how their lines appeared when their lips are puckered. More than 90% of the subjects reported to be satisfied or very satisfied 8 weeks after initial treatment and the rate of satisfaction remained at more than 88% at 52 weeks (the scale grades were: very satisfied, satisfied, neither satisfied nor dissatisfied, dissatisfied or very dissatisfied).

More than 78% of the subjects received repeat treatment. The effectiveness and safety profiles after repeat treatment were similar to that after initial treatment.

CLINICAL STUDY OF RHA® REDENSITY MEPI

The safety and effectiveness of the RHA® Redensity Mepi in the correction of moderate to severe perioral rhytids were evaluated in comparison to RHA® Redensity (lidocaine) in a U.S. pivotal clinical study described hereafter. The purpose of this short-term 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 duration of the effectiveness of the anesthetic agent (mepivacaine or lidocaine) is less than a day.

1. Pivotal Study Design

A controlled, randomized, double-blinded, within-subject (split-face), multicenter, prospective pivotal clinical study was to compare the level of pain using the dermal filler RHA® Redensity (lidocaine) with the level of pain using the dermal filler RHA® Redensity Mepi (mepivacaine) in the treatment of perioral rhytids. Subjects were treated RHA® Redensity Mepi with mepivacaine in a randomly selected sequence (first or second injection) into the perioral rhytids in one side of the face and RHA® 1 with into the contralateral perioral rhytids. RHA® Redensity Mepi and RHA® Redensity were administered into the dermis and superficial dermis for the treatment of moderate to severe perioral rhytids. The follow-up period consisted of safety and effectiveness follow-up visits one month after the initial treatment. A safety phone call visit was performed by the Treating Investigators (TI) 72 hours after the initial treatment.

2. Study Endpoints

The primary endpoint was the analysis of the non-inferiority of the injection site pain felt during injection assessed by the subject immediately following injection with RHA® Redensity Mepi (using a 100 mm Visual Analog Scale –VAS) compared to the injection site pain felt during injection immediately assessed following injection with RHA® Redensity.

The subject rated each side of the face independently and was blinded to which side of the face has been injected with which product. Additional pre-procedure anesthesia was prohibited.

Secondary anesthetic assessments were the pain assessment by the subject using the VAS ruler at 15, 30, 45, and 60 minutes following the injection and the duration of the anesthetic effect as assessed by the subject every hour until returning to normal sensation commencing 60 minutes post-injection.

Secondary effectiveness endpoints included change in the severity of the perioral rhytids as measured by the TI using the PR-SRS, as measured by the TI, Global Aesthetic Improvement (GAI), as assessed by the subject and by the TI, impact and effectiveness of study treatment procedures from the subjects' perspective as assessed by the nasolabial fold domain of the FACE-Q®, and subject satisfaction.

Safety endpoints were evaluated throughout the study, with a 30-day study diary capturing post-injection signs/symptoms following every study injection and AE assessments at each visit. Safety endpoints also included assessments of lip functions and visual disturbances before and after injection and at each visit.

3. Demographics

A total of 30 subjects (48 to 78 years old) were enrolled and randomized, these 30 subjects were included in the intent to treat (ITT) population (and per protocol (PP) population). Subjects' demographics are presented in Table 7.

Table 7. Demographics

Number / % of subjects	RHA® Redensity Mepi versus RHA® Redensity N=30
Age	
Mean (SD)	64.3 (8.2)
min max	48 78
Gender	
Female	30 100.0%
Male	0 0.0%
Race	
Caucasian	30 100.0%
Black	0 0.0%
Am. Indian/N. Alask.	0 0.0%
N. Hawaiian/P. Isl.	0 0.0%
Asian	0 0.0%
Other	0 0.0%
Ethnicity	
Hispanic/Latino	11 36.7%
Not Hispanic/Latino	19 63.3%
Fitzpatrick Skin Phototype	
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%

^a Number of subjects in the ITT population

4. Treatment Characteristics

The study protocol allowed a maximum of 6.0 mL per treatment session. The average volume injected was nearly identical between treatment groups with volumes of 0.41 mL and 0.40 mL in the RHA® Redensity Mepi and RHA® Redensity group respectively. The total volume to achieve optimal correction result (OCR) is the sum of both groups, as it was a split face study.

In general, a linear threading, fan-like technique, or a combination of linear threading with multiple punctuate pools, was used for all subjects treated with RHA® Redensity Mepi.

5. Effectiveness Results

The primary effectiveness endpoint was met for RHA® Redensity Mepi. The levels of pain felt by the subject during injection with RHA® Redensity Mepi (with mepivacaine) and RHA® Redensity™ (with lidocaine) were 25.0 mm and 22.4 mm respectively as measured using the VAS. This resulted in a non-significant difference between groups of -2.6 (p-value=0.0002).

For both treatment groups, the level of pain decreased over time with no statistically significant difference at all time points (at 15, 30, 45, and 60 minutes post-injection). The injection pain was reduced to 6.8 mm for RHA® Redensity Mepi and 6.3 mm RHA® Redensity after 15 minutes and gone (0.0 mm) after 60 minutes post-injection. Finally, the duration of anesthetic effect was also reported by the subject to be similar between treatment groups, lasting around 3.6 hours for the side treated with RHA® Redensity Mepi (with mepivacaine) and 3 hours for the side treated with RHA® Redensity (with lidocaine). Results are presented in Table 8 and Table 9.

Table 8. Injection Site Pain during injection – ITT population

VAS pain (mm)	RHA® Redensity Mepi N=30	RHA® Redensity N=30	VAS Difference (mm) N=30
Mean (SD)	25.0 (25.63)	22.4 (23.21)	-2.6 (10.33)
Min, Max	0, 100	0, 86	-27, 10

^a Number of subjects in the ITT population

Table 9. Injection Site Pain after injection – ITT population

VAS pain (mm) Mean (SD)	RHA® Redensity Mepi N=30	RHA® Redensity N=30	VAS Difference (mm) N=30
Time point:			
- 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)

^a Number of subjects in the ITT population

Secondary endpoints demonstrated no difference between RHA® Redensity Mepi and RHA® Redensity regarding clinical performance.

A similar improvement in the PR-SRS scores was observed one month post-injection, with a score improvement of 1.5 points in both RHA® Redensity Mepi and RHA® Redensity treatment groups.

Responder rate was nearly similar after the injection, with 93.3% of treated subjects with RHA® Redensity Mepi versus 96.7% with RHA® Redensity. Responder rate was similar for both treatment groups one-month post-injection, with 96.7% of treated subjects.

On GAI scale, RHA® Redensity Mepi and RHA® Redensity demonstrated identical GAI scores as assessed by both TIs and subjects. 100% of the subjects were deemed by the TI to have their perioral rhytids treated improved or very much improved at one-month post-injection. 100% of the subjects reported having their perioral rhytids treated improved or very much improved.

The subjects also reported similar improvement based on the Perioral Rhytids domain of the FACE-Q® questionnaire with the mean score increasing by 64.7 and 60.9 points in the RHA® Redensity Mepi and RHA® Redensity treatment group, respectively. More than 96% of the subjects reported being satisfied or very satisfied one month after their treatment with no distinction between the treatment groups.

Similar effectiveness and safety profiles were observed by Fitzpatrick skin type (I to IV), ethnicity and age groups.

Results of RHA® Redensity long term safety and effectiveness are applicable to RHA® Redensity Mepi.

DIRECTIONS FOR ASSEMBLY OF THE NEEDLE TO THE SYRINGE

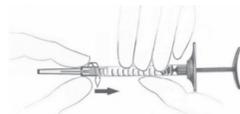
1. Remove the stopper from the syringe by pulling it off.



2. Insert the screw thread of the needle firmly into the syringe end-piece.



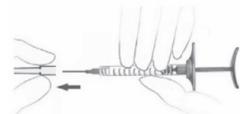
3. Screw the needle clockwise, while maintaining slight pressure between the needle and the syringe.



4. Continue screwing until the edge of the cap of the needle contacts the body of the syringe. There must be no space between these two parts. Failure to follow this instruction means that the needle could be ejected and/or leak at the Luer-lock.



5. Remove the needle's protective cap by pulling it firmly with one hand while holding the body of the syringe with the other.



DIRECTION FOR INJECTIONS

Before and after treatment, health care practitioners are encouraged to conduct vision assessments, including visual acuity, extraocular motility, and visual field testing. Health care practitioners are encouraged to be prepared with the following in the event of an intravascular injection:

- Ensuring supplies are immediately available, as recommended by the American Society for Dermatologic Surgery guidelines.
- Identifying a local ophthalmologist or ophthalmology subspecialist to be available in the event of an ophthalmic adverse event related to a dermal filler injection.
- Conducting a basic neurologic examination in the event of an ophthalmic adverse event due to the association of such events with central nervous system deficits.

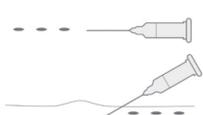
PRE-TREATMENT GUIDELINES

- Prior to treatment, the patient should avoid taking medications or supplements which thin the blood (e.g., aspirin, nonsteroidal anti-inflammatory medications, St. John's Wort, high doses of Vitamin E supplements, anti-coagulants) as these agents may increase bruising and bleeding at the injection site.
- Before starting treatment, a complete medical history should be taken from the patient and the patient should be counseled on appropriate indications, risks, and should be informed about the expected treatment results, and expected responses. The patient should be advised of the necessary precautions before commencing the procedure.
- Prior to treatment with RHA® Redensity Mepi the patient should be assessed for appropriate anesthetic treatment for managing comfort (e.g., topical anesthetic, local or nerve block). The patient's face should be washed with soap and water and dried with a clean towel. Cleanse the area to be treated with alcohol or another suitable antiseptic solution.
- Sterile gloves are recommended while injecting RHA® Redensity Mepi.
- Before injecting, prime the needle by carefully pressing the syringe plunger until a small droplet of the gel is visible at the tip of the needle.

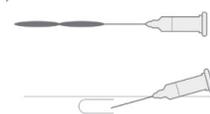
INJECTION TECHNIQUES

- RHA® Redensity Mepi can be administered by using a thin gauge needle (30 G x ½") and with a number of different techniques that depend on the injector's experience and preference, and patient characteristics.

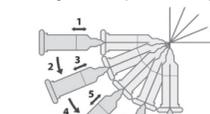
A. Preclinical testing between the following needles brands (TSK HPC, TSK PRC, Terumo TW, Terumo ETW) and the syringe has confirmed that the interoperability and compatibility is reliable and safe. **Serial puncture:** consists of multiple injections, evenly and closely spaced perpendicular to the lines. This technique is considered to be more precise, but may result in more discomfort for the patient due to the number of punctures.



B. **Linear threading:** the needle is fully introduced in the wrinkle or the fold, and the product is injected along the line, as a "thread", while withdrawing (retrograde) or pushing (anterograde) the needle.



C. **Fanning technique:** the needle is introduced as for the *Linear threading technique*, and the product is injected along several closely spaced lines, by changing the direction of the needle, all using the same puncture site (the needle is not withdrawn).



- RHA® Redensity Mepi are injected slowly into the dermis. If the injection is made too deeply, i.e. into sub-cutaneous tissue, the correction may not be as expected. It is possible to tell when an injection is being made too deeply because subcutaneous tissue, unlike the dermis, does not offer any resistance to product injection, the injected product may not be visible as a raised elevation on the skin and correction of the lines may not be achieved.
- The injection should be stopped before withdrawing the needle from the skin, to prevent product from leaking out, or product misplacement (too superficially in the skin).
- The volume to be injected depends on the correction to be performed, but it is important to not overcorrect. Based on the US clinical study, patients should be limited to 6.0 mL per patient per treatment session in perioral rhytids. The safety of injecting greater amounts has not been established.
- Any blanching appearing through the vascular flow may represent a vessel occlusion. If normal skin coloring does not return, do not continue with the injection. Treat in accordance with American Society for Dermatologic Surgery guidelines, which include hyaluronidase injection.
- If the perioral lines need further treatment with RHA® Redensity Mepi, the same procedure should be repeated until a satisfactory result is obtained.

POST-TREATMENT GUIDELINES

- When the injection is completed, the treated site may be gently massaged so that it conforms to the contour of the surrounding tissues. If an overcorrection has occurred, massage the area firmly between your fingers or against an underlying area to obtain optimal results.
- If the treated area is swollen immediately after the injection, an ice pack can be applied to the site for a short period (e.g., 5-10 minutes). Ice should be used with caution if the area is still numb from anesthetic to avoid thermal injury.
- After use, syringes may be potential biohazards. Follow national, local, or institutional guidelines for use and disposal of medical biohazard devices. Obtain prompt medical attention if injury occurs.

STERILE NEEDLES

- After use, needles are potential biohazards. Follow national, local, or institutional guidelines for use and disposal of medical sharp devices (e.g. discard uncapped needles in approved sharps containers).
- Disposal should be in accordance with accepted medical practice and applicable local, State and Federal requirements.
- To help avoid needle breakage, do not attempt to straighten a bent needle, discard it and complete the procedure with a replacement needle.
- Do not recap needles. Recapping by hand is a hazardous practice and should be avoided.
- RHA® Redensity Mepi are provided with 2 needles that do not contain engineered injury protection. Administration of RHA® Redensity Mepi requires direct visualization and complete and gradual insertion of the needle making engineered protection devices not feasible. To avoid needle stick injury and sharp exposure, take care to inject in appropriate conditions.
- Obtain prompt medical attention if injury with used needle occurs.

PATIENT INSTRUCTIONS

A patient information brochure is available on request, or via the website www.revance.com.

It is recommended that the following information be shared with patients:

- Patients should be advised not to wear make-up during 12 hours following injection.

- Patient should be advised not to take high-dose Vitamin E, aspirin, anti-inflammatories or anti-coagulants during the week prior to the injection. Patients must not discontinue such treatment without talking with their prescribing physician.
- Patients should minimize exposure of the treated area to excessive sun, UV lamp exposure and extreme temperatures (e.g. cold weather, sauna) at least within the first 24 hours, or until initial swelling and redness has resolved. Exposure to any of the above may cause/exacerbate and/or extend the duration of temporary redness, swelling, and/or itching at the treatment sites.
- Patients should notify the injector if any of the following occurs:
 - Changes in vision
 - Unusual pain during or shortly after treatment
 - Significant pain away from the injection site
 - Signs of a stroke
 - Any redness and/or visible swelling that lasts for more than a week
 - Any side effect other than those described above or that occur weeks or months after injection
- Adverse reactions should be reported to Revance Therapeutics, Inc. at 877-3REV-NOW (877-373-8669) and to Medical-us@teoxane.com.

HOW SUPPLIED

RHA® Redensity Mepi are supplied in individual blisters containing a 1 mL treatment syringe with two 30 G x ½" needles as indicated on the carton. The content of the syringe is sterile and non-pyrogenic. Do not re-sterilize. Do not use if package is opened or damaged. Each syringe is packaged into a blister with two unique device identifier traceability labels.

SHELF-LIFE AND STORAGE

RHA® Redensity Mepi must be used prior to the expiration date printed on the package. Store at room temperature (up to 25°C/77°F). Do not expose to direct sunlight. DO NOT FREEZE. Do not store partially used syringes.

RxOnly

Manufactured by:
TEOXANE S.A.
Rue de Lyon 105
CH 1203 Geneva
(Switzerland)

Distributed by:
Revance Therapeutics, Inc.
1222 Demonbreun Street,
Suite 2000
Nashville, Tennessee 37203

RHA® is a registered trademark of TEOXANE SA.
RHA Redensity is a trademark filed by TEOXANE SA.

US Patent N° 9,353,194; 9,498,562; 9,421,198; 10,786,601; 10,413,637; 11,406,738

SYMBOLS

- Manufacturer's name and address
- Catalog number
- Lot / batch number
- Expiration date (YYYY-MM-DD)
- Consult Instructions for use
- Single use only
- Sterilized using steam
- Do not use if the package is damaged
- Caution: Federal law restricts this device to sale by or on the order of a physician or license practitioner

TEOXANE

TEOXANE

RHA® 2 Mepi

CAUTION: FEDERAL LAW RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A PHYSICIAN OR LICENSED PRACTITIONER. BEFORE USING RHA® 2 Mepi, PLEASE READ THE FOLLOWING INFORMATION THOROUGHLY.

DEVICE DESCRIPTION

RHA® 2 Mepi is a viscoelastic, sterile, non-pyrogenic, clear, colorless, homogeneous, and biodegradable gel implant. It is produced with sodium Hyaluronic Acid (NaHA) with a concentration of 23 mg/g obtained from bacterial fermentation using the *Streptococcus equi* bacterial strain, crosslinked with 1,4-butanediol diglycidyl ether (BDDE), and reconstituted in a physiological buffer (pH 7.3). RHA® 2 Mepi also contains 0.3% mepivacaine hydrochloride to reduce pain on injection.

INTENDED USE / INDICATIONS

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.

CONTRAINDICATIONS

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

WARNINGS

- Introduction of product into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction. To avoid this:
 - Do not inject into blood vessels
 - Take extra care when injecting soft-tissue fillers, inject the product slowly and apply the least amount of pressure necessary.
- 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. If a patient exhibits any of the following symptoms: changes in vision, signs of a stroke, blanching of the skin, or unusual pain during or shortly after the procedure, immediately stop the injection. Patients should receive prompt medical attention and possibly evaluation by an appropriate health care practitioner specialist should an intravascular injection occur.
- Product use at specific sites in which an active inflammatory process (skin eruptions such as cysts, pimples, rashes, or hives), infection or skin injury is present should be deferred until the underlying process has been controlled.
- Treatment site reactions consist mainly of short-term inflammatory symptoms (e.g., swelling, redness, tenderness, or pain) and generally resolve within 14 days. Refer to the ADVERSE EXPERIENCES section for details.
- Inflammatory reaction, anaphylactic reaction, edema, implant migration, acne, blisters, scarring, papules, and delayed onset of granulomas have been reported following the use of dermal fillers.

PRECAUTIONS

- In order to minimize the risks of potential complications, this product should only be used by experienced health care practitioners who have appropriate training in filler injection techniques, and who are knowledgeable about the anatomy at and around the site of injection.
- Health care practitioners are encouraged to discuss all potential risks of soft tissue injection with their patients prior to treatment and ensure that patients are aware of signs and symptoms of potential complications.
- The safety and effectiveness for the treatment of anatomic regions other than those described in the INTENDED USE / INDICATIONS section have not been established in controlled clinical studies.
- As with all transcutaneous procedures, dermal filler implantation carries a risk of infection. Standard precautions associated with injectable materials should be followed.
- The safety in patients with known susceptibility to keloid formation, hypertrophic scarring, and pigmentation disorders has not been studied.
- The safety for use in sites in the presence of other implants (including permanent implants) has not been studied.
- The safety for use during pregnancy, in breastfeeding females, and patients under 22 years of age has not been established.
- RHA® 2 Mepi should be used with caution in patients on immunosuppressive therapy.
- Bruising or bleeding may occur at RHA® 2 Mepi injection sites. RHA® 2 Mepi should be used with caution in patients who are using substances that can prolong bleeding (such as thrombolytics, anticoagulants, or inhibitors of platelet aggregation).

