

# 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 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 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".

- 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.

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 of 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.

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 responders ( $\geq 1$  grade difference from pre-treatment on the PR-SRS) at 8 weeks after injection, as measured by the Blinded Live Evaluation (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, T1 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 IT 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
<b>Age</b>		
Mean (SD)	61.6 (7.2)	60 (7.6)
min max	38-81	46-77
<b>Gender</b>		
Female	98.0%	51 (98.1%)
Male	2.0%	1 (1.9%)
<b>Race</b>		
White	95.3%	52 (100%)
Black or African American	2.7%	0 (0.0%)
Am. Indian/N. Alask.	0.7%	0 (0.0%)
N. Hawaiian/P. Isl.	0.0%	0 (0.0%)
Asian	1.3%	0 (0.0%)
Other	0.0%	0 (0.0%)
<b>Ethnicity</b>		
Hispanic/Latino	16.7%	10 (19.2%)
Non-Hispanic/Latino	83.3%	42 (80.8%)
<b>Fitzpatrick Skin Phototype</b>		
I-III	147 (72.8%)	
I	18	12.0%
II	37	24.7%
III	55	36.7%
IV-VI	55 (27.2%)	
IV	29	19.3%
V	8	5.3%
VI	3	2.0%

<sup>a</sup> 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%.

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

Common Treatment Responses

RHA® Redensity (N=199)

Duration<sup>a</sup>

1-3 Days

4-7 Days

8-14 Days

Last Day<sup>b</sup>

Redness

78 (39.2%)

35 (17.6%)

18 (9.0%)

8 (4.0%)

Pain

38 (19.1%)

10 (5.0%)

6 (3.0%)

(0.5%)

Tenderness

55 (27.6%)

29 (14.6%)

21 (10.6%)

10 (5.0%)

(5.0%)

Firmness

63 (31.7%)

24 (12.1%)

28 (14.1%)

18 (9.0%)

(9.0%)

Swelling

72 (36.2%)

40 (20.1%)

34 (17.1%)

10 (5.0%)

(5.0%)

Lumps/Bumps

53 (26.6%)

29 (14.6%)

33 (16.6%)

26 (13.1%)

(13.1%)

Bruising

30 (15.1%)

64 (32.2%)

60 (30.2%)

15 (7.5%)

(7.5%)

Itching

21 (10.6%)

8 (4.0%)

2 (1.0%)

(1.5%)

Discoloration

39 (19.6%)

34 (17.1%)

21 (10.6%)

5 (2.5%)

(2.5%)

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  $\geq 1$ -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  $\geq 70\%$  and; 3) the difference between the responder rate for subjects treated with RHA® Redensity and the No-Treatment group must be  $\geq 50$  points. The proportion of responders, showing  $\geq 1$ -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 <sup>a</sup>
Week 8	N <sup>b</sup>	150	51
	Responder	121 (80.7%)	4 (7.8%)
	Not responder	29 (19.3%)	47 (92.2%)
	Missing values	0	0

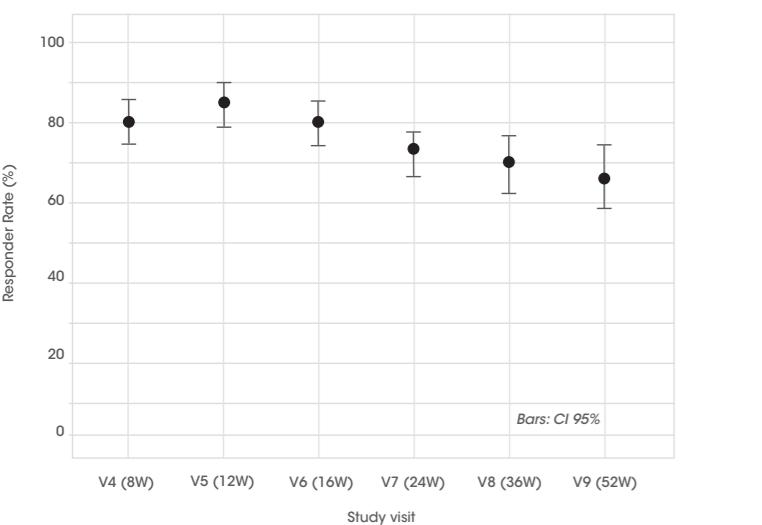
<sup>a</sup> ITT population – BLE assessment – Last Observation Carried Forward (LOCF)

<sup>b</sup> 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 ( $\geq 1$  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:  $\geq 1$  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.