- Injection of RHA® 2 Mepi into patients with a history of previous herpetic eruption may be associated with reactivation of herpes.
- If laser treatment, chemical peeling, or any other procedure based on active dermal response is considered after treatment with RHA® 2 Mepi, there is a possible risk of eliciting an inflammatory reaction at the implant site. This also applies if RHA® 2 Mepi is administered before the skin has healed completely after such a procedure.
- RHA® 2 Mepi is to be used as supplied. Modification or use of the product outside the Instructions for Use may adversely impact the sterility, safety, homogeneity, or performance of the product.
- RHA® 2 Mepi is packaged for single-patient use. Do not reuse a syringe between two treatments and/or between two patients. Do not sterilize.
- Do not use if the package is opened or damaged. The sterility of the product is not guaranteed in the case of failure to comply with this precaution. RHA® 2 Mepi is a clear, colorless gel without particulates. In the event the content of a syringe shows signs of separation and/or appears cloudy, do not use the syringe; contact Revance Therapeutics, Inc. 877-3REV-NOW (877-373-8669).
- Failure to comply with the needle attachment instructions could result in needle disengagement and/or product leakage at the Luer-lock and needle hub connection.

ADVERSE EXPERIENCES

RHA® 2 Mepi and RHA® 2 have the same formulation except for a difference in the anesthetic agent: RHA® 2 Mepi contains mepivacaine (0.3% w/w), while RHA® 2 contains lidocaine (0.3% w/w). Mepivacaine and lidocaine have many similar and equivalent physico-chemical characteristics and properties, they are also pharmacologically related. Due to the similarities in the formulation of RHA® 2 Mepi and RHA® 2, the U.S. clinical evaluation of RHA® 2 to support the indication for the correction of moderate to severe dynamic wrinkles and folds, such as NLF, provided safety and effectiveness information about RHA® 2 Mepi for the indication for the correction of moderate to severe dynamic wrinkles and folds, such as NLF. This safety information from this long-term study apply to both RHA® 2 Mepi and RHA® 2, and are summarized below under **“Clinical Evaluation of RHA® 2 in the NLFs”**.

A second U.S. study was conducted for the indication for the correction of moderate to severe dynamic wrinkles and folds, such as NLFs to evaluate the safety of RHA® 2 Mepi when compared to RHA® 2. The safety information from this clinical study is summarized below under **“Clinical Evaluation of RHA® Mepi in the NLFs”**.

1. Clinical Evaluation of RHA® 2 in the NLFs

Clinical study TEO-RHA-1302 was a multicenter, controlled, randomized, double-blinded, within-subject (split-face), prospective US study designed to compare the safety of RHA® 2 versus a control treatment for the treatment of moderate to severe nasolabial folds and demonstrated similar safety profiles. The expected signs and symptoms that occur following the injection of a hyaluronic acid-based dermal filler (i.e., Common Treatment Responses; CTR) were individually assessed by subjects in a preprinted 14-day diary after each injection. Subjects were asked to rate each CTR as None, Mild, Moderate, or Severe:

- Mild: Little discomfort, no effect on daily activities, no medication or make-up required.
- Moderate: some discomfort, some effect on daily activities, possibly medication or make-up required.
- Severe: Great discomfort, daily activities compromised, very likely medication or make-up required.

Subjects were asked to rate each CTR as None, Mild, Moderate, or Severe:

- The most frequent CTRs were firmness, redness, tenderness, swelling, lumps/bumps, and bruising.
- Proportions of subjects experiencing at least one CTR of each category were similar between RHA® 2 and control treatment.
- More than 70% of the CTRs had resolved by Day 7.
- The vast majority (more than 85%) of CTRs had resolved by Day 14.
- There were no notable differences between RHA® 2 and control treatment with regard to the small proportion of subjects who reported a severe CTR.
- For nearly all CTRs (more than 93%) experienced by any treatment group (initial treatment or touch-up treatment), the maximal severity reported was “Mild” or “Moderate”.

On the last day of the diary, nearly all ongoing CTRs had improved to mild.

Table 1. Common Treatment Responses by maximum severity after initial treatment with RHA® 2 and the control device reported in subject 14-day diary – Safety Population

Common Treatment Responses	TOTALS					RHA® 2 (N=72 NLF)				Control Device (N=72 NLF)			
	RHA® 2 n° (%)	CTRL ^c n° (%)	Mild n° (%)	Mod ^d n° (%)	Sev ^e n° (%)	Mild n° (%)	Mod ^d n° (%)	Sev ^e n° (%)	Mild n° (%)	Mod ^d n° (%)	Sev ^e n° (%)		
Bruising	36 (50.0%)	41 (56.9%)	15 (20.8%)	16 (22.2%)	5 (6.9%)	23 (31.9%)	9 (12.5%)	9 (12.5%)	23 (31.9%)	9 (12.5%)	9 (12.5%)		
Discoloration	24 (33.3%)	27 (37.5%)	12 (16.7%)	7 (9.7%)	5 (6.9%)	14 (19.4%)	8 (11.1%)	5 (6.9%)	14 (19.4%)	8 (11.1%)	5 (6.9%)		
Firmness	46 (63.9%)	48 (66.7%)	23 (31.9%)	20 (27.8%)	4 (5.6%)	27 (37.5%)	20 (27.8%)	1 (1.4%)	27 (37.5%)	20 (27.8%)	1 (1.4%)		
Itching	12 (16.7%)	15 (20.8%)	9 (12.5%)	3 (4.2%)	0 (0.0%)	10 (13.9%)	4 (5.6%)	1 (1.4%)	10 (13.9%)	4 (5.6%)	1 (1.4%)		
Lumps/Bumps	38 (52.8%)	37 (51.4%)	21 (29.2%)	14 (19.4%)	3 (4.2%)	22 (30.6%)	13 (18.1%)	2 (2.8%)	22 (30.6%)	13 (18.1%)	2 (2.8%)		
Pain	19 (26.4%)	22 (30.6%)	13 (18.1%)	6 (8.3%)	0 (0.0%)	11 (15.3%)	5 (6.9%)	0 (0.0%)	11 (15.3%)	5 (6.9%)	0 (0.0%)		
Redness	45 (62.5%)	49 (68.1%)	31 (43.1%)	13 (18.1%)	1 (1.4%)	36 (50.0%)	13 (18.1%)	2 (2.8%)	36 (50.0%)	13 (18.1%)	2 (2.8%)		
Swelling	42 (58.3%)	45 (62.5%)	27 (37.5%)	13 (18.1%)	2 (2.8%)	31 (43.1%)	13 (18.1%)	1 (1.4%)	31 (43.1%)	13 (18.1%)	1 (1.4%)		
Tenderness	44 (61.1%)	40 (55.6%)	34 (47.2%)	10 (13.9%)	0 (0.0%)	31 (43.1%)	9 (12.5%)	0 (0.0%)	31 (43.1%)	9 (12.5%)	0 (0.0%)		

- ^a Number of subjects' NLF treated with the respective device
- ^b Number of subjects' NLF with any specific Common Treatment Response
- ^c CTRL = Control Treatment
- ^d Mod = Moderate
- ^e Sev = Severe

Table 2. Duration of Common Treatment Responses after initial treatment with RHA® 2 and the control device reported in subject 14-day diary – Safety Population

Common Treatment Responses	RHA® 2 (N=72 NLF) n° (%)				Control Device (N=72 NLF) n° (%)			
	1-3 Days	4-7 Days	8-14 Days	Last Day ^d	1-3 Days	4-7 Days	8-14 Days	Last Day ^d
Bruising	7 (9.7%)	13 (18.1%)	16 (22.2%)	5 (6.6%)	10 (13.9%)	16 (22.2%)	15 (20.8%)	4 (5.6%)
Discoloration	11 (15.3%)	4 (5.6%)	9 (12.5%)	3 (4.2%)	8 (11.1%)	10 (13.9%)	9 (12.5%)	3 (4.2%)
Firmness	13 (18.1%)	11 (15.3%)	22 (30.6%)	14 (19.4%)	16 (22.2%)	13 (18.1%)	19 (26.4%)	12 (16.7%)
Itching	5 (6.9%)	4 (5.6%)	3 (4.2%)	3 (4.2%)	9 (12.5%)	2 (2.8%)	4 (5.6%)	3 (4.2%)
Lumps/Bumps	11 (15.3%)	13 (18.1%)	14 (19.4%)	12 (16.7%)	14 (19.4%)	11 (15.3%)	12 (16.7%)	6 (8.3%)
Pain	11 (15.3%)	4 (5.6%)	4 (5.6%)	3 (4.2%)	7 (9.7%)	5 (6.9%)	4 (5.6%)	2 (2.8%)
Redness	28 (38.9%)	13 (18.1%)	5 (6.9%)	1 (1.4%)	29 (40.3%)	14 (19.4%)	6 (8.3%)	3 (4.2%)
Swelling	19 (26.4%)	11 (15.3%)	12 (16.7%)	5 (6.9%)	22 (30.6%)	15 (20.8%)	8 (11.1%)	4 (5.6%)
Tenderness	23 (31.9%)	9 (12.5%)	12 (16.7%)	5 (6.9%)	21 (29.2%)	10 (13.9%)	9 (12.5%)	1 (1.4%)

- ^a Number of subject NLF treated with the respective device
- ^b Number of subject NLF with each specific CTR by maximum duration
- ^c Duration refers to number of days cited in the patient diary, irrespective of date of injection
- ^d The CTR numbers indicated in the “Last Day” column are also included in the “8-14 Days” column

An adverse event (AE) was defined as a treatment-related event that was not considered typical in type and/or duration and/or severity. Also, CTRs from the patient's diary that were recorded on the last day of diary were automatically elevated to the status of adverse event, regardless of severity.

- All treatment-related AEs were mild or moderate in severity.
- All treatment-related AEs experienced by both treatment groups were typical of the expected signs and symptoms observed following an injection of a hyaluronic acid-based dermal filler.
- All treatment-related AEs were temporally associated with a recent device (RHA® 2 or control treatment) injection (no late onset).
- All treatment-related AEs were based on subjects' diary entries (CTRs) except one (injection site bruising; mild) that was reported by the Treating Investigator at time of initial injection and which resolved in 12 days.
- No events were deemed to be a granuloma.
- There were no late onset treatment-related AEs.
- There were no treatment-related serious AEs.

2. Clinical Evaluation of RHA® Mepi in the NLFs

The safety of the RHA® Mepi family of dermal fillers with mepivacaine indicated for injection into the nasolabial folds was performed with RHA® 4 Mepi and results were also applicable to RHA® 2 Mepi and RHA® 3 Mepi because they have the same indication and have similar physico-chemical characteristics. RHA® 4 Mepi was considered the worst case of the three formulations because it is injected into the deeper layers of the dermis (deep dermis to superficial subcutaneous). RHA® 4 Mepi was studied against the approved RHA® 4 dermal filler with lidocaine in the clinical study TEO-RHA-1802, a multicenter, controlled, randomized, double-blinded, within-subject (split-face), prospective US clinical study for the treatment of moderate to severe nasolabial folds with RHA® 4 Mepi versus RHA® 4. Similar safety profiles between RHA® 4 Mepi and RHA® 4 were demonstrated. Since the results are applicable to RHA® 2 Mepi, RHA® 3 Mepi and RHA® 4 Mepi, the product is hereafter referenced as RHA® Mepi.

- The expected signs/symptoms that occur following the injection (i.e., CTRs) were captured by subjects in a 30-day diary. Injection sites on each side of the face were individually assessed by subjects over 30 days following study injections. CTRs by severity and duration are presented respectively, in Table 3 and Table 4.
- The most frequent CTRs were firmness, tenderness, lumps/bumps, redness, swelling, and bruising.
- Proportions of subjects experiencing at least one CTR of each category were similar between RHA® Mepi and RHA® treatments.
- The majority (91.3%) of CTRs resolved within 14 days.
- There were no notable differences between RHA® Mepi and RHA® with regard to the proportion of subjects (3.8%) who reported a severe CTR, the most common severe CTRs reported being firmness and redness.
- For nearly all CTRs (96.2%) experienced by any treatment group, the maximal severity reported was “Mild” or “Moderate”.

Importantly, on the last day of diary all ongoing CTRs (10 CTRs from 5 subjects) were reported by the subjects mild in severity and deemed by the Investigators to be mild in severity and not clinically significant. There were all elevated to Treatment-Related AEs.

Table 3. Common Treatment Responses by maximum severity after initial treatment with RHA® Mepi and the control device RHA® reported in subject 30-day diary – Safety Population

Common Treatment Responses	TOTALS			RHA® Mepi (N=30 NLF)			RHA® (N=30 NLF)		
	RHA® Mepi n° (%)	RHA® n° (%)	Mild n° (%)	Mod ^d n° (%)	Sev ^e n° (%)	Mild n° (%)	Mod ^d n° (%)	Sev ^e n° (%)	
Bruising	19 (63.3%)	21 (70.0%)	7 (23.3%)	12 (40.0%)	0 (0.0%)	10 (33.3%)	11 (36.7%)	0 (0.0%)	
Discoloration	11 (36.7%)	12 (40.0%)	8 (26.7%)	2 (6.7%)	1 (3.3%)	8 (26.7%)	4 (13.3%)	0 (0.0%)	
Firmness	24 (80.0%)	22 (73.3%)	12 (40.0%)	10 (33.3%)	6 (20.0%)	9 (30.0%)	11 (36.7%)	2 (6.7%)	
Itching	7 (23.3%)	6 (20.0%)	7 (23.3%)	0 (0.0%)	0 (0.0%)	6 (20.0%)	0 (0.0%)	0 (0.0%)	
Lumps/Bumps	22 (73.3%)	21 (70.0%)	10 (33.3%)	11 (36.7%)	3 (10.0%)	11 (36.7%)	10 (33.3%)	0 (0.0%)	
Pain	12 (40.0%)	9 (30.0%)	10 (33.3%)	1 (3.3%)	0 (0.0%)	10 (33.3%)	11 (36.7%)	0 (0.0%)	
Redness	21 (70.0%)	20 (66.7%)	12 (40.0%)	2 (6.7%)	1 (3.3%)	14 (46.7%)	4 (13.3%)	2 (6.7%)	
Swelling	21 (70.0%)	23 (76.7%)	11 (36.7%)	9 (30.0%)	1 (3.3%)	14 (46.7%)	9 (30.0%)	0 (0.0%)	
Tenderness	24 (80.0%)	24 (80.0%)	8 (26.7%)	8 (26.7%)	0 (0.0%)	18 (60.0%)	6 (20.0%)	0 (0.0%)	
Others ^a	1 (3.3%)	0 (0.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	

- ^a Number of subjects' NLF treated with the respective device
- ^b Number of subjects' NLF with any specific Common Treatment Response
- ^c Mod = Moderate
- ^d Sev = Severe
- ^e One patient reported mild paresthesia on the corner of the mouth treated with RHA® Mepi dermal filler and which resolved in 2 days.

Table 4. Duration of Common Treatment Responses after initial treatment with RHA® Mepi and RHA® reported in subject 30-day diary – Safety Population

CTR Duration ^a	Group (N=30 NLF)	1-3 Days	4-7 Days	8-14 Days	15-21 Days	22-30 Days	Last Day ^d
		n° (%)	n° (%)	n° (%)	n° (%)	n° (%)	n° (%)
Bruising	RHA® Mepi	8 (26.7%)	5 (16.7%)	5 (16.7%)	1 (3.3%)	0 (0.0%)	0 (0.0%)
	RHA®	9 (30.0%)	8 (26.7%)	4 (13.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Discoloration	RHA® Mepi	6 (20.0%)	5 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	RHA®	7 (23.3%)	3 (10.0%)	2 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Firmness	RHA® Mepi	5 (16.7%)	4 (13.3%)	9 (30.0%)	3 (10.0%)	5 (16.7%)	3 (10.0%)
	RHA®	2 (6.7%)	6 (20.0%)	6 (20.0%)	6 (20.0%)	2 (6.7%)	4 (13.3%)
Itching	RHA® Mepi	5 (16.7%)	1 (3.3%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	1 (3.3%)
	RHA®	4 (13.3%)	1 (3.3%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	1 (3.3%)
Lumps/Bumps	RHA® Mepi	8 (26.7%)	2 (6.7%)	9 (30.0%)	3 (10.0%)	2 (6.7%)	1 (3.3%)
	RHA®	5 (16.7%)	4 (13.3%)	6 (20.0%)	5 (16.7%)	1 (3.3%)	0 (0.0%)
Pain	RHA® Mepi	9 (30.0%)	3 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	RHA®	7 (23.3%)	2 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Redness	RHA® Mepi	12 (40.0%)	2 (6.7%)	2 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	RHA®	13 (43.3%)	6 (20.0%)	3 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Swelling	RHA® Mepi	9 (30.0%)	7 (23.3%)	5 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	RHA®	10 (33.3%)	8 (26.7%)	4 (13.3%)	1 (3.3%)	1 (3.3%)	0 (0.0%)
Tenderness	RHA® Mepi	10 (33.3%)	8 (26.7%)	4 (13.3%)	1 (3.3%)	1 (3.3%)	0 (0.0%)
	RHA®	12 (40.0%)	8 (26.7%)	3 (10.0%)	3 (10.0%)	1 (3.3%)	0 (0.0%)
Others ^a	RHA® Mepi	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	RHA®	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

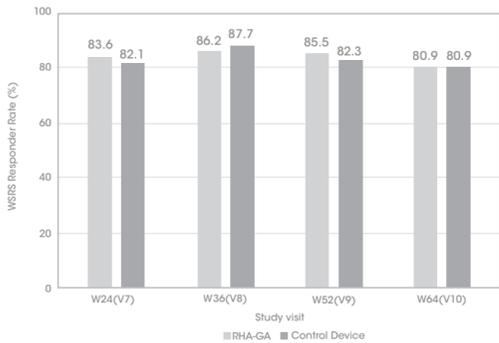
- ^a Number of subject NLF treated with the respective device
- ^b Number of subject NLF with each specific CTR by maximum duration
- ^c Duration refers to number of days cited in the patient diary, irrespective of date of injection
- ^d The CTR numbers indicated in the “Last Day” column are also included in the “22-30 Days” column
- ^e One patient reported mild paresthesia on the corner of the mouth treated with RHA® Mepi dermal filler and which resolved in 2 days

- Both RHA® Mepi and RHA® treatment groups presented with very similar adverse event profiles with an overall of 5 subjects experiencing a total of 11 treatment-related AEs.
- All treatment-related AEs were mild in severity and none were considered by Investigators to be clinically significant. All events resolved spontaneously by the time of the study exit (30 days) except the injection site mass for one subject. This event had resolved spontaneously by 46 days post-injection without the need for medical therapy.
- All treatment-related AEs experienced by both treatment groups were typical of the expected signs and symptoms observed following an injection of a hyaluronic acid-based dermal filler except one (paresthesia; mild) that was reported by the subject in the “other” category of the 30-day diary and which resolved in 2 days.
- All treatment-related AEs were based on subjects' diary entries (CTRs).
- No events were deemed to be a granuloma.
- There were no late onset treatment-related AEs.
- There were no treatment-related serious AEs.
- There were no subjects who withdrew from the study due to AEs.
- Safety profile by Fitzpatrick skin type, ethnicity and age was not different.

3. Post-marketing Surveillance

Post Marketing surveillance data are based on RHA® 2 containing lidocaine, these data are representative and applicable to RHA® 2 Mepi. The following adverse events were reported as part of postmarketing surveillance on the use of RHA® 2 worldwide with a prevalence equal or superior to 1 occurrence for 100,000 syringes: Injection site masses (lumps and bumps), skin edema, skin swelling, vascular complication (such as vessel compression/occlusion), skin discoloration, ecchymosis, erythema, inflammatory reaction, allergic reaction, pain and skin induration. Additionally, other less frequent adverse reactions have also been reported and included dermatitis, granuloma, skin necrosis, implant migration, skin discoloration/Tyndall effect, skin infection, herpes breakout, pruritus, paresthesia, abscess, acne, angioedema, blister, scabs, fainting, product misplacement, puffiness, tenderness, injection site movement impairment, papules, pustules, dry skin, scabs, syncope and telangiectasia.

Figure 1. Proportion of responders on the NLF-Wrinkle Severity Rating Scale measured by a Blinded Live Evaluator for RHA® 2 and the Control Device



	Week 24	Week 36	Week 52	Week 64
■ RHA® 2	83.6%	86.2%	85.5%	80.9%
■ Control Device	82.1%	87.7%	82.3%	80.9%

PP populations at the respective follow-up visits
Rate of responders: ≥ 1 grade difference from pre-treatment on the NLF-WSRS

On the Global Aesthetic Improvement (GAI) scale, more than 84% of the subjects and the BLEs reported that the NLF treated with RHA® 2 was improved or very much improved from week 24 to week 64. The subjects consistently reported improvement up to 64 weeks based on the NLF module of the FACE-Q® questionnaire with the mean score improving from 24 to more than 60 throughout the follow-up period. More than 90% of the subjects reported to be satisfied or very satisfied 24 weeks after initial treatment and the rate of satisfaction remained at more than 86% at 64 weeks (the scale grades were: very satisfied, satisfied, neither satisfied nor dissatisfied, dissatisfied or very dissatisfied).

More than 78% of the subjects received repeat treatment. The effectiveness and safety profiles after repeat treatment were similar to those after initial treatment.

CLINICAL STUDY OF RHA® MEPI

The safety and effectiveness of RHA® 4 Mepi in the correction of moderate to severe facial wrinkles and folds were evaluated in comparison to RHA® 4 (lidocaine) in a U.S. pivotal clinical study described hereafter. 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 duration of the effectiveness of the anesthetic agent (mepivacaine or lidocaine) is less than a day.

The results of this clinical study are applicable to RHA® 2 Mepi as both RHA® 4 Mepi and RHA® 2 Mepi are from the same family of products, with similar physico-chemical characteristics and with the same indication. RHA® 4 Mepi was considered worst case of the RHA® family of products for this indication (including RHA® 2 Mepi) as it was injected into the deeper layers of the dermis (deep dermis to subcutaneous).

1. Pivotal Study Design

A controlled, randomized, double-blinded, within-subject (split-face), multicenter, prospective pivotal clinical study was to compare the level of pain using the dermal filler RHA® 4 (lidocaine) with the level of pain using the dermal filler RHA® 4 Mepi (mepivacaine) in the treatment of nasolabial folds (NLF).

Subjects were treated RHA® Mepi with mepivacaine in a randomly selected sequence (first or second injection) into the nasolabial fold in one side of the face and RHA® with into the contralateral nasolabial fold. RHA® Mepi and RHA® were administered into deep dermis to superficial subcutaneous tissue for the treatment of moderate to severe nasolabial folds.

The follow-up period consisted of safety and effectiveness follow-up visits one month after the initial treatment. A safety phone call visit was performed by the Treating Investigators (TI) 72 hours after the initial treatment.

2. Study Endpoints

The primary endpoint was the analysis of the non-inferiority of the injection site pain felt during injection assessed by the subject immediately following injection with RHA® Mepi (using a 100 mm Visual Analog Scale – VAS) compared to the injection site pain felt during injection immediately assessed following injection with RHA®.

The subject rated each side of the face independently and was blinded to which side of the face has been injected with which product. Additional pre-procedure anesthesia was prohibited.

Secondary anesthetic assessments were the pain assessment by the subject using the VAS ruler at 15, 30, 45, and 60 minutes following the injection and the duration of the anesthetic effect as assessed by the subject every hour until returning to normal sensation commencing 60 minutes post-injection.

Secondary effectiveness endpoints included change in the severity of the NLF as measured by the TI using the NLF-WSRS, the rates of responders (≥ 1-grade difference from pre-treatment on the WSRS), as measured by the TI, Global Aesthetic Improvement (GAI), as assessed by the subject and by the TI, impact and effectiveness of study treatment procedures from the subjects' perspective as assessed by the nasolabial fold domain of the FACE-Q®, and subject satisfaction.

Safety endpoints were evaluated throughout the study, with a 30-day subject diary capturing post-injection signs/symptoms following every study injection and AE assessments at each visit. Safety endpoints also included assessment of visual disturbances before and after injection and at each visit.

3. Demographics

A total of 30 subjects (33 to 79 years old) were enrolled and randomized, these 30 subjects were included in the intent-to-treat (ITT) population (and per protocol (PP) population).

Subjects' demographics are presented in Table 7.

Table 7. Demographics

Number / % of subjects	RHA® Mepi versus RHA® N=30	
Age		
Mean (SD)	57	(9.7)
min max	33	79
Gender		
Female	27	90.0%
Male	3	10.0%
Race		
Caucasian	27	90.0%
Black	3	10.0%
Am. Indian/N. Alask.	0	0.0%
N. Hawaiian/P. Isl.	0	0.0%
Asian	0	0.0%
Other	0	0.0%
Ethnicity		
Hispanic/Latino	12	40.0%
Not Hispanic/Latino	18	60.0%
Fitzpatrick Skin Phototype		
I	1	3.3%
II	8	26.7%
III	10	33.3%
IV	8	26.7%
V	0	0.0%
VI	3	10.0%

* Number of subjects in the ITT population

4. Treatment Characteristics

The study protocol allowed a maximum of 3.0 ml in a single NLF per treatment session. The average volume injected into a single NLF was nearly identical between treatment groups with volumes of 1.09 ml and 1.08 ml in the RHA® Mepi and RHA® groups, respectively. The total volume to achieve optimal correction result (OCR) is the sum of both groups, as it was a split face study. In general, a linear threading, fan-like technique, or a combination of linear threading with multiple punctuate pools, was used for 96.6% of the subjects treated with RHA® Mepi.

5. Effectiveness Results

The primary effectiveness endpoint was met for RHA® Mepi. The levels of pain felt by the subject during injection with RHA® Mepi (with mepivacaine) and RHA® (with lidocaine) were 17.1 mm and 16.3 mm, respectively, as measured using the VAS. This resulted in a non-significant difference between groups of -0.8 (p-value <0.0001).

For both treatment groups, the level of pain decreased over time with no statistically significant difference at all time points (at 15, 30, 45, and 60 minutes post-injection). The injection pain was reduced to 4.9 mm for RHA® Mepi and 5.1 mm for RHA® after 15 minutes and almost gone after 60 minutes post-injection.

Finally, the duration of anesthetic effect was also reported by the subject to be similar between treatment groups, lasting around 6 hours for the side treated with RHA® Mepi (with mepivacaine) and 4 hours for the side treated with RHA® (with lidocaine). Results are presented in Table 8 and Table 9.

Table 8. Injection Site Pain during injection – PP population

VAS pain (mm)	RHA® Mepi N=30	RHA® N=30	VAS Difference (mm) N=30
Mean (SD)	17.1 (18.38)	16.3 (18.89)	-0.8 (8.09)
Min, Max	0.55	0.70	-20, 20

* Number of subjects in the PP population

Table 9. Injection Site Pain after injection – ITT population

VAS pain (mm) Mean (SD)	RHA® Mepi N=30	RHA® N=30	VAS Difference (mm) N=30
Time point:			
- 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)
- 60 Min	0.0 (0.00)	1.9 (10.22)	1.9 (10.22)

* Number of subjects in the ITT population

Secondary endpoints demonstrated no difference between RHA® Mepi and RHA® regarding clinical performance.

A similar improvement in the NLF-WSRS scores was observed one month post-injection, with a score improvement of 1.9 points in the RHA® Mepi treatment group and 1.8 points in the RHA® treatment group.

Responder rate was similar for both treatment groups after the injection, with 100% of treated subjects, and 96.7% with RHA® versus 100% with RHA® Mepi at one-month post-injection.

On GAI scale, RHA® Mepi and RHA® demonstrated nearly identical GAI scores as assessed by both TIs and subjects. More than 96% of the subjects were deemed by the TI to have their NLFs treated improved or very much improved at one-month post-injection. 100% of the subjects reported having their NLFs treated improved or very much improved.

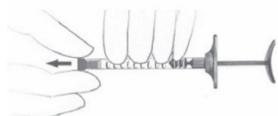
The subjects also reported similar improvement based on the NLF module of the FACE-Q® questionnaire with the mean score increasing by 63.8 and 64.2 points in the RHA® Mepi and RHA® treatment groups, respectively.

More than 96% of the subjects reported being satisfied or very satisfied one month after their treatment with no distinction between the treatment groups.

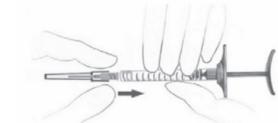
Similar effectiveness and safety profiles were observed by Fitzpatrick skin type, ethnicity and age groups. Results of RHA® 2 long term safety and effectiveness are applicable to RHA® 2 Mepi.

DIRECTIONS FOR ASSEMBLY OF THE NEEDLE TO THE SYRINGE

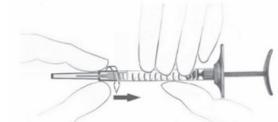
1. Remove the stopper from the syringe by pulling it off.



2. Insert the screw thread of the needle firmly into the syringe end-piece.



3. Screw the needle clockwise, while maintaining slight pressure between the needle and the syringe.



4. Continue screwing until the edge of the cap of the needle contacts the body of the syringe. There must be no space between these two parts. Failure to follow this instruction means that the needle could be ejected and/or leak at the Luer-lock.



5. Remove the needle's protective cap by pulling it firmly with one hand while holding the body of the syringe with the other.



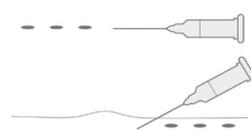
PRE-TREATMENT GUIDELINES

- Prior to treatment, the patient should avoid taking medications or supplements which thin the blood (e.g., aspirin, nonsteroidal anti-inflammatory medications, St. John's Wort, or high doses of Vitamin E supplements) as these agents may increase bruising and bleeding at the injection site.
- Before starting treatment, a complete medical history should be taken from the patient and the patient should be counseled on appropriate indications, risks, and should be informed about the expected treatment results, and expected responses. The patient should be advised of the necessary precautions before commencing the procedure.
- Prior to treatment with RHA® 2 Mepi, the patient should be assessed for appropriate anesthetic treatment for managing comfort (e.g., topical anesthetic, local or nerve block). The patient's face should be washed with soap and water and dried with a clean towel. Cleanse the area to be treated with alcohol or another suitable antiseptic solution.
- Sterile gloves are recommended while injecting RHA® 2 Mepi.
- Before injecting, prime the needle by carefully pressing the syringe plunger until a small droplet of the gel is visible at the tip of the needle.

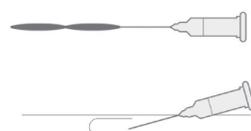
INJECTION TECHNIQUES

- RHA® 2 Mepi is administered by using a thin gauge needle (30 G x ½"). The needle is inserted into the mid-to-deep dermis at an approximate angle of 15° to 30° parallel to the length of the wrinkle or fold.
- RHA® 2 Mepi can be injected by a number of different techniques that depend on the injector's experience and preference, and patient characteristics.

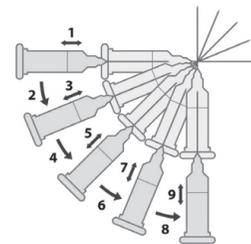
A. Serial puncture: consists of multiple injections, evenly and closely spaced all along wrinkles or folds. This technique is considered to be more precise, but may result in more discomfort for the patient due to the number of punctures.



B. Linear threading: the needle is fully introduced in the wrinkle or the fold, and the product is injected along the line, as a "thread", while withdrawing (retrograde) or pushing (antegrade) the needle.



C. Fanning technique: the needle is introduced as for the *Linear Threading technique*, and the product is injected along several closely spaced lines, by changing the direction of the needle, all using the same puncture site (the needle is not withdrawn).



- RHA® 2 Mepi is injected slowly into the mid-to-deep dermis. If the injection is made too deeply, i.e. into subcutaneous tissue, the correction may not be as expected. It is possible to tell when an injection is being made too deeply because subcutaneous tissue does not offer any resistance to product injection, unlike the dermis.
- If the color of the needle can be seen through the skin during injection, this means that the injection is too superficial. This should be avoided as the results of the correction could be irregular.
- The injection should be stopped before pulling the syringe out of the skin, to prevent product from leaking out, or product misplacement (too superficially in the skin).

- The volume to be injected depends on the corrections to be performed, but it is important to not overcorrect. Based on the US clinical study, patients should be limited to 6.0 ml per patient per treatment session in wrinkles and folds such as NLFs. The safety of injecting greater amounts has not been established.
- If blanching is observed (e.g., the overlying skin turns a whitish color), the injection should be stopped immediately and the area massaged until it returns to a normal color. Blanching may represent a vessel occlusion. If normal skin coloring does not return, do not continue with the injection. Treat in accordance with American Society for Dermatologic Surgery guidelines, which include hyaluronidase injection.
- If the wrinkles need further treatment with RHA® 2 Mepi, the same procedure should be repeated until a satisfactory result is obtained.

POST-TREATMENT GUIDELINES

- When the injection is completed, the treated site may be gently massaged so that it conforms to the contour of the surrounding tissues. If an overcorrection has occurred, massage the area firmly between your fingers or against an underlying area to obtain optimal results.
- If the treated area is swollen immediately after the injection, an ice pack can be applied to the site for a short period (e.g., 5-10 minutes). Ice should be used with caution if the area is still numb from anesthetic to avoid thermal injury.
- After use, syringes may be potential biohazards. Follow national, local, or institutional guidelines for use and disposal of medical biohazard devices. Obtain prompt medical attention if injury occurs.

STERILE NEEDLES

- After use, needles are potential biohazards. Follow national, local, or institutional guidelines for use and disposal of medical sharp devices (e.g. discard uncapped needles in approved sharps containers).
- Disposal should be in accordance with accepted medical practice and applicable local, State and Federal requirements.
- To help avoid needle breakage, do not attempt to straighten a bent needle, discard it and complete the procedure with a replacement needle.
- Do not recap needles. Recapping by hand is a hazardous practice and should be avoided.
- RHA® 2 Mepi is provided with 2 needles that do not contain engineered injury protection. Administration of RHA® 2 Mepi requires direct visualization and complete and gradual insertion of the needle making engineered protection devices not feasible. To avoid needle stick injury and sharp exposure, take care to inject in appropriate conditions.
- Obtain prompt medical attention if injury with used needle occurs.

PATIENT INSTRUCTIONS

Patient information brochure is available on request, or via the website www.revance.com.

It is recommended that the following information be shared with patients:

- Patients should be advised not to wear make-up during 12 hours following injection.
- Patient should be advised not to take high-dose Vitamin E, aspirin, anti-inflammatories, or anti-coagulants during the week prior to the injection. Patients must not discontinue such treatment without talking with their prescribing physician.
- Patients should minimize exposure of the treated area to excessive sun, UV lamp exposure, and extreme temperatures (e.g. cold weather, sauna) at least within the first 24 hours, or until initial swelling and redness have resolved. Exposure to any of the above may cause/exacerbate and/or extend the duration of temporary redness, swelling, and/or itching at the treatment sites.
- Patients should notify the injector if any of the following occurs:
 - Changes in vision
 - Unusual pain during or shortly after treatment
 - Significant pain away from the injection site
 - Signs of a stroke
 - Any redness and/or visible swelling that lasts for more than a week
 - Any side effect other than those described above or that occur weeks or months after injection
- Adverse reactions should be reported to Revance Therapeutics, Inc at 877-3REV-NOW (877-373-8669) and to Medical-us@teoxane.com.

HOW SUPPLIED

RHA® 2 Mepi is supplied in individual blisters containing a 1 ml treatment syringe with two 30 G x ½" needles as indicated on the carton. The content of the syringe is sterile and non-pyrogenic. Do not resterilize. Do not use if the package is opened or damaged. Each syringe is packaged into a blister with two unique device identifier traceability labels.

SHELF-LIFE AND STORAGE

RHA® 2 Mepi must be used prior to the expiration date printed on the package. Store at room temperature (up to 25°C/77°F). Do not expose to direct sunlight. DO NOT FREEZE. Do not store partially used syringes.

RxOnly

Manufactured by:

TEOXANE S.A.
Rue de Lyon 105
CH 1203 Geneva
(Switzerland)

Distributed by:

Revance Therapeutics, Inc.
1222 Demonbreun Street,
Suite 2000
Nashville, Tennessee 37203

RHA® is a registered trademark of TEOXANE SA.