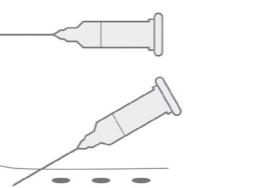
Before injecting, prime the needle by carefully pressing the syringe plunger until a small droplet of the gel is visible at the tip of the needle.

## INJECTION TECHNIQUES

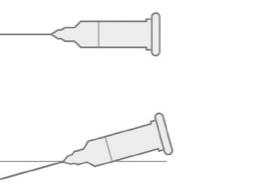
RHA® Redensity can be administered by using a thin gauge needle (30 G x  $\frac{1}{2}$ ") and with a number of different techniques that depend on the injector's experience and preference, and patient characteristics.

**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

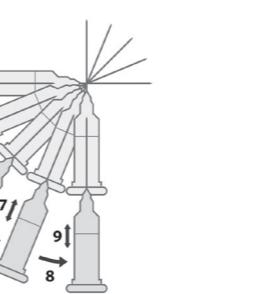
result in more discomfort for the patient due to the number of punctures.



**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.

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 occurs 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  $\frac{1}{2}$ " 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.

## 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.

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  
1222 Demonbrun Street,  
Suite 2000  
Nashville, Tennessee 37203  
(Switzerland)

Distributed by:

Revance Therapeutics, Inc.  
1222 Demonbrun Street,  
Suite 2000  
Nashville, Tennessee 37203  
(Switzerland)

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 ; 9,558,322.

## 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 license practitioner

# TEOXANE

## 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 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.

- As with all transcutaneous procedures, dermal filler implantation carries a risk of infection. Standard precautions associated with injectable materials should be followed.
- 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 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".
- 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.

<sup>a</sup> Number of subject NLF treated with the respective device

<sup>b</sup> Number of subject NLF with each specific CTR by maximum duration

<sup>c</sup> Duration refers to number of days cited in the patient diary, irrespective of date of injection

<sup>d</sup> The CTR numbers indicated in the "Last Day" column are also included in the "8-14 Days" column.

**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 <sup>a</sup>	1-3 Days	4-7 Days	8-14 Days	Last Day <sup>a</sup>
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%	12 16.7%	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%	2 2.8%	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%	20 28.0%	8 11.1%	5 7.1%
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%

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.

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%

<sup>a</sup> Number of subjects in the ITT populations

### 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. Retreatment 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.

#### 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

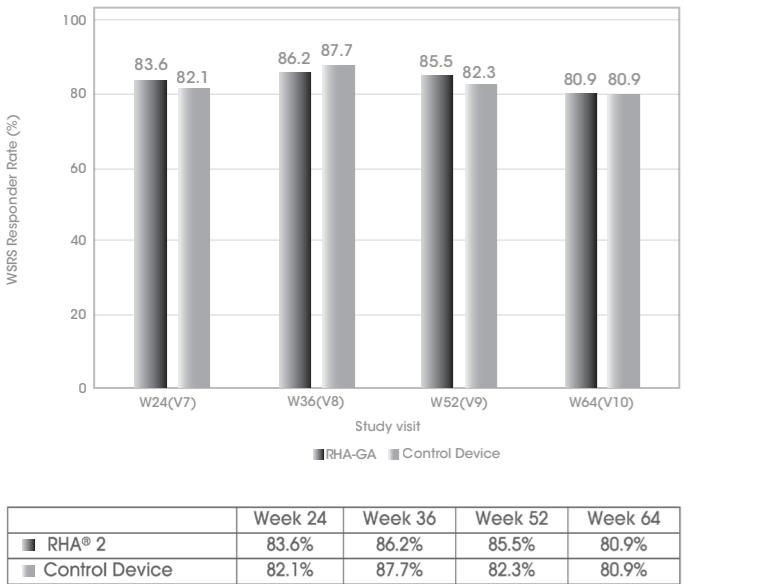
The primary effectiveness endpoint was met for RHA® 2. The primary effectiveness endpoint was the aesthetic improvement from pre-injection of the NLF treated with RHA® 2 compared to the improvement from pre-injection of the NLF treated with the control treatment, as assessed (using the WSRS) by the BLE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