US Patent N° 9,353,194; 9,498,562; 9,421,198; 10,786,601; 10,413,637; 11,406,738

SYMBOLS

Manufacturer's name and address

Catalog number

Lot / batch number

Expiration date (YYYY-MM-DD)

Consult Instructions for use

Single use only

Sterilized using steam

Do not use if the package is damaged

RxOnly Caution: Federal law restricts this device to sale by or on the order of a physician or licensed practitioner

TEOXANE



CAUTION: FEDERAL LAW RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A PHYSICIAN OR LICENSED PRACTITIONER. BEFORE USING RHA® 3 Mepi, PLEASE READ THE FOLLOWING INFORMATION THOROUGHLY

DEVICE DESCRIPTION

RHA® 3 Mepi is a viscoelastic, sterile, non-pyrogenic, clear, colorless, homogeneous and biodegradable gel implant. It is produced with sodium Hyaluronic Acid (NHA) with a concentration of 23 mg/g obtained from bacterial fermentation using the *Streptococcus equi* bacterial strain, crosslinked with 1,4-butanediol diglycidyl ether (BDDE) and reconstituted in a physiological buffer (pH 7.3). RHA® 3 Mepi also contains 0.3% mepivacaine hydrochloride to reduce pain on injection.

INTENDED USE / INDICATIONS

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® 3 Mepi is indicated for injection into the vermilion border, vermilion border and oral commissure to achieve lip augmentation and lip fullness, in adults aged 22 years or older.

CONTRAINDICATIONS

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

WARNINGS

- Introduction of product into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction. To avoid this:
 - Do not inject into blood vessels.
 - Take extra care when injecting soft tissue fillers, inject the product slowly and apply the least amount of pressure necessary.
- 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. If a patient exhibits any of the following symptoms: changes in vision, signs of a stroke, blanching of the skin, or unusual pain during or shortly after the procedure, immediately stop the injection. Patients should receive prompt medical attention and possibly evaluation by an appropriate health care practitioner specialist should an intravascular injection occur.
- Product use of specific sites which is an active inflammatory process (skin eruptions such as cysts, pimples, rashes, or hives), infection or skin injury is present should be deferred until the underlying process has been controlled.
- Treatment site reactions consist mainly of short-term inflammatory symptoms (e.g., swelling, redness, tenderness, or pain) and generally resolve within 14 days. Refer to the ADVERSE EXPERIENCES section for details.
- Inflammatory reaction, anaphylactic reaction, edema, implant migration, acne, blisters, scarring, papules, and delayed onset of granulomas have been reported following the use of dermal fillers.

PRECAUTIONS

- In order to minimize the risks of potential complications, this product should only be used by experienced health care practitioners who have appropriate training in filler injection techniques, and who are knowledgeable about the anatomy of and around the site of injection.
- Health care practitioners are encouraged to discuss all potential risks of soft tissue injection with their patients prior to treatment and ensure that patients are aware of signs and symptoms of potential complications.
- The safety and effectiveness for the treatment of anatomical regions other than those described in the INTENDED USE / INDICATIONS section have not been established in controlled clinical studies.
- As with all transcutaneous procedures, dermal filler implantation carries a risk of infection. Standard precautions associated with injectable materials should be followed.
- The safety in patients with known susceptibility to keloid formation, hypertrophic scarring, and pigmentation disorders has not been studied.
- The safety for use in sites in the presence of other implants (including permanent implants) has not been studied.
- The safety for use during pregnancy, in breastfeeding females, and in patients under 22 years of age has not been established.
- RHA® 3 Mepi should be used with caution in patients on immunosuppressive therapy.
- Bruising or bleeding may occur at RHA® 3 Mepi injection sites. RHA® 3 Mepi should be used with caution in patients who are using substances that can prolong bleeding (such as thrombolytics, anticoagulants, or inhibitors of platelet aggregation).
- Injection of RHA® 3 Mepi into patients with a history of previous herpetic eruption may be associated with reactivation of herpes.
- If laser treatment, chemical peeling or any other procedure based on an active dermal response is considered after treatment with RHA® 3 Mepi, there is a possible risk of eliciting an inflammatory reaction at the implant site. This also applies if RHA® 3 Mepi is administered before the skin has healed completely after such a procedure.
- RHA® 3 Mepi is to be used as supplied. Modification or use of the product outside the Instructions for Use may adversely impact the sterility, safety, homogeneity, or performance of the product.
- RHA® 3 Mepi is packaged for single-patient use. Do not reuse a syringe between two treatments and/or between two patients. Do not resterilize.
- Do not use if package is opened or damaged. The sterility of the product is not guaranteed in the case of failure to comply with this precaution. RHA® 3 Mepi is a clear, colorless gel without particulates. In the event the content of a syringe shows signs of separation and/or appears cloudy, do not use the syringe; contact Revance Therapeutics, Inc. 877-3REVA (877-373-6669).
- Failure to comply with the needle attachment instructions could result in needle disengagement and/or product leakage of the Luer-lock and needle hub connection.

ADVERSE EXPERIENCES

RHA® 3 Mepi and RHA® 3 have the same formulation except for a difference in the anesthetic agent. RHA® 3 Mepi contains mepivacaine (0.3% w/w), while RHA® 3 contains lidocaine (0.3% w/w). Mepivacaine and lidocaine have many similar and equivalent physico-chemical characteristics and properties, they are also pharmacologically related.

Due to the similarities in the formulation of RHA® 3 Mepi and RHA® 3, the U.S. clinical evaluation of RHA® 3 to support the indication for the correction of moderate to severe dynamic wrinkles and folds, such as NLF,

provided safety and effectiveness information about RHA® 3 Mepi for the indication for the correction of moderate to severe dynamic wrinkles and folds, such as NLF. This safety information from this long-term study applies to both RHA® 3 Mepi and RHA® 3, and is summarized below under "Clinical Evaluation of RHA® 3 in the NLFs".

A second U.S. study was conducted for the indication for the correction of moderate to severe dynamic wrinkles and folds, such as NLFs to evaluate the safety of RHA® 3 Mepi when compared to RHA® 3. The safety information from this clinical study is summarized below under "Clinical Evaluation of RHA® 3 Mepi in the NLFs". Due to the similarities in the formulation of RHA® 3 Mepi and RHA® 3, the U.S. clinical evaluation of RHA® 3 to support the indication for injection into the vermilion border and oral commissure to achieve lip augmentation and lip fullness, provided safety and effectiveness information about RHA® 3 Mepi for the indication of lip augmentation and lip fullness. The safety and effectiveness information from this long-term study applies to both RHA® 3 Mepi and RHA® 3, and is summarized below under "Clinical Evaluation of RHA® 3 into the lips".

1. Clinical Evaluation of RHA® 3 in the NLFs
 Clinical study TEO-RHA-1302 was a multicenter, controlled, randomized, double-blinded, within-subject (split-face), prospective U.S. study designed to compare the safety of RHA® 3 versus a control treatment for the treatment of moderate to severe nasolabial folds and demonstrated similar safety profiles. The expected signs and symptoms that occur following the injection of a hyaluronic acid-based dermal filler (i.e., Common Treatment Responses; CTR) were individually assessed by subjects in a preprinted 14-day diary after each injection. Subjects were asked to rate each CTR as None, Mild, Moderate or Severe.

- Mild: Little discomfort, no effect on daily activities, no medication or make-up required
 - Moderate: some discomfort, some effect on daily activities, possible medication or make-up required
 - Severe: Great discomfort, daily activities compromised, very likely medication or make-up required
- CTRs by severity and duration are presented respectively, in Table 1 and Table 2.
- The most frequent CTRs were firmness, redness, tenderness, swelling, lumps/bumps, and bruising
 - Proportions of subjects experiencing at least one CTR of each category was similar between RHA® 3 and control treatment.
 - More than 60% of the CTRs had resolved by Day 7.
 - The majority (more than 88%) of CTRs had resolved by Day 14.
 - There were no notable differences between RHA® 3 and control treatment with regard to the small proportion of subjects who reported a severe CTR.
 - For the majority of CTRs (more than 84%) experienced by any treatment group (initial treatment or touch-up treatment), the maximal severity reported was "Mild" or "Moderate".
 - On the last day of the diary, nearly all ongoing CTR had improved to mild.

Table 1. Common Treatment Responses by maximum severity after initial treatment with RHA® 3 and the control device reported in subject 14-day diary – Safety Population

Common Treatment Responses	TOTALS			RHA® 3 (N=75 NLF)			Control Device (N=75 NLF)		
	RHA® 3 n° (%)	CTRL n° (%)	Mild n° (%)	Mod° n° (%)	Sev° n° (%)	Mild n° (%)	Mod° n° (%)	Sev° n° (%)	
Bruising	42 (56.0%)	38 (50.3%)	20 (26.7%)	15 (20.0%)	7 (9.3%)	12 (16.0%)	20 (26.7%)	6 (8.0%)	
Discoloration	22 (29.3%)	22 (29.3%)	7 (9.3%)	14 (18.7%)	5 (6.7%)	13 (17.3%)	10 (13.3%)	5 (6.7%)	
Firmness	48 (64.0%)	45 (60.0%)	21 (28.0%)	21 (28.0%)	6 (8.0%)	22 (29.3%)	28 (37.3%)	2 (2.7%)	
Itching	13 (17.3%)	11 (14.7%)	7 (9.3%)	4 (5.3%)	2 (2.7%)	5 (6.7%)	4 (5.3%)	2 (2.7%)	
Lumps/Bumps	49 (65.3%)	40 (53.3%)	21 (28.0%)	21 (28.0%)	9 (12.0%)	22 (29.3%)	18 (24.0%)	4 (5.3%)	
Pain	40 (53.3%)	30 (40.0%)	26 (34.7%)	8 (10.7%)	3 (4.0%)	24 (32.0%)	19 (25.3%)	1 (1.3%)	
Redness	43 (57.3%)	38 (50.3%)	24 (32.0%)	14 (18.7%)	4 (5.3%)	34 (45.3%)	20 (26.7%)	1 (1.3%)	
Swelling	41 (54.7%)	38 (50.3%)	22 (29.3%)	15 (20.0%)	4 (5.3%)	22 (29.3%)	20 (26.7%)	1 (1.3%)	
Tenderness	44 (58.7%)	37 (49.3%)	29 (38.7%)	12 (16.0%)	4 (5.3%)	26 (34.7%)	20 (26.7%)	3 (4.0%)	

- Number of subjects' NLF treated with the respective device
- Number of subjects' NLF with any specific Common Treatment Response
- CTRL = Control treatment
- Mod = Moderate
- Sev = Severe

Table 2. Duration of Common Treatment Responses after initial treatment with RHA® 3 and the control device reported in subject 14-day diary – Safety Population

Common Treatment Responses	RHA® 3 (N=75 NLF)				Control Device (N=75 NLF)			
	1-3 Days	4-7 Days	8-14 Days	Last Day*	1-3 Days	4-7 Days	8-14 Days	Last Day*
Bruising	11 (14.7%)	19 (25.3%)	12 (16.0%)	5 (6.7%)	11 (14.7%)	16 (21.3%)	11 (14.7%)	1 (1.3%)
Discoloration	13 (17.3%)	6 (8.0%)	8 (10.7%)	5 (6.7%)	13 (17.3%)	6 (8.0%)	5 (6.7%)	4 (5.3%)
Firmness	18 (24.0%)	7 (9.3%)	23 (30.7%)	12 (16.0%)	19 (25.3%)	16 (21.3%)	14 (18.7%)	3 (4.0%)
Itching	9 (12.0%)	4 (5.3%)	0 (0.0%)	0 (0.0%)	10 (13.3%)	4 (5.3%)	0 (0.0%)	0 (0.0%)
Lumps/Bumps	17 (22.7%)	11 (14.7%)	21 (28.0%)	16 (21.3%)	17 (22.7%)	13 (17.3%)	12 (16.0%)	8 (10.7%)
Pain	21 (28.0%)	7 (9.3%)	2 (2.7%)	0 (0.0%)	27 (36.0%)	4 (5.3%)	2 (2.7%)	1 (1.3%)
Redness	27 (36.0%)	12 (16.0%)	9 (12.0%)	2 (2.7%)	27 (36.0%)	10 (13.3%)	6 (8.0%)	2 (2.7%)
Swelling	18 (24.0%)	12 (16.0%)	11 (14.7%)	5 (6.7%)	19 (25.3%)	11 (14.7%)	8 (10.7%)	4 (5.3%)
Tenderness	17 (22.7%)	13 (17.3%)	14 (18.7%)	6 (8.0%)	17 (22.7%)	13 (17.3%)	9 (12.0%)	3 (4.0%)

- Number of subject NLF treated with the respective device
- Number of subject NLF with each specific CTR by maximum duration
- Duration refers to number of days cited in the patient diary, irrespective of date of injection
- The CTR numbers indicated in the "Last Day" column are also included in the "8-14 Days" column

An adverse event (AE) was defined as a treatment-related event that was not considered typical in type and/or duration and/or severity. Also, CTRs from the patient's diary that were recorded on the last day of diary were automatically elevated to the status of adverse event, regardless of severity.

- All treatment-related AEs were mild or moderate in severity.
- All treatment-related AEs experienced by both treatment groups were typical of the expected signs and symptoms observed following an injection of a hyaluronic acid-based dermal filler.
- All treatment-related AEs were temporally associated with a recent device (RHA® 3 or control treatment) injection (no late onset).
- Treatment-related AEs were based on subjects' diary entries.
- No events were deemed to be a granuloma.
- There were no late onset treatment-related AEs.
- There were no treatment-related serious AEs.

2. Clinical Evaluation of RHA® Mepi in the NLFs

The safety of the RHA® Mepi family dermal filler with mepivacaine indicated for injection into the nasolabial folds was performed with RHA® 4 Mepi and results were also applicable to RHA® 2 Mepi and RHA® 3 Mepi because they have the same indication and have similar physico-chemical characteristics. RHA® 4 Mepi was considered the worst case of the three formulations because it is injected into the deeper layers of the dermis (deep dermis to superficial/subcutaneous). RHA® 4 Mepi was studied against the approved RHA® 4 dermal filler with lidocaine in a multicenter, controlled, randomized, double-blinded, within-subject (split-face), prospective U.S. clinical study for the treatment of moderate to severe nasolabial folds with RHA® 4 Mepi versus RHA® 4. Similar safety profiles between RHA® 4 Mepi and RHA® 4 Mepi were demonstrated. Since the results are applicable to RHA® 2 Mepi, RHA® 3 Mepi and RHA® 4 Mepi, the product is hereafter referred to as RHA® Mepi. The expected signs/symptoms that occur following the injection (i.e., CTRs) were captured by subjects in a 30-day diary. Injection sites on each side of the face were individually assessed by subjects over 30 days following study injections.

- CTRs by severity and duration are presented respectively, in Table 3 and Table 4.
- The most frequent CTRs were firmness, tenderness, lumps/bumps, redness, swelling, and bruising.
- Proportions of subjects experiencing at least one CTR of each category were similar between RHA® Mepi and RHA® treatments.
- The majority (91.3%) of CTRs resolved within 14 days.
- There were no notable differences between RHA® Mepi and RHA® with regard to the proportion of subjects who reported a severe CTR, the most common severe CTRs reported being firmness and redness.
- For nearly all CTRs (96.2%) experienced by any treatment group, the maximal severity reported was "Mild" or "Moderate".

Importantly, on the last day of diary all ongoing CTRs (10 CTRs from 5 subjects) were reported by the subjects mild in severity and deemed by the Investigators to be mild in severity and not clinically significant. There were all elevated to Treatment-Related AEs.

Table 3. Common Treatment Responses by maximum severity after initial treatment with RHA® Mepi and the control device RHA® reported in subject 30-day diary – Safety Population

Common Treatment Responses	TOTALS			RHA® Mepi (N=30 NLF)			RHA® (N=30 NLF)		
	RHA® Mepi n° (%)	RHA® n° (%)	Mild n° (%)	Mod° n° (%)	Sev° n° (%)	Mild n° (%)	Mod° n° (%)	Sev° n° (%)	
Bruising	19 (63.3%)	21 (70.0%)	7 (23.3%)	12 (40.0%)	0 (0.0%)	10 (33.3%)	11 (36.7%)	0 (0.0%)	
Discoloration	11 (36.7%)	12 (40.0%)	8 (26.7%)	2 (6.7%)	3 (10.0%)	8 (26.7%)	3 (10.0%)	0 (0.0%)	
Firmness	80 (0.0%)	73 (3.3%)	40 (0.0%)	33 (3.3%)	6 (7.3%)	30 (0.0%)	36 (7.3%)	6 (7.3%)	
Itching	7 (23.3%)	6 (20.0%)	7 (23.3%)	0 (0.0%)	0 (0.0%)	6 (20.0%)	0 (0.0%)	0 (0.0%)	
Lumps/Bumps	22 (73.3%)	21 (70.0%)	11 (36.7%)	11 (36.7%)	3 (10.0%)	10 (33.3%)	11 (36.7%)	0 (0.0%)	
Pain	12 (40.0%)	10 (33.3%)	11 (36.7%)	0 (0.0%)	0 (0.0%)	10 (33.3%)	11 (36.7%)	0 (0.0%)	
Redness	21 (66.7%)	20 (66.7%)	12 (40.0%)	2 (6.7%)	3 (10.0%)	14 (46.7%)	4 (13.3%)	2 (6.7%)	
Swelling	21 (70.0%)	23 (76.7%)	11 (36.7%)	3 (10.0%)	3 (10.0%)	14 (46.7%)	3 (10.0%)	0 (0.0%)	
Tenderness	24 (80.0%)	24 (80.0%)	16 (53.3%)	8 (26.7%)	0 (0.0%)	18 (60.0%)	6 (20.0%)	0 (0.0%)	
Others*	3 (3.3%)	0 (0.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	

- Number of subjects' NLF treated with the respective device
- Number of subjects' NLF with any specific Common Treatment Response
- Mod = Moderate
- Sev = Severe
- One patient reported mild paresthesia on the corner of the mouth treated with RHA®-M dermal filler and which resolved in 2 days.

Table 4. Duration of Common Treatment Responses after initial treatment with RHA® Mepi and RHA® reported in subject 30-day diary – Safety Population

CTR Duration*	Group (N=30 NLF)	1-3 Days	4-7 Days	8-14 Days	15-21 Days	22-30 Days	Last Day*
		n° (%)	n° (%)	n° (%)	n° (%)	n° (%)	n° (%)
Bruising	RHA® Mepi	8 (26.7%)	5 (16.7%)	6 (18.8%)	3 (9.4%)	0 (0.0%)	0 (0.0%)
	RHA®	6 (30.0%)	5 (25.0%)	3 (15.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Discoloration	RHA® Mepi	7 (23.3%)	3 (10.0%)	2 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	RHA®	5 (25.0%)	4 (20.0%)	2 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Firmness	RHA® Mepi	5 (16.7%)	13 (40.0%)	3 (9.4%)	6 (18.8%)	2 (6.3%)	4 (12.1%)
	RHA®	6 (30.0%)	10 (50.0%)	2 (10.0%)	6 (30.0%)	4 (20.0%)	1 (5.0%)
Itching	RHA® Mepi	5 (16.7%)	3 (9.4%)	3 (9.4%)	0 (0.0%)	0 (0.0%)	3 (9.4%)
	RHA®	4 (20.0%)	1 (5.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	3 (15.0%)
Lumps/Bumps	RHA® Mepi	8 (26.7%)	2 (6.3%)	9 (27.3%)	3 (9.4%)	2 (6.3%)	3 (9.4%)
	RHA®	5 (25.0%)	4 (20.0%)	6 (30.0%)	5 (25.0%)	0 (0.0%)	0 (0.0%)
Pain	RHA® Mepi	9 (30.0%)	7 (23.3%)	2 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	RHA®	7 (35.0%)	2 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Redness	RHA® Mepi	12 (40.0%)	6 (20.0%)	2 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	RHA®	13 (65.0%)	6 (30.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Swelling	RHA® Mepi	10 (33.3%)	3 (10.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	RHA®	10 (50.0%)	8 (40.0%)	4 (20.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)
Tenderness	RHA® Mepi	12 (40.0%)	8 (26.7%)	3 (10.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)
	RHA®	12 (60.0%)	8 (40.0%)	3 (15.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)
Others*	RHA® Mepi	3 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	RHA®	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

- Number of subject NLF treated with the respective device
- Number of subject NLF with each specific CTR by maximum duration

- * Duration refers to number of days cited in the patient diary, irrespective of date of injection
- * The CTR numbers indicated in the "Last Day" column are also included in the "22-30 days" column
- * One patient reported mild paresthesia on the corner of the mouth treated with RHA® Mepi dermal filler and which resolved in 2 days

- Both RHA® Mepi and RHA® treatment groups presented with very similar adverse event profiles with an overall of 5 subjects experiencing a total of 11 treatment-related AEs.
- All treatment-related AEs were mild in severity and none were considered by Investigators to be clinically significant. All events resolved spontaneously by the time of the study exit (30 days) except the injection site mass for one subject. This event had resolved spontaneously by 46 days post-injection without the need for medical therapy.
- All treatment-related AEs experienced by both treatment groups were typical of the expected signs and symptoms observed following an injection of a hyaluronic acid-based dermal filler except one (paresthesia; mild) that was reported by the subject in the "other" category of the 30-day diary and which resolved in 2 days.
- All treatment-related AEs were based on subjects' diary entries (CTRs).
- No events were deemed to be a granuloma.
- There were no late onset treatment-related AEs.
- There were no treatment-related serious AEs.
- There were no subjects who withdrew from the study due to AEs.

3. Clinical Evaluation of RHA® 3 into the lips

The safety of the RHA® 3 indicated for lip augmentation was studied against a control treatment in a multicenter, controlled, randomized, double-blinded, between-subject, prospective U.S. clinical study. Similar safety profiles between RHA® 3 and its comparator were demonstrated. The expected signs/symptoms that occur following the injection (i.e., CTRs) were captured by subjects in a 30-day diary. Injection sites on each side of the face were individually assessed by subjects over 30 days following study injections.

Table 5. Common Treatment Responses by maximum severity after initial treatment with RHA® 3 and the control device reported in subject 30-day diary – Safety Population

Common Treatment Responses	TOTALS			RHA® 3 (N=153)			Control (N=49)		
	RHA® 3 n° (%)	Control n° (%)	Mild n° (%)	Mod° n° (%)	Sev° n° (%)	Mild n° (%)	Mod° n° (%)	Sev° n° (%)	
At least 1 CTR	95.2%	97.9%	41.8%	36.4%	22.1%	36.2%	40.4%	23.4%	
Bruising	102 (69.4%)	25 (52.1%)	51 (33.3%)	34 (16.7%)	17 (8.5%)	18 (7.2%)	6 (4.0%)	4 (2.0%)	
Discoloration	65 (44.2%)	20 (41.7%)	30 (60.0%)	19 (29.2%)	10 (15.2%)	12 (24.0%)	7 (14.0%)	1 (2.0%)	
Firmness	115 (78.2%)	38 (79.2%)	56 (47.7%)						

On the Global Aesthetic Improvement (GAI) scale, more than 81% of the subjects and the BLE reported that the NLF treated with RHA[®] 3 was improved or very much improved from week 24 to week 64. The subjects consistently reported improvement up to 64 weeks based on the NLF module of the FACE-Q[®] questionnaire with the mean score improving from 29 to more than 63 throughout the follow-up period. More than 90% of the subjects reported to be satisfied or very satisfied 24 weeks after initial treatment and the rate of satisfaction remained of more than 82% at 64 weeks (the scale grades were: very satisfied, satisfied, neither satisfied nor dissatisfied, dissatisfied or very dissatisfied). More than 77% of the subjects received repeat treatment. The effectiveness and safety profiles after repeat treatment were similar to that after initial treatment.

TEO-RHA-1802 – CLINICAL STUDY OF RHA[®] 3 Mepi

The safety and effectiveness of RHA[®] 4 Mepi in the correction of moderate to severe facial wrinkles and folds were evaluated in comparison to their lidocaine-analog RHA[®] 4 (lidocaine) in a US pivotal clinical study described hereafter. 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 duration of the anesthetic agent (mepivacaine or lidocaine) is less than a day. The results of this clinical study are applicable to RHA[®] 3 Mepi as both RHA[®] 4 Mepi and RHA[®] 4 Mepi are from the same family of products, with similar physico-chemical characteristics and with the same indication. RHA[®] 4 Mepi was considered worst case of the RHA[®] family of products for this indication (including RHA[®] 3 Mepi) as it was injected into the deeper layers of the dermis (deep dermis to subcutaneous).

1. TEO-RHA-1802 – Pivotal Study Design: Clinical Evaluation of RHA[®] 3 Mepi in the NLFs

A controlled, randomized, double-blinded, within-subject (split-face), multicenter, prospective pivotal clinical study was to compare the level of pain using the dermal filler RHA[®] 3 Mepi (with the level of pain using the dermal filler RHA[®] 4 Mepi (mepivacaine) in the treatment of nasolabial folds (NLF). Subjects were treated RHA[®] 3 Mepi with mepivacaine in a randomly selected sequence (first or second injection) into the nasolabial fold in one side of the face and RHA[®] 4 Mepi with lidocaine in the contralateral nasolabial fold. RHA[®] 3 Mepi and RHA[®] 4 Mepi were administered into deep dermis to superficial subcutaneous tissue for the treatment of moderate to severe nasolabial folds. The follow-up period consisted of safety and effectiveness follow-up visits one month after the initial treatment. A safety phone call visit was performed by the treating investigators (TI) 72 hours after the initial treatment.

2. Study Endpoints

The primary endpoint was the analysis of the non-inferiority of the injection site pain felt during injection assessed by the subject immediately following injection with RHA[®] 3 Mepi (using a 100 mm Visual Analog Scale –VAS) compared to the injection site pain felt during injection immediately assessed following injection with RHA[®] 4 Mepi. The subject rated each side of the face independently at 15, 30, 45, and 60 minutes post-injection. Secondary effectiveness endpoints included change in the severity of the NLF as measured by the TI using the NLF-WSRS, the rates of responders (≥ 1-grade difference from pre-treatment on the WSRS), as measured by the TI, Global Aesthetic Improvement (GAI), as assessed by the subject and by the TI, impact and effectiveness of study treatment procedures from the subjects' perspective as assessed by the nasolabial fold domain of the FACE-Q[®], and subject satisfaction. Safety endpoints were evaluated throughout the study, with a 30-day subject diary capturing post-injection signs/symptoms following every study injection and AE assessments at each visit. Safety endpoints also included assessment of visual disturbances before and after injection and at each visit.

3. Demographics

A total of 30 subjects (33 to 79 years old) were enrolled and randomized, these 30 subjects were included in the intent-to-treat (ITT) population (and per protocol (PP) population). Subjects' demographics are presented in Table 9.

Table 9. Demographics

Number / % of subjects	RHA [®] Mepi versus RHA [®] N=30	
	RHA [®] Mepi	RHA [®]
Age		
Mean (SD)	57	(9.7)
min max	33	79
Gender		
Female	27	90.0%
Male	3	10.0%
Race		
Caucasian	27	90.0%
Black	3	10.0%
Am. Indian/N. Alask.	0	0.0%
N. Hawaiian/P. Isl.	0	0.0%
Asian	0	0.0%
Other	0	0.0%
Ethnicity		
Hispanic/Latino	12	40.0%
Not Hispanic/Latino	18	60.0%
Fitzpatrick Skin Phototype		
I	1	3.3%
II	8	26.7%
III	10	33.3%
IV	8	26.7%
V	0	0.0%
VI	3	10.0%

* Number of subjects in the ITT population

4. Treatment Characteristics

The study protocol allowed a maximum of 3.0 ml in a single NLF per treatment session. The average volume injected into a single NLF was nearly identical between treatment groups with volumes of 1.09 ml and 1.08 ml in the RHA[®] Mepi and RHA[®] groups, respectively. The total volume to achieve optimal correction result (OCR) is the sum of both groups, as it was a split face study. In general, a linear threading, fan-like technique, or a combination of linear threading with multiple punctate pools, was used for 96.6% of the subjects treated with RHA[®] Mepi.

5. Effectiveness Results

The primary effectiveness endpoint was met for RHA[®] Mepi. The levels of pain felt by the subject during injection with RHA[®] Mepi (with mepivacaine) and RHA[®] (with lidocaine) were 17.1 mm and 16.3 mm, respectively, as measured using the VAS. This resulted in a non-significant difference between groups of -0.8 (p-value <0.0001). For both treatment groups, the level of pain decreased over time with no statistically significant difference of all time points (at 15, 30, 45, and 60 minutes post-injection). The injection pain was reduced to 4.9 mm for RHA[®] Mepi and 5.1 mm for RHA[®] after 15 minutes and almost gone after 60 minutes post-injection. Finally, the duration of anesthetic effect was also reported by the subject to be similar between treatment groups, lasting around 6 hours for the side treated with RHA[®] Mepi (with mepivacaine) and 4 hours for the side treated with RHA[®] (with lidocaine). Results are presented in Table 10 and Table 11.

Table 10. Injection Site Pain during injection – PP population

VAS pain (mm)	RHA [®] Mepi N=30	RHA [®] N=30	VAS Difference (mm) N=30
Mean (SD)	17.1 (18.38)	16.3 (18.89)	-0.8 (8.09)
Min, Max	0.55	0.70	-20.20

* Number of subjects in the PP population

Table 11. Injection Site Pain after injection – ITT population

VAS pain (mm) Mean (SD)	RHA [®] Mepi N=30	RHA [®] N=30	VAS Difference (mm) N=30
Time point:			
- 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)
- 60 Min	0.0 (0.00)	1.9 (10.22)	1.9 (10.22)

* Number of subjects in the ITT population

Secondary endpoints demonstrated no difference between RHA[®] Mepi and RHA[®] regarding clinical performance. A similar improvement in the NLF-WSRS scores was observed one month post-injection, with a score improvement of 1.9 points in the RHA[®] Mepi treatment group and 1.8 points in the RHA[®] treatment group. Responder rate was similar for both treatment groups after the injection, with 100% of treated subjects, and 100% with RHA[®] Mepi versus 96.7% with RHA[®] at one-month post-injection. On GAI scale, RHA[®] Mepi and RHA[®] demonstrated nearly identical GAI scores as assessed by both TIs and subjects. More than 96% of the subjects were deemed by the TI to have their NLFs treated improved or very much improved at one-month post-injection. 100% of the subjects reported having their NLFs treated improved or very much improved. The subjects also reported similar improvement based on the NLF module of the FACE-Q[®] questionnaire with the mean score increasing by 63.8 and 64.2 points in the RHA[®] Mepi and RHA[®] treatment groups, respectively. More than 96% of the subjects reported being satisfied or very satisfied one month after their treatment with no distinction between the treatment groups. Similar effectiveness and safety profiles were observed by Fitzpatrick skin type, ethnicity and age groups. Results of RHA[®] 3 long term safety and effectiveness are applicable to RHA[®] 3 Mepi.

TEO-RHA-1806 – RHA[®] 3 CLINICAL STUDY FOR RHA[®] 3 INTO THE LIPS

RHA[®] 3 Mepi is strictly identical to RHA[®] 3 except for the small amount of anesthetic medicine. RHA[®] 3 Mepi contains mepivacaine and RHA[®] 3 contains lidocaine. Both anesthetic agents are of the same family with the same mechanisms of effect. RHA[®] 3 Mepi and RHA[®] 3 have the same indication. The long-term safety and effectiveness of RHA[®] 3 Mepi were evaluated in a clinical study using RHA[®] 3. The long-term safety and effectiveness of RHA[®] 3 for the injection into the vermilion body, vermilion border and oral commissures to achieve lip augmentation and lip fullness were evaluated in a US pivotal clinical study described hereafter. The safety and effectiveness of the RHA[®] 3 indicated for lip augmentation were evaluated in comparison to a control in a U.S. pivotal clinical study described hereafter.

1. TEO-RHA-1806 - Pivotal Study Design: Clinical Evaluation of RHA[®] 3 into the lips

A prospective, double-blinded, randomized, controlled, multicenter clinical study was conducted to evaluate the clinical safety and effectiveness of RHA[®] 3 versus control for injection into the lips (vermilion body, vermilion border, and oral commissures) for lip augmentation. A total of 202 subjects were randomized and underwent treatment with either RHA[®] 3 (N = 153) or control (N = 49) in the vermilion border, vermilion body and oral commissure for the lip augmentation and lip fullness (touch-up), with the same study device used for initial treatment. The follow-up period consisted of safety and effectiveness follow-up visits at 4, 8, 12, 24, 36, and 52 weeks after the last treatment. Subjects were eligible for optional retreatment if necessary at Weeks 36 or 52, and were then followed for 1 month after retreatment or until all Adverse Events (AEs) resolved or TI determines that follow-up is no longer necessary. Retreatment was provided using RHA[®] 3 (the control device was not used).

2. Study Endpoints

The primary effectiveness endpoint was the analysis of non-inferiority of RHA[®] 3 versus control in terms of change from Baseline (pre-injection) 12 weeks after injection, as measured by a Blinded Live Evaluator (BLE) using the proprietary and validated 5-grade Teoxane Lip Fullness Scale (TLFS). The co-primary endpoint was the proportion of responders with a ≥1-grade point increase on the TLFS at 12 weeks when compared to pretreatment, which should be ≥ 70%. Secondary effectiveness endpoints included TLFS change from Baseline and rates of responders, as assessed by the BLE at each study visits (see data in Table 8 and Figure 2). Global Aesthetic Improvement (GAI), as assessed by the subject, and by the BLE, impact and effectiveness of study treatment procedures from the subjects' perspective as assessed by the lip domain and satisfaction of the outcome module of the FACE-Q[®], and subject satisfaction. Safety endpoints were evaluated throughout the study, with a 30-day subject diary capturing post-injection signs/symptoms following every study injection, and AE assessments and lip functionality at each visit, and included self-assessment of injection site pain by the subject using a 100mm Visual Analog Scale. Safety endpoints also included assessment of visual disturbances before and after injection and at each visit.

3. Demographics

A total of 202 subjects (22 to 76 years old) were enrolled and included in the Safety population with 153 subjects allocated to RHA[®] 3 treatment, and 49 allocated to the control treatment. Subjects' demographics are presented in Table 12. A total of 181 subjects were enrolled and included in the mITT population, with 137 subjects allocated to RHA[®] 3 treatment, and 44 allocated to the control treatment. The mITT population consisted of all enrolled subjects who received treatment and had at least one post-Baseline primary effectiveness visit, excluding subjects with high TLFS grades at Baseline TLFS (a few subjects with FST V and VI to be followed for safety only).

Table 12. Demographics

Number / % of subjects	RHA [®] 3 N=153	Control N=49	Total N=202
Age			
Mean (SD)	48.8 (13.19)	48.5 (11.69)	48.7 (12.82)
min max	22, 76	24, 68	22, 76
Gender			
Female	151 (98.7%)	48 (98.0%)	199 (98.5%)
Male	2 (1.3%)	1 (2.0%)	3 (1.5%)
Race			
Am. Indian/N. Alask.			
Asian	2 (1.3%)	1 (2.0%)	3 (1.5%)
Black or African	4 (2.6%)	1 (2.0%)	5 (2.5%)
American	15 (9.8%)	2 (4.1%)	17 (8.4%)
N. Hawaiian/P. Isl.	2 (1.3%)	0	2 (1.0%)
White	130 (85.0%)	45 (91.8%)	175 (86.6%)
Ethnicity			
Hispanic/Latino	32 (20.9%)	13 (26.5%)	45 (22.3%)
Not Hispanic/Latino	118 (77.1%)	35 (71.4%)	153 (75.7%)
Not available	3 (2.0%)	1 (2.0%)	4 (2.0%)

Fitzpatrick Skin Phototype	RHA [®] 3 N=153	Control N=49	Total N=202
I-II	114 (74.5%)	35 (71.5%)	149 (73.8%)
I	10 (6.5%)	7 (14.3%)	17 (8.4%)
II	46 (30.1%)	9 (18.4%)	55 (27.2%)
III	58 (37.9%)	19 (38.8%)	77 (38.2%)
IV-VI	39 (25.5%)	14 (28.6%)	53 (26.2%)
IV	22 (14.4%)	10 (20.4%)	32 (15.8%)
V	10 (6.5%)	3 (6.1%)	13 (6.4%)
VI	7 (4.6%)	1 (2.0%)	8 (4.0%)

* Number of subjects in the safety populations

4. Treatment Characteristics

The study protocol allowed a maximum of 1.5 ml per lip at each treatment session. The overall total mean volume of RHA[®] 3 injected to achieve optimal correction (OCR) (initial + touch-up) was 1.78±0.64 ml. Injection volumes into the lips tended to be lower after retreatment, with total mean injection volume being 1.03±0.45 ml after retreatment. Similar mean injection volumes were used in subjects treated with the control device: 1.95±0.73 ml to achieve OCR and 1.03±0.41 ml after retreatment. The proportion of subjects who received touch-up treatment at Week 4 was lower with RHA[®] 3 (58.2%, 89/153) than with control (73.5%, 36/49). In general, a linear threading, either as a stand-alone technique or in combination with other techniques such as multiple punctate pools or fan like injection, was used for the vast majority of subjects in both treatment groups.

5. Effectiveness Results

The primary effectiveness endpoint was the fullness improvement from pre-injection of the lips treated with RHA[®] 3 compared to the improvement from pre-injection of the lip treated with the control treatment, using the TLFS, as assessed by the BLE at 12 weeks; results are presented in Table 13, Table 14 shows the number of responders and the responder rate as assessed by the BLE 12 weeks after last treatment based on the TLFS grade at Baseline 1, 2 and/or 3.