**Table 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 <sup>b</sup> n %	Mild n %	Mod <sup>c</sup> n %	Sev <sup>d</sup> n %	Mild n %	Mod <sup>c</sup> n %	Sev <sup>d</sup> 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%	19.4% 11.1%	14 16.7%	8 10.8%
Firmness	46 63.9%	48 66.7%	23 31.9%	20 27.8%	3 4.2%	27 37.5%	20 26.4%	1 1.4%
Itching	12 16.7%	15 20.8%	9 12.5%	4 5.6%	0 0%	10 13.9%	4 5.6%	1 1.4%
Lumps/Bumps	38 5							

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 ( $\geq 1$  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



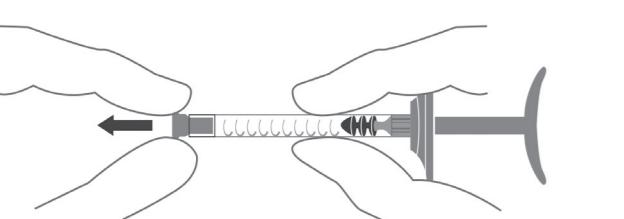
PP populations at the respective follow-up visits  
Rate of responders:  $\geq 1$  grade difference from pre-treatment on the WSRS

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.

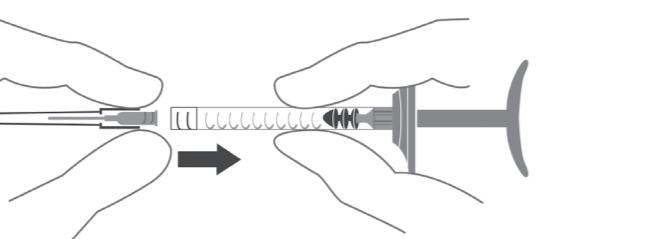
More than 78% of the subjects received repeat treatment. The effectiveness and safety profiles after repeat treatment were similar to that after initial treatment.

## DIRECTIONS FOR ASSEMBLY OF THE NEEDLE TO THE SYRINGE

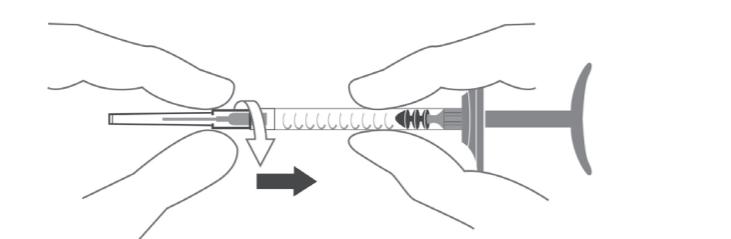
1. Remove the stopper from the syringe by pulling it off.



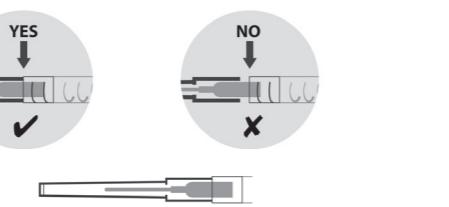
2. Insert the screw thread of the needle firmly into the syringe end-piece.