Table 13. TLFS Grade Change from Baseline as assessed by the BLE

	RHA [®] 3 (N=137)		Control (N=44)	
	Mean TLFS score (SD)	Mean TLFS change from Baseline (SD)	Mean TLFS score (SD)	Mean TLFS change from Baseline (SD)
Baseline	2.4 (0.62)		2.3 (0.60)	
Week 12 ^{2a}	3.4 (0.61)	1.0 (0.65)	3.1 (0.65)	0.8 (0.70)
Week 24	3.3 (0.75)	0.8 (0.64)	2.8 (0.69)	0.5 (0.63)
Week 36	3.1 (0.78)	0.7 (0.65)	2.8 (0.73)	0.5 (0.63)
Week 52	3.0 (0.75)	0.5 (0.64)	2.5 (0.67)	0.1 (0.63)

^a Primary effectiveness endpoint

^b Estimate of difference in means RHA3 – control is 0.19 (-0.03, -0.42) calculated by Bootstrap estimate using 1000 samples. mITT population

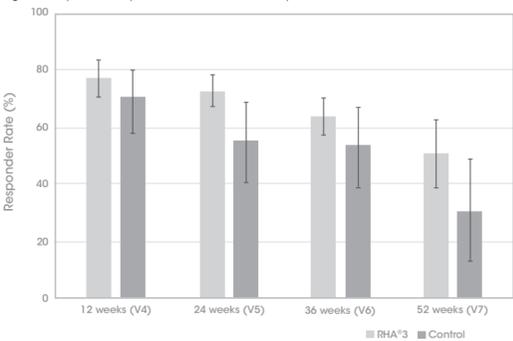
Table 14. TLFS responder rate (BLE) at Week 12 – mITT Population

	RHA [®] 3	Control
Baseline TLFS grades 1, 2 & 3		
N	137	44
# of responders (%) [95% CI]	107 (78.1%) [70.5 - 84.2%]	29 (65.9%) [51.1 - 78.1%]
Baseline TLFS grades 1 & 2		
N	68	27
# of responders (%) [95% CI]	64 (94.1%) [85.8-97.7%]	24 (88.9%) [71.9-96.1%]
Baseline TLFS grade 3		
N	69	17
# of responders (%) [95% CI]	43 (62.3%) [50.5-72.8%]	5 (29.4%) [13.3-53.1%]

mITT population

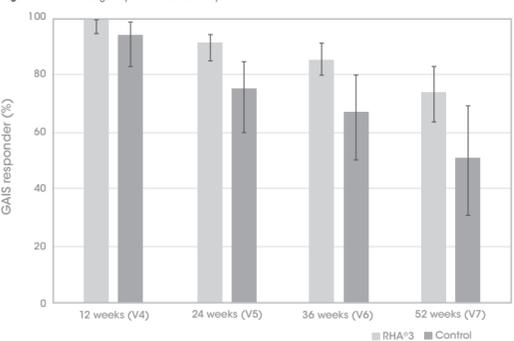
The results demonstrated that non-inferiority to the control in terms of mean TLFS change from baseline was achieved for RHA[®] 3 at 12 weeks for lip augmentation. However, for the co-primary endpoint, the responder rate for the control group did not meet the performance goal of 70%. Throughout the follow-up period, the aesthetic improvement of the RHA[®] 3 continued to be clinically significant (≥ 1 grade difference from pre-treatment on the TLFS) for 61% (81/132) of the subjects at 36 weeks after last treatment, and for 48% (38/79) at 52 weeks after last treatment (Figure 2).

Figure 2. Proportion of responders on the TLFS measured by the BLE for RHA[®] 3 and the Control Device



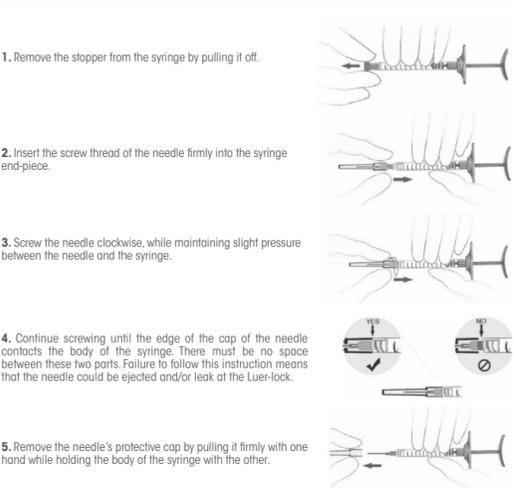
On the Global Aesthetic Improvement (GAI) scale, more than 73% (99%, 134/135 at 12 weeks, 92%, 122/132 at 24 weeks, 86%, 113/132 at 36 weeks and 73%, 58/79 at 52 weeks) of the subjects and the BLE reported that the lips treated with RHA[®] 3 was improved or very much improved from week 12 to week 52. GAI responder rate was similar at Week 12 between RHA[®] 3 and control as assessed by BLE, and GAI responder rates in the RHA3 group are higher than the GAI responder rates in the control group at all subsequent visits (24, 36 and 52 weeks after last treatment; Figure 3).

Figure 3. GAI through 1 year as assessed by the BLE



The subjects treated with RHA[®] 3 consistently reported improvement up to 52 weeks based on the Satisfaction with Lips module of the FACE-Q[®] questionnaire with the mean score improving from Baseline by 51 points at Week 12 to more than 36 points throughout the follow-up period (46 at Week 24, 41 at Week 36 and 36 at Week 52). Similar results were found with the Satisfaction with Outcomes module of the FACE-Q[®] questionnaire. 84% (113/135) of the subjects reported to be satisfied or very satisfied 12 weeks after treatment and the rate of satisfaction was 83% (67/81) at 52 weeks (the scale grades were: very satisfied, satisfied, neither satisfied nor dissatisfied, dissatisfied, or very dissatisfied). 59% (90/153) of the subjects received repeat treatment. The effectiveness and safety profiles after repeat treatment were similar to that after initial treatment and touch-up.

DIRECTIONS FOR ASSEMBLY OF THE NEEDLE TO THE SYRINGE

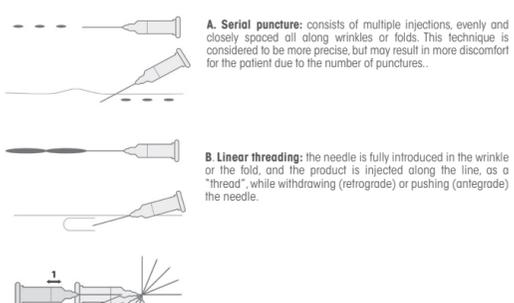


PRE-TREATMENT GUIDELINES

- Prior to treatment, the patient should avoid taking medications or supplements which thin the blood (e.g., aspirin, nonsteroidal anti-inflammatory medications, St. John's Wort, or high doses of Vitamin E supplements) as these agents may increase bruising and bleeding at the injection site.
- Before starting treatment, a complete medical history should be taken from the patient and the patient should be counseled on appropriate indications, risks, and should be informed about the expected treatment results, and expected responses. The patient should be advised of the necessary precautions before commencing the procedure.
- Prior to treatment with RHA[®] 3 Mepi the patient should be assessed for appropriate anesthetic treatment for managing comfort (e.g., topical anesthetic, local or nerve block). The patient's face should be washed with soap and water and dried with a clean towel. Cleanse the area to be treated with alcohol or another suitable antiseptic solution.
- Sterile gloves are recommended while injecting RHA[®] 3 Mepi.
- Before injecting, prime the needle by carefully pressing the syringe plunger until a small droplet of the gel is visible at the tip of the needle.

INJECTION TECHNIQUES

- RHA[®] 3 Mepi is administered by using a thin gauge needle (27 G x ½"). For the treatment of the NLFs, the needle is inserted into the mid-to-deep dermis at an approximate angle of 15° to 30° parallel to the length of the wrinkle or fold. For lip augmentation, RHA[®] 3 Mepi is injected into the lip mucosa and/or mid to deep dermis as appropriate.
- RHA[®] 3 Mepi can be injected by a number of different techniques that depend on the injector's experience and preference, and patient characteristics.



- If the color of the needle can be seen through the skin during injection, this means that the injection is too superficial. This should be avoided as the results of the correction could be irregular.
- The injection should be stopped before pulling the syringe out of the skin, to prevent product from leaking out, or product displacement (too superficially in the skin).
- The volume to be injected depends on the corrections to be performed, but it is important to not overcorrect.
- Based on the US clinical study, patients should be limited to 6.0ml per patient per treatment session in wrinkles and folds such as NLFs, and should not exceed 1.5ml per upper lip and 1.5 ml per lower lip per treatment session. The safety of injecting greater amounts has not been established.
- If blanching is observed (e.g., the overlying skin turns a whitish color), the injection should be stopped immediately and the area massaged until it returns to a normal color. Blanching may represent a vessel occlusion. If normal skin coloring does not return, do not continue with the injection. Treat in accordance with American Society for Dermatologic Surgery guidelines, which include hyaluronidase injection.
- If the wrinkles or lips need further treatment with RHA[®] 3 Mepi, the same procedure should be repeated until a satisfactory result is obtained.

- When the injection is completed, the treated site may be gently massaged so that it conforms to the contour of the surrounding tissues. If an overcorrection has occurred, massage the area firmly between your fingers or against an underlying area to obtain optimal results.
- If the treated area is swollen immediately after the injection, an ice pack can be applied to the site for a short period (e.g., 5-10 minutes). Ice should be used with caution if the area is still numb from anesthetic to avoid thermal injury.
- After use, syringes may be potential biohazards. Follow national, local, or institutional guidelines for use and disposal of medical biohazard devices. Obtain prompt medical attention if injury occurs.

POST-TREATMENT GUIDELINES

- After use, needles are potential biohazards. Follow national, local, or institutional guidelines for use and disposal of medical sharp devices (e.g. discard uncapped needles in approved sharps containers).

TEOXANE

RHA[®] DYNAMIC VOLUME

CAUTION: FEDERAL LAW RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A PHYSICIAN OR LICENSED PRACTITIONER. BEFORE USING RHA[®] DYNAMIC VOLUME, PLEASE READ THE FOLLOWING INFORMATION THOROUGHLY

DEVICE DESCRIPTION

RHA[®] Dynamic Volume is a viscoelastic, sterile, non-pyrogenic, clear, colorless, homogeneous and biodegradable gel implant. It is produced with sodium Hyaluronate (NtHA) with a concentration of 23 mg/g obtained from bacterial fermentation using the *Streptococcus* ovi bacterial strain, crosslinked with 1,4-butanediol diglycidyl ether (BDDE) and reconstituted in a physiological buffer (pH 7.3). RHA[®] Dynamic Volume also contains 0.3% mepivacaine hydrochloride to reduce pain on injection.

INTENDED USE / INDICATIONS

RHA[®] Dynamic Volume is indicated for injection into the deep dermis to superficial subcutaneous tissue for the correction of moderate to severe dynamic facial wrinkles and folds, such as nasolabial folds (NLF), in adults aged 22 years or older. RHA[®] Dynamic Volume is indicated for injection into the subcutaneous to supraperiosteal layers for cheek augmentation and/or correction of age-related midface contour deficiencies, in adults aged 22 years or older.

CONTRAINDICATIONS

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

WARNINGS

- Introduction of product into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction. Do avoid this.
 - Do not inject into blood vessels.
 - Take extra care when injecting soft tissue fillers, inject the product slowly and apply the least amount of pressure necessary.
- 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. If a patient exhibits any of the following symptoms: changes in vision, signs of a stroke, blanching of the skin, or unusual pain during or shortly after the procedure, immediately stop the injection. Patients should receive prompt medical attention and possibly evaluation by an appropriate health care practitioner specialist should be contacted on intravascular injection occur.
- Product use at specific sites in which an active inflammatory process (skin eruptions such as cysts, pimples, rashes, or hives), infection or skin injury is present should be deferred until the underlying process has been controlled.
- Treatment site reactions consist mainly of short-term inflammatory symptoms (e.g., swelling, redness, tenderness, or pain) and generally resolve within 14 days. Refer to the ADVERSE EXPERIENCES section and the Post-marketing Surveillance section for more details.
- Inflammatory reaction, anaphylactic reaction, edema, implant migration papule, acne, blisters, scarring, papules, unsatisfactory results, scarring and delayed onset of granulomas have been reported following the use of dermal fillers.

PRECAUTIONS

- In order to minimize the risks of potential complications, this product should only be used by experienced health care practitioners who have appropriate training in filler injection techniques, and who are knowledgeable about the anatomy of and around the site of injection.
- Health care practitioners are encouraged to discuss all potential risks of soft tissue injection with their patients prior to treatment and ensure that patients are aware of signs and symptoms of potential complications.
- The safety and effectiveness for the treatment of anatomical regions other than those described in the INTENDED USE/INDICATIONS section have not been established in controlled clinical studies.
- The safety and effectiveness of cannula injection for cheek augmentation have only been clinically evaluated with TSK STERIGLIDE[™] cannulas that were 25G and 2 inches in length.
- As with all transcutaneous procedures, dermal filler implantation carries a risk of infection. Standard precautions associated with injectable materials should be followed.
- The safety in patients with known susceptibility to keloid formation, hypertrophic scarring, and pigmentation disorders has not been studied.
- The safety for use in sites in the presence of other implants (including permanent implants) has not been studied.
- The safety for use during pregnancy, in breastfeeding females, and in patients under 22 years of age has not been established.
- RHA[®] Dynamic Volume should be used with caution in patients on immunosuppressive therapy.
- Bruising or bleeding may occur at RHA[®] Dynamic Volume injection sites. RHA[®] Dynamic Volume should be used with caution in patients who are using substances that can prolong bleeding (such as thrombolytics, anticoagulants, or inhibitors of platelet aggregation).
- Injection of RHA[®] Dynamic Volume into patients with a history of previous herpes eruption may be associated with reactivation of herpes.
- If laser treatment, chemical peeling, or any other procedure based on active dermal response is considered after treatment with RHA[®] Dynamic Volume, there is a possible risk of eliciting an inflammatory reaction at the implant site. This also applies if RHA[®] Dynamic Volume is administered before the skin has healed completely after such a procedure.
- RHA[®] Dynamic Volume is to be used as supplied. Modification or use of the product outside the Instructions for Use may adversely impact the safety, safety, homogeneity, or performance of the product.
- RHA[®] Dynamic Volume is packaged for single-patient use. Do not reuse a syringe between two treatments and/or between two patients. Do not sterilize.
- Do not use if package is opened or damaged. The sterility of the product is not guaranteed in the case of failure to comply with this precaution.
- RHA[®] Dynamic Volume is a clear, colorless gel without particulates. In the event the content of a syringe shows signs of separation and/or appears cloudy, do not use the syringe; contact Revance Therapeutics, Inc. 877-3REV-NOW (877-373-8667).
- Failure to comply with the needle/blunt cannula attachment instructions could result in needle/blunt cannula disengagement and/or product leakage at the Luer-lock and needle/blunt cannula hub connection.

ADVERSE EXPERIENCES

RHA[®] Dynamic Volume and RHA[®] 4 have the same formulation except for a difference in the anesthetic agent: RHA[®] Dynamic Volume contains mepivacaine (0.3% w/w), while RHA[®] 4 contains lidocaine (0.3% w/w). Mepivacaine and lidocaine have very similar and similar equivalent physico-chemical characteristics and properties, they are also pharmacologically related.

Due to the similarities in the formulation of RHA[®] Dynamic Volume and RHA[®] 4, the U.S. clinical evaluation of RHA[®] 4 to support the indication for the correction of moderate to severe dynamic wrinkles and folds, such as NLF, provided safety and effectiveness information about RHA[®] Dynamic Volume for the indication for the correction of moderate to severe dynamic wrinkles and folds, such as NLF. This safety information from this long-term study applies to both RHA[®] Dynamic Volume and RHA[®] 4, and is summarized below under "Clinical Evaluation of RHA[®] 4 in the NLFs". A second U.S. study was conducted for the indication for the correction of moderate to severe dynamic wrinkles and folds, such as NLF, to evaluate the safety of RHA[®] Dynamic Volume when compared to RHA[®] 4. The safety information from this clinical study are summarized below under "Clinical Evaluation of RHA[®] Dynamic Volume in the NLFs".

A third clinical study was conducted in support of the indication for cheek augmentation and/or correction of age-related midface contour deficiencies. The safety information from this clinical study is summarized below under "Clinical Evaluation of RHA[®] 4 for midface volume deficiency".

- Clinical Evaluation of RHA[®] 4 in the NLFs**
Clinical study TEO-RHA-1402 was a multicenter, controlled, randomized, double-blinded, within-subject (split-face), prospective US study designed to compare the safety of RHA[®] 4 versus a Control treatment for the treatment of moderate to severe nasolabial folds and demonstrated similar safety profiles. The expected signs and symptoms that occur following the injection of a hyaluronic acid-based dermal filler (i.e., Common Treatment Responses; CTR) were individually assessed by subjects in a preprinted 14-day diary after each injection. Subjects were asked to rate each CTR as None, Mild, Moderate or Severe.
 - Mild: Little discomfort, no effect on daily activities, no medication or make-up required.
 - Moderate: some discomfort, some effect on daily activities, possibly medication or make-up required.
 - Severe: Great discomfort, daily activities compromised, very likely medication or make-up required.

- CTRs by severity and duration are presented respectively, in Table 1 and Table 2.
- The most frequent CTRs were swelling, firmness, tenderness, redness, lumps/bumps, pain, and bruising.
- Proportion of subjects experiencing at least one CTR of each category was similar between RHA[®] 4 and Control treatment.
- More than 67% of the CTRs had resolved by Day 7.
- The majority (80%) of CTRs had resolved by Day 14.
- There were almost 3 times less subjects who reported severe CTR with RHA[®] 4 than with Control treatment.
- For nearly all CTRs (more than 90%) experienced by any treatment group (initial treatment or touch-up treatment), the maximal severity reported was "Mild" or "Moderate".

Table 1. Common Treatment Responses by maximum severity after initial treatment with RHA[®] 4 and the control device reported in subject 14-day diary – Safety Population

Common Treatment Responses	TOTALS		RHA [®] 4 (N=120 NLF)			Control Device (N=120 NLF)		
	RHA [®] 4 n [°] (%)	CTRL ² n [°] (%)	Mild n [°] (%)	Mod ³ n [°] (%)	Sev ⁴ n [°] (%)	Mild n [°] (%)	Mod ³ n [°] (%)	Sev ⁴ n [°] (%)
Bruising	70 (58.3%)	72 (60.0%)	35 (29.2%)	26 (21.7%)	9 (7.5%)	37 (30.8%)	25 (20.8%)	10 (8.3%)
Discoloration	50 (41.7%)	56 (46.7%)	30 (25.0%)	16 (13.3%)	4 (3.3%)	30 (25.0%)	20 (16.7%)	6 (5.0%)
Firmness	91 (75.8%)	93 (77.5%)	36 (30.0%)	46 (38.3%)	9 (7.5%)	13 (10.8%)	50 (41.7%)	30 (25.0%)
Itching	30 (25.0%)	44 (36.7%)	25 (20.8%)	5 (4.2%)	0 (0.0%)	28 (23.3%)	14 (11.7%)	2 (1.7%)
Lumps/Bumps	81 (67.5%)	90 (36.0%)	36 (30.0%)	33 (27.5%)	12 (10.0%)	28 (23.3%)	37 (30.8%)	25 (20.8%)
Pain	66 (55.0%)	87 (72.5%)	42 (35.0%)	19 (15.8%)	5 (4.2%)	30 (25.0%)	40 (33.3%)	17 (14.2%)
Redness	84 (70.0%)	91 (75.8%)	42 (35.0%)	31 (25.8%)	3 (3.3%)	32 (26.7%)	42 (35.0%)	17 (14.2%)
Swelling	97 (80.8%)	104 (86.7%)	41 (34.2%)	44 (36.7%)	12 (10.0%)	21 (17.5%)	38 (31.7%)	45 (37.5%)
Tenderness	90 (75.0%)	95 (79.2%)	53 (44.2%)	30 (25.0%)	7 (5.8%)	23 (19.2%)	45 (37.5%)	22 (22.5%)

- a** Number of subjects' NLF treated with the respective device
- b** Number of subjects' NLF with any specific Common Treatment Response
- c** CTRL = Control treatment
- d** Mod = Moderate
- e** Sev = Severe

Table 2. Duration of Common Treatment Responses after initial treatment with RHA[®] 4 and the control device reported in subject 14-day diary – Safety Population

Common Treatment Responses	RHA [®] 4 (N=120 NLF) N [°] (%)				Control Device (N=120 NLF) N [°] (%)			
	1-3 Days	4-7 Days	8-14 Days	Last Day ⁵	1-3 Days	4-7 Days	8-14 Days	Last Day ⁵
Bruising	22 (18.3%)	28 (23.3%)	20 (16.7%)	8 (6.7%)	37 (30.8%)	28 (23.3%)	7 (5.8%)	4 (3.3%)
Discoloration	28 (23.3%)	10 (8.3%)	12 (10.0%)	10 (8.3%)	34 (28.3%)	14 (11.7%)	6 (5.0%)	4 (3.3%)
Firmness	16 (13.3%)	20 (16.7%)	55 (45.8%)	35 (29.2%)	13 (10.8%)	26 (21.7%)	54 (45.0%)	26 (21.7%)
Itching	20 (16.7%)	8 (6.7%)	2 (1.7%)	2 (1.7%)	24 (20.0%)	14 (11.7%)	6 (5.0%)	3 (2.5%)
Lumps/Bumps	19 (15.8%)	14 (11.7%)	48 (40.0%)	36 (30.0%)	25 (20.8%)	24 (20.0%)	41 (34.2%)	27 (22.5%)
Pain	48 (40.0%)	12 (10.0%)	6 (5.0%)	3 (2.5%)	54 (45.0%)	25 (20.8%)	8 (6.7%)	2 (1.7%)
Redness	42 (35.0%)	30 (25.0%)	12 (10.0%)	8 (6.7%)	42 (35.0%)	37 (30.8%)	12 (10.0%)	7 (5.8%)
Swelling	36 (30.0%)	29 (24.2%)	32 (26.7%)	16 (13.3%)	27 (22.5%)	50 (41.7%)	27 (22.5%)	11 (9.2%)
Tenderness	41 (34.2%)	22 (18.3%)	27 (22.5%)	14 (11.7%)	26 (21.7%)	39 (32.5%)	26 (21.7%)	8 (6.7%)

- a** Number of subject NLF treated with the respective device
- b** Number of subject NLF with each specific CTR by maximum duration

^c Duration refers to number of days cited in the patient diary, irrespective of date of injection
^d The CTR numbers indicated in the "Last Day" column are also included in the "8-14 Days" column

- An adverse event (AE) was defined as a treatment-related event that was not considered typical in type and/or duration and/or severity. Also, CTRs from the patient's diary that were recorded on the last day of diary were automatically elevated to the status of adverse event, regardless of severity.
- All treatment-related AEs were mild or moderate in severity.
- The vast majority of treatment-related AEs experienced by both treatment groups were typical of the expected signs and symptoms observed following an injection of a dermal filler.
- All treatment-related AEs were temporally associated with a recent device (RHA[®] 4 or Control treatment) injection (no late onset).
- Nearly all treatment-related AEs were based on subjects' diary entries (CTRs). Also, there were 11 treatment-related AEs (all of mild severity) in 11 subjects with RHA[®] 4 reported by the Treating Investigator which consisted of acne, discoloration, firmness, headache, pain, swelling, telangiectasia, and tenderness.
- No events were deemed to be a granuloma.
- There were no late onset treatment-related AEs.
- There were no treatment-related serious AEs.

2. Clinical Evaluation of RHA[®] Dynamic Volume in the NLFs

The safety of the RHA[®] Mepe family of dermal fillers with mepivacaine indicated for injection into the nasolabial folds was performed with RHA[®] Dynamic Volume and was studied against the approved RHA[®] 4 dermal filler with lidocaine in a multicenter, controlled, randomized, double-blinded, within-subject (split-face), prospective US clinical study for the treatment of moderate to severe nasolabial folds with RHA[®] Dynamic Volume versus RHA[®] 4. Similar safety profiles between RHA[®] Dynamic Volume and RHA[®] 4 were demonstrated. RHA[®] Dynamic Volume is strictly identical to RHA[®] 4 except for the small amount of anesthetic medicine: RHA[®] Dynamic Volume contains mepivacaine and RHA[®] 4 contains lidocaine. Both anesthetics agents are of the same family with the same mechanisms of effect. This clinical study also serves as the support to leverage the clinical data of RHA[®] 4 when injected into the midface with RHA[®] Dynamic Volume when injected into the midface. The expected signs/symptoms that occur following the injection (i.e., CTRs) were captured by subjects in a 30-day diary. Injection sites on each side of the face were individually assessed by subjects over 30 days following study injections. CTRs by severity and duration are presented respectively, in Table 3 and Table 4.

- The most frequent CTRs were firmness, tenderness, lumps/bumps, redness, swelling, and bruising.
- Proportion of subjects experiencing at least one CTR of each category were similar between RHA[®] Dynamic Volume and RHA[®] 4 treatments.
- The majority (91.3%) of CTRs resolved within 14 days.
- There were no notable differences between RHA[®] Dynamic Volume and RHA[®] 4 with regard to the proportion of subjects (3.8%) who reported a severe CTR, the most common severe CTRs reported being firmness and redness.
- For nearly all CTRs (96.2%) experienced by any treatment group, the maximal severity reported was "Mild" or "Moderate".

Importantly, on the last day of diary all ongoing CTRs (10 CTRs from 5 subjects) were reported by the subjects mild in severity and deemed by the Investigators to be mild in severity and not clinically significant. There were all elevated to Treatment-Related AEs.

Table 3. Common Treatment Responses by maximum severity after initial treatment with RHA[®] Dynamic Volume and the control device RHA[®] 4 reported in subject 30-day diary – Safety Population

Common Treatment Responses	TOTALS		RHA [®] Dynamic Volume (N=30 NLF)			RHA [®] 4 (N=30 NLF)		
	RHA [®] Dynamic Volume n [°] (%)	RHA [®] 4 n [°] (%)	Mild n [°] (%)	Mod ³ n [°] (%)	Sev ⁴ n [°] (%)	Mild n [°] (%)	Mod ³ n [°] (%)	Sev ⁴ n [°] (%)
Bruising	19 (63.3%)	21 (70.0%)	7 (23.3%)	12 (40.0%)	0 (0.0%)	10 (33.3%)	11 (36.7%)	0 (0.0%)
Discoloration	11 (36.7%)	12 (40.0%)	8 (26.7%)	2 (6.7%)	1 (3.3%)	8 (26.7%)	4 (13.3%)	0 (0.0%)
Firmness	24 (80.0%)	22 (73.3%)	12 (40.0%)	10 (33.3%)	2 (6.7%)	9 (30.0%)	11 (36.7%)	0 (0.0%)
Itching	7 (23.3%)	6 (20.0%)	7 (23.3%)	0 (0.0%)	0 (0.0%)	6 (20.0%)	0 (0.0%)	0 (0.0%)
Lumps/Bumps	22 (73.3%)	21 (70.0%)	10 (33.3%)	11 (36.7%)	1 (3.3%)	10 (33.3%)	11 (36.7%)	0 (0.0%)
Pain	12 (40.0%)	9 (30.0%)	10 (33.3%)	6 (20.0%)	0 (0.0%)	10 (33.3%)	11 (36.7%)	0 (0.0%)
Redness	21 (70.0%)	20 (66.7%)	12 (40.0%)	6 (20.0%)	3 (10.0%)	14 (46.7%)	4 (13.3%)	2 (6.7%)
Swelling	21 (70.0%)	23 (76.7%)	11 (36.7%)	9 (28.3%)	1 (3.3%)	14 (46.7%)	9 (30.0%)	0 (0.0%)
Tenderness	24 (80.0%)	24 (80.0%)	16 (53.3%)	8 (26.7%)	0 (0.0%)	18 (60.0%)	6 (20.0%)	0 (0.0%)
Others ^a	3 (3.3%)	0 (0.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

- a** Number of subjects' NLF treated with the respective device
- b** Number of subjects' NLF with any specific Common Treatment Response
- c** Mod = Moderate
- d** Sev = Severe
- e** One patient reported mild paresthesia on the corner of the mouth treated with RHA[®] Dynamic Volume dermal filler which resolved in 2 days

Table 4. Duration of Common Treatment Responses after initial treatment with RHA[®] Dynamic Volume and RHA[®] 4 reported in subject 30-day diary – Safety Population

CTR Duration ⁵	Group (N= 30 NLF)	1-3 Days	4-7 Days	8-14 Days	15-21 Days	22-30 Days	Last Day ⁵
		n [°] (%)					
Bruising	RHA [®] Dynamic Volume	8 (26.7%)	5 (16.7%)	16 (51.7%)	1 (3.3%)	0 (0.0%)	0 (0.0%)
	RHA [®] 4	9 (30.0%)	8 (26.7%)	13 (43.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Discoloration	RHA [®] Dynamic Volume	6 (20.0%)	5 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	RHA [®] 4	7 (23.3%)	3 (10.0%)	2 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Firmness	RHA [®] Dynamic Volume	5 (16.7%)	4 (13.3%)	9 (30.0%)	3 (10.0%)	1 (3.3%)	0 (0.0%)
	RHA [®] 4	2 (6.7%)	6 (20.0%)	6 (20.0%)	6 (20.0%)	2 (6.7%)	4 (13.3%)

	RHA [®] Dynamic Volume	5	1	1	0	0	1
		(16.7%)	(3.3%)	(3.3%)	(0.0%)	(0.0%)	(3.3%)
Itching	RHA [®] 4	4 (13.3%)	1 (3.3%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	1 (3.3%)
	RHA [®] Dynamic Volume	8 (26.7%)	2 (6.7%)	9 (30.0%)	1 (3.3%)	2 (6.7%)	1 (3.3%)
Lumps/Bumps	RHA [®] 4	5 (16.7%)	4 (13.3%)	6 (20.0%)	1 (3.3%)	1 (3.3%)	0 (0.0%)
	RHA [®] Dynamic Volume	9 (30.0%)	3 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pain	RHA [®] 4	7 (23.3%)	2 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	RHA [®] Dynamic Volume	12 (40.0%)	7 (23.3%)	2 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Redness	RHA [®] 4	13 (43.3%)	6 (20.0%)	3 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	RHA [®] Dynamic Volume	9 (30.0%)	7 (23.3%)	5 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Swelling	RHA [®] 4	10 (33.3%)	8 (26.7%)	4 (13.3%)	1 (3.3%)	0 (0.0%)	0 (0.0%)
	RHA [®] Dynamic Volume	10 (33.3%)	8 (26.7%)	4 (13.3%)	1 (3.3%)	1 (3.3%)	0 (0.0%)
Tenderness	RHA [®] 4	12 (40.0%)	8 (26.7%)	3 (10.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)
	RHA [®] Dynamic Volume	10 (33.3%)	8 (26.7%)	4 (13.3%)	1 (3.3%)	1 (3.3%)	0 (0.0%)
Others ^a	RHA [®] 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	RHA [®] Dynamic Volume	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

- a** Number of subject NLF treated with the respective device
- b** Number of subject NLF with each specific CTR by maximum duration
- c** Duration refers to number of days cited in the patient diary, irrespective of date of injection
- d** The CTR numbers indicated in the "Last Day" column are also included in the "22-30 Days" column
- e** One patient reported mild paresthesia on the corner of the mouth treated with RHA[®] Dynamic Volume dermal filler which resolved in 2 days

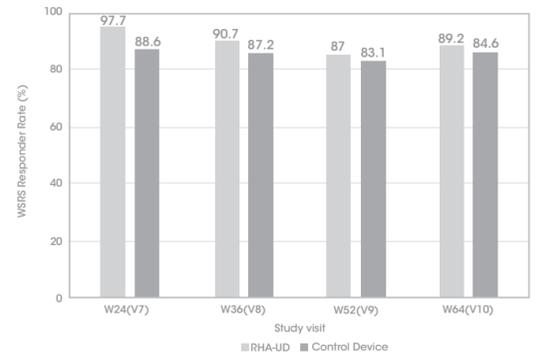
- Both RHA[®] Dynamic Volume and RHA[®] 4 treatment groups presented with very similar adverse event profiles with an overall of 5 subjects experiencing a total of 11 treatment-related AEs.
- All treatment-related AEs were mild in severity and none were considered by Investigators to be clinically significant. All events resolved spontaneously by the time of the study

c Mean NLF-Wrinkle Severity Rating Scale improvement from pre-treatment (higher scores mean more improvement from pre-treatment)

d Primary effectiveness endpoint

The results demonstrated that non-inferiority to the control was achieved for RHA[®] 4 at 24 weeks for the treatment of NLFs. Results also showed that RHA[®] 4 was non-inferior to the control treatment at all study visits. Throughout the follow-up period, the aesthetic improvement of the RHA[®] 4 treated NLF continued to be clinically significant (≥ 1 grade difference from pre-treatment on the NLF-WSRS) for more than 89% of the subjects at 64 weeks after initial treatment (Figure 1).

Figure 1. Proportion of responders on the Wrinkle Severity Rating Scale measured by a Blinded Live Evaluator for RHA[®] 4 and the Control Device



	Week 24	Week 36	Week 52	Week 64
■ RHA [®] 4	97.7%	90.7%	87.0%	89.2%
■ Control Device	88.6%	87.2%	83.1%	84.6%

PP populations of the respective follow-up visits

Rate of responders: ≥ 1 grade difference from pre-treatment on the NLF-WSRS

On the Global Aesthetic Improvement (GA) scale, (the scale included the following grades: 1-Much improved 2-Improved 3-A change 4-Worse 5-Much worse) more than 87% of the subjects and the BLE reported that the NLF treated with RHA[®] 4 was improved or very much improved from week 24 to week 64. The subjects consistently reported improvement up to 64 weeks based on the NLF module of the FACE-Q[®] questionnaire with the mean score improving from 24 to more than 70 throughout the follow-up period. More than 93% of the subjects reported to be satisfied or very satisfied from week 24 to week 64 (the scale grades were: very satisfied, satisfied, neither satisfied nor dissatisfied, dissatisfied or very dissatisfied).

More than 75% of the subjects received repeat treatment. The effectiveness and safety profiles after repeat treatment were similar to that after initial treatment.

CLINICAL STUDY OF RHA[®] DYNAMIC VOLUME INTO THE NLFs

The safety and effectiveness of the RHA[®] Dynamic Volume in the correction of moderate to severe facial wrinkles and folds were evaluated in comparison to RHA[®] 4 (lidocaine) in a US pivotal clinical study described hereafter. The purpose of this short-term clinical study was to compare RHA[®] Dynamic Volume containing mepivacaine with RHA[®] 4 containing lidocaine in terms of reducing pain during injection into the nasolabial folds. The duration of the effectiveness of the anesthetic agent (mepivacaine or lidocaine) is less than a day.

1. Pivotal Study Design

A controlled, randomized, double-blinded, within-subject (split-face), multicenter, prospective pivotal clinical study was conducted to evaluate the clinical safety and effectiveness of RHA[®] 4 (lidocaine) with the level of pain using the dermal filler RHA[®] Dynamic Volume (mepivacaine) in the treatment of nasolabial folds (NLF). Subjects were treated RHA[®] Dynamic Volume with mepivacaine in a randomly selected sequence (first or second injection) into the nasolabial fold on one side of the face and RHA[®] 4 with into the contralateral nasolabial fold. RHA[®] Dynamic Volume and RHA[®] 4 were administered into deep dermis to superficial subcutaneous tissue for the treatment of moderate to severe nasolabial folds.

The follow-up period consisted of safety and effectiveness follow-up visits one month after the initial treatment. A safety phone call visit was performed by the Treating Investigators (TI) 72 hours after the initial treatment.

2. Study Endpoints

The primary endpoint was the analysis of the non-inferiority of the injection site pain felt during injection assessed by the subject immediately following injection with RHA[®] Dynamic Volume (using a 100 mm Visual Analogue Scale – VAS) compared to the injection site pain felt during injection immediately assessed following injection with RHA[®] 4. The subject rated each side of the face independently and was blinded to which side of the face has been injected with which product. Additional pre-procedure anesthesia was prohibited.

Secondary anesthetic assessments were the pain assessment by the subject using the VAS ruler at 15, 30, 45, and 60 minutes following the injection and the duration of the anesthetic effect as assessed by the subject every hour until returning to normal sensation commencing 60 minutes post-injection.

Secondary effectiveness endpoints included change in the severity of the NLF as measured by the TI using the WSRS, the rates of responders (≥ 1-grade difference from pre-treatment on the NLF-WSRS), as measured by the TI, Global Aesthetic Improvement (GA), as assessed by the subject and by the TI, impact and effectiveness of study treatment procedures from the subjects' perspective as assessed by the nasolabial fold domain of the FACE-Q[®], and subject satisfaction.

Safety endpoints were evaluated throughout the study, with a 30-day subject diary capturing post-injection signs/symptoms following every study injection and AE assessments at each visit. Safety endpoints also included assessment of visual disturbances before and after injection and each visit.

3. Demographics

A total of 30 subjects (33 to 79 years old) were enrolled and randomized, these 30 subjects were included in the intent-to-treat (ITT) population (and per protocol (PP) population). Subjects' demographics are presented in Table 9.

Table 9. Demographics

Number / % of subjects	RHA [®] Dynamic Volume versus RHA [®] 4 N=30	
Age		
Mean (SD)	57	(9.7)
min max	33	79
Gender		
Female	27	90.0%
Male	3	10.0%

Race			
Caucasian	27	90.0%	
Black	3	10.0%	
Am. Indian/N. Alask.	0	0.0%	
N. Hawaiian/P. Isl.	0	0.0%	
Asian	0	0.0%	
Other	0	0.0%	
Ethnicity			
Hispanic/Latino	12	40.0%	
Not Hispanic/Latino	18	60.0%	
Fitzpatrick Skin Phototype			
I	1	3.3%	
II	8	26.7%	
III	10	33.3%	
IV	8	26.7%	
V	0	0.0%	
VI	3	10.0%	

a Number of subjects in the ITT population

4. Treatment Characteristics

The study protocol allowed a maximum of 3.0 ml in a single NLF per treatment session. The average volume injected into a single NLF was nearly identical between treatment groups with volumes of 1.09 ml and 1.08 ml in the RHA[®] Dynamic Volume and RHA[®] 4 groups, respectively. The total volume to achieve optimal correction result (OCR) is the sum of both groups, as it was a split face study.

In general, a linear threading, fan-like technique, or a combination of linear threading with multiple punctate pools, was used for 96.6% of the subjects treated with RHA[®] Dynamic Volume.

5. Effectiveness Results

The primary effectiveness endpoint was met for RHA[®] Dynamic Volume.

The levels of pain felt by the subject during injection with RHA[®] Dynamic Volume (with mepivacaine) and RHA[®] 4 (with lidocaine) were 17.1 mm and 16.3 mm, respectively, as measured using the VAS. This resulted in a non-significant difference between groups of -0.8 (p-value <0.0001).

For both treatment groups, the level of pain decreased over time with no statistically significant difference of all time points (at 15, 30, 45, and 60 minutes post-injection). The injection pain was reduced to 4.9 mm for RHA[®] Dynamic Volume and 5.1 mm for RHA[®] 4 after 15 minutes and almost gone after 60 minutes post-injection.

Finally, the duration of anesthetic effect was also reported by the subject to be similar between treatment groups, lasting around 6 hours for the side treated with RHA[®] Dynamic Volume (with mepivacaine) and 4 hours for the side treated with RHA[®] 4 (with lidocaine).

Results are presented in Table 10 and Table 11.

Table 10. Injection Site Pain during injection – PP population

VAS pain (mm)	RHA [®] Dynamic Volume N=30	RHA [®] 4 N=30	VAS Difference (mm) N=30
Mean (SD)	17.1 (18.38)	16.3 (18.89)	-0.8 (8.09)
Min, Max	0, 55	0, 70	-20, 20

a Number of subjects in the PP population

Table 11. Injection Site Pain after injection – ITT population

VAS pain (mm)	RHA [®] Dynamic Volume N=30	RHA [®] 4 N=30	VAS Difference (mm) N=30
Time point:			
- 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)
- 60 Min	0.0 (0.00)	1.9 (10.22)	1.9 (10.22)

a Number of subjects in the ITT population

Secondary endpoints demonstrated no difference between RHA[®] Dynamic Volume and RHA[®] 4 regarding clinical performance.

A similar improvement in the NLF-WSRS scores was observed one month post-injection, with a score improvement of 1.9 points in the RHA[®] Dynamic Volume treatment group and 1.8 points in the RHA[®] 4 treatment group.

Responder rate was similar for both treatment groups after the injection, with 100% of treated subjects, and 100% with RHA[®] Dynamic Volume versus 96.7% with RHA[®] 4 at one-month post-injection.

On GA scale, RHA[®] Dynamic Volume and RHA[®] 4 demonstrated nearly identical GA scores as assessed by both TIs and subjects. More than 96% of the subjects were deemed by the TI to have their NLFs treated improved or very much improved at one-month post-injection. 100% of the subjects reported having their NLFs treated improved or very much improved.

The subjects also reported similar improvement based on the NLF module of the FACE-Q[®] questionnaire with the mean score increasing by 63.8 and 64.2 points in the RHA[®] Dynamic Volume and RHA[®] 4 treatment groups, respectively.

More than 96% of the subjects reported being satisfied or very satisfied one month after their treatment with no distinction between the treatment groups.

Similar effectiveness and safety profiles were observed by Fitzpatrick skin type, ethnicity and age groups. Results of RHA[®] 4 long term safety and effectiveness are applicable to RHA[®] Dynamic Volume.

Pivotal STUDY of RHA[®] 4 for midface volume deficiency

RHA[®] Dynamic Volume is strictly identical to RHA[®] 4 except for the small amount of anesthetic medicine: RHA[®] Dynamic Volume contains mepivacaine and RHA[®] 4 contains lidocaine. Both anesthetics agents are of the same family with the same mechanisms of effect. RHA[®] Dynamic Volume and RHA[®] 4 have the same indication. The long-term safety and effectiveness of RHA[®] Dynamic Volume were evaluated in a clinical study using RHA[®] 4.

The long-term safety and effectiveness of RHA[®] 4 for the treatment of midface volume deficiency was evaluated in a US pivotal clinical study described hereafter.

1. Pivotal Study Design

A controlled, randomized, double-blinded, between-subject, multicenter, prospective pivotal clinical study was conducted to evaluate the clinical safety and effectiveness of RHA[®] 4 for cheek augmentation and/or correction of age-related midface contour deficiency.

A total of 201 subjects were randomized and underwent treatment with either RHA[®] 4 (N = 152) or Control treatment (N = 49) in the midface area for cheek augmentation and/or correction of age-related midface contour deficiencies. Injection was performed with a needle and/or cannula. If deemed necessary to achieve optimal correction, additional midface correction was performed after 4 weeks (touch-up), with the same study device used for initial treatment.

The follow-up period consisted of safety and effectiveness follow-up visits at 2, 4, 8, 16, 24, 36, and 52 weeks after the last treatment.

Subjects were eligible for optional retreatment if necessary, after Weeks 52, and were then followed for 3 months after retreatment or until all Adverse Events (AEs) resolved or TI determined that follow-up was no longer necessary. Retreatments were provided using RHA[®] 4 (the Control device was not used).

2. Study Endpoints

The primary effectiveness endpoint was the analysis of non-inferiority of RHA[®] 4 versus Control in terms of change from Baseline (pre-injection) 8 weeks after injection, as measured by a Blinded Live Evaluator (BLE) using the proprietary and validated 5-grade Teoxane Midface Volume Deficit Scale (TMVDS). Secondary effectiveness endpoints included TMVDS change from Baseline and rates of responders, as assessed by the BLE at each study visits (see data in Table 13 and Figure 2), Global Aesthetic Improvement (GA), as assessed by the subject, TI and BLE, impact and effectiveness of study treatment procedures from the subjects' perspective as

assessed by the satisfaction with cheeks module (at rest and when smiling) of the FACE-Q[®], and subject satisfaction. Safety endpoints were evaluated throughout the study, with a 30-day subject diary capturing post-injection signs/symptoms following every study injection, and AE assessments at each visit, and included self-assessment of injection site pain by the subject using a 100mm Visual Analogue Scale.

3. Demographics

A total of 201 subjects (24 to 79 years old) were enrolled and included in the ITT and the Safety population, with 152 subjects allocated to RHA[®] 4 treatment, and 49 allocated to the Control treatment. Subjects' demographics are presented in Table 12.

Table 12. Demographics

Number / % of subjects	RHA [®] 4 N=152	Control N=49	Total N=201
Age			
Mean (SD)	55.4 (9.97)	55.6 (7.85)	55.5 (9.48)
min max	24, 79	34, 68	24, 79
Gender			
Female	134 (88.2%)	46 (93.9%)	180 (89.6%)
Male	18 (11.8%)	3 (6.1%)	21 (10.4%)
Race^a			
Am. Indian/N. Alask.	0	1 (2.1%)	1 (0.5%)
Asian	3 (2.0%)	0	3 (1.5%)
Black or African American	19 (12.5%)	6 (12.5%)	25 (12.5%)
White	132 (86.8%)	42 (87.5%)	174 (87.0%)
Ethnicity			
Hispanic/Latino	31 (20.4%)	9 (18.4%)	40 (19.9%)
Not Hispanic/Latino	120 (78.9%)	39 (79.6%)	159 (79.1%)
Not available	1 (0.7%)	1 (2.0%)	2 (1.0%)
Fitzpatrick Skin Phototype			
I-III	107 (70.4%)	36 (73.5%)	143 (71.1%)
I	5 (3.3%)	0	5 (2.5%)
II	40 (26.3%)	15 (30.6%)	55 (27.4%)
III	62 (40.8%)	21 (42.9%)	83 (41.3%)
IV-VI	45 (29.6%)	13 (26.5%)	58 (28.9%)
IV	23 (15.1%)	7 (14.3%)	30 (14.9%)
V	14 (9.2%)	4 (8.2%)	18 (9.0%)
VI	8 (5.3%)	2 (4.1%)	10 (5.0%)

a Number of subjects in the ITT/Safety populations

b a subject can be counted in several categories

4. Treatment Characteristics

The study protocol allowed a maximum of 6 mL at each treatment session, with a maximum of 3 mL per cheek per treatment session. The overall total median volume of RHA[®] 4 injected to achieve optimal correction (initial + touch-up) was 3.50 mL. Injection volumes into the cheeks tended to be lower after retreatment, with total median injection volume being 1.30 mL after retreatment. Similar injection volumes were used in subjects treated with the Control device to achieve OCR. However, after retreatment, the median injection volume for the group initially treated with RHA4 was 1.30 mL while subjects who were initially treated with the Control treatment received 2.30 mL. The proportion of subjects who received touch-up treatment at Week 4 was lower with RHA[®] 4 (63.2%) than with Control treatment (83.7%).

In general, cannula only or combination of cannula + needle was the preferred injection method in both treatment groups. Multilayering technique (i.e., both subcutaneous and supraperiosteal injection depths) were used in 75% of subjects in RHA[®] 4 group and 73.5% in Control group.

5. Effectiveness Results

The primary effectiveness endpoint was met for RHA[®] 4. The primary effectiveness endpoint was the volume improvement of the cheeks treated with RHA[®] 4 from pre-injection compared to the improvement from pre-injection of the cheeks treated with the Control treatment, using the TMVDS, as assessed by the BLE at 8 weeks; results are presented in Table 13.

Table 13. Effectiveness results through 1 year as assessed by the BLE/Mean TMVDS change from Baseline (SD)

	RHA [®] 4	Control
Week 8^a	-1.3 (0.78)	-1.3 (0.63)
Week 16	-1.2 (0.83)	-1.3 (0.75)
Week 24	-1.1 (0.79)	-1.0 (0.76)
Week 36	-0.9 (0.81)	-0.9 (0.66)
Week 52	-0.9 (0.79)	-0.8 (0.69)

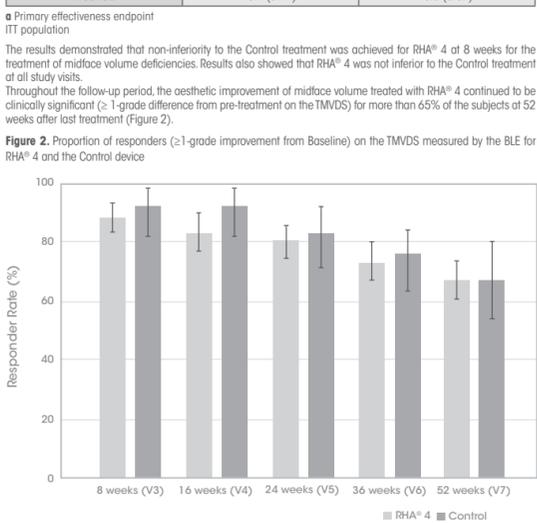
a Primary effectiveness endpoint

ITT population

The results demonstrated that non-inferiority to the Control treatment was achieved for RHA[®] 4 at 8 weeks for the treatment of midface volume deficiencies. Results also showed that RHA[®] 4 was not inferior to the Control treatment at all study visits.

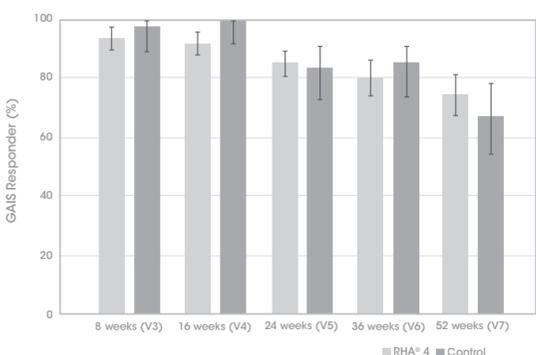
Throughout the follow-up period, the aesthetic improvement of midface volume treated with RHA[®] 4 continued to be clinically significant (≥ 1-grade difference from pre-treatment on the TMVDS) for more than 65% of the subjects at 52 weeks after last treatment (Figure 2).

Figure 2. Proportion of responders (≥1-grade improvement from Baseline) on the TMVDS measured by the BLE for RHA[®] 4 and the Control device



On the Global Aesthetic Improvement (GA) scale, more than 75% of the subjects and the BLE reported that the cheeks treated with RHA[®] 4 were improved or very much improved from week 8 to week 52. GAIS responder rate was similar between RHA[®] 4 and Control treatment as assessed by BLE from Week 8 to Week 52 (Figure 3).

Figure 3. GAIS responder rate (improved or very much improved) through 1 year as assessed by the BLE



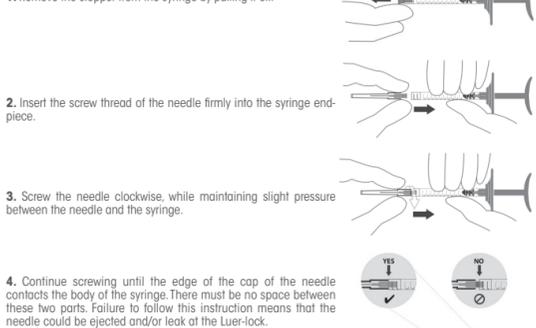
The subjects treated with RHA[®] 4 consistently reported improvement up to 52 weeks based on the Satisfaction with cheeks module, at rest and when smiling, of the FACE-Q[®] questionnaire with the mean score improving from Baseline by 53 and 56 points at Week 8, respectively, to more than 38 points throughout the follow-up period. RHA[®] 4 demonstrated durability throughout the study with a slow decline over time.

More than 89% of the subjects reported to be satisfied or very satisfied 8 weeks after treatment and the rate of satisfaction remained at more than 82% at 52 weeks (the scale grades were: very satisfied, satisfied, neither satisfied nor dissatisfied, dissatisfied, or very dissatisfied).

Repeat treatment with RHA[®] 4 only, irrespective of their initial group assignment, was provided to 50.7% and 59.2% of subjects initially assigned to the RHA[®] 4 and Control treatment groups, respectively, at the end of the study. The effectiveness and safety profiles after repeat treatment were similar to that after initial treatment and touch-up treatments.

DIRECTIONS FOR ASSEMBLY OF THE NEEDLE TO THE SYRINGE

1. Remove the stopper from the syringe by pulling it off.



5. Remove the needle's protective cap by pulling it firmly with one hand while holding the body of the syringe with the other.

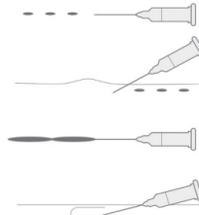
PRE-TREATMENT GUIDELINES

- Prior to treatment, the patient should avoid taking medications or supplements which thin the blood (e.g., aspirin, nonsteroidal anti-inflammatory medications, St. John's Wort, or high doses of Vitamin E supplements) as these agents may increase bruising and bleeding at the injection site.
- Before starting treatment, a complete medical history should be taken from the patient and the patient should be counseled on appropriate indications, risks, and should be informed about the expected treatment results, and expected responses. The patient should be advised of the necessary precautions before commencing the procedure.
- Prior to treatment with RHA[®] Dynamic Volume the patient should be assessed for appropriate anesthetic treatment for managing comfort (e.g., topical anesthetic, local or nerve block). The patient's face should be washed with soap and water and dried with a clean towel. Cleanse the area to be treated with alcohol or another suitable antiseptic solution.
- Sterile gloves are recommended while injecting RHA[®] Dynamic Volume.
- Before injecting, prime the needle by carefully pressing the syringe plunger until a small droplet of the gel is visible at the tip of the needle.

INJECTION TECHNIQUES

- RHA[®] Dynamic Volume is administered for injection into dynamic facial wrinkles and folds by using a thin gauge needle (27 G x ½") or a blunt lip cannula (25 G x 2"). RHA[®] 4 is supplied with 27 G x ½" needles. The TSK STERIGLIDE[™] cannulas were used in the clinical trials and are recommended for use with RHA[®] Dynamic Volume.
- RHA[®] Dynamic Volume is administered for injection for midface volume deficiency using a thin gauge needle (27 G x ½") or a blunt lip cannula (25 G x 2"). The TSK STERIGLIDE[™] cannula was used in the clinical trials and is recommended for use with RHA[®] Dynamic Volume.

- When using a needle, the needle is inserted into the deep dermis to superficial subcutaneous on an approximate angle of 15° to 30° parallel to the length of the wrinkle or fold.
- When injecting into supraperiosteal layer with a needle the needle is inserted bevel down with an angle of 90° to the skin surface until touching the bone.
- When using a cannula, an entry point is made in the skin with the provided pre-hole needle.
- RHA[®] Dynamic Volume can be injected by a number of different techniques that depend on the injector's experience and preference, treated area, and patient characteristics.



Code : 230695/01	VERSION	COULEURS
PRODUIT : IFU_RHA Dynamic Volume	INITIALES : AB - PICTURAL MB	RECTO/VERSO
PAYS : USA	VERSIONS - DATE : 1 - 16/06/25 - 15h 2 - 16/06/25 - 09h30 3 - 08/10/25 - 11h00 4 - 13/10/25 - 15h55	 NOIR
Format ouvert : 630 mm (L) x 280 mm (H) +/- 1 mm Format plié : 280 mm x 45.75 mm +/- 0.7 mm – la notice ne doit pas dépasser 46.5 mm		
Texte : corps = 5,5 pts	ANNULE ET REMPLACE : 230695/00 (AC-21-009)	