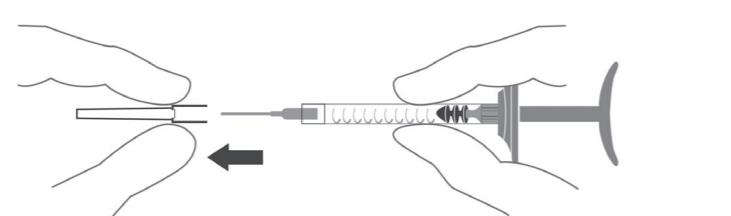
3. Screw the needle clockwise, while maintaining slight pressure between the needle and the syringe.



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.

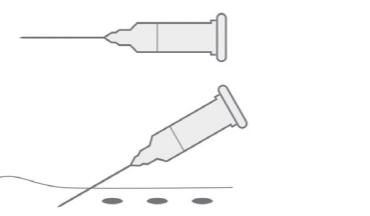
- Sterile gloves are recommended while injecting RHA® 2.
- Before injecting, prime the needle by carefully pressing the syringe plunger until a small droplet of the gel is visible at the tip of the needle.

## INJECTION TECHNIQUES

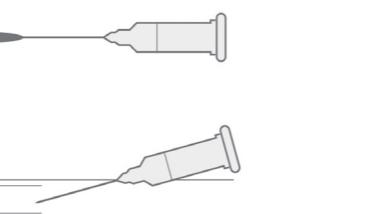
- RHA® 2 is administered by using a thin gauge needle (30 G x  $\frac{1}{2}$ "). The needle is inserted into the mid-to-deep dermis at an approximate angle of 15° to 30° parallel to the length of the wrinkle or fold.

- RHA® 2 can be injected by a number of different techniques that depend on the injector's experience and preference, and patient characteristics.

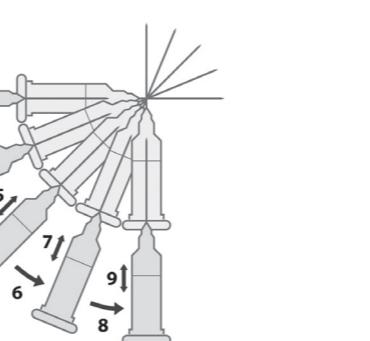
**A. Serial puncture:** consists of multiple injections, evenly and closely spaced all along wrinkles or folds. This technique is considered to be more precise, but may result in more discomfort for the patient due to the number of punctures.



**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).



## PATIENT INSTRUCTIONS

Patient information brochure is available on request, or via the website [www.teoxane.com](http://www.teoxane.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](mailto:Medical-us@teoxane.com)

## 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

## HOW SUPPLIED

RHA® 2 is supplied in individual blisters containing a 1ml treatment syringe with two 30 G x  $\frac{1}{2}$ " 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.

## 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.

RxOnly

# 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 wrinkles and folds, such as nasolabial folds (NLFs), in adults aged 22 years or older.

RHA® 3 is indicated for injection into the vermillion body, vermillion 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:
  - 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 ischemic 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.
- 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 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 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:

- 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.

#### 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.

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.

The most frequent 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 <sup>a</sup> n%	Mild n%	Mod <sup>b</sup> n%	Sev <sup>c</sup> n%	Mild n%	Mod <sup>b</sup> n%	Sev <sup>c</sup> 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%	8.0%	29.3%	28.0%	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%

<sup>a</sup> Number of subjects' NLF treated with the respective device

<sup>b</sup> Number of subjects' NLF with any specific Common Treatment Response

<sup>c</sup> CTRL = Control treatment

<sup>d</sup> Mod = Moderate

<sup>e</sup> 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%			Control Device (N=75 NLF) n%		
	1-3 Days	4-7 Days	8-14 Days	1-3 Days	4-7 Days	8-14 Days
Duration <sup>a</sup>	11	19	12	4	11	16
	14.7%	25.3%	16.0%	5.3%	14.7%	21.3%

Discoloration	10	6	6	4	13	5	4	3
	13.3%	8.0%	8.0%	5.3%	17.3%	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%	
Lumps/Bumps	22	7	14	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	2	27	10	5	2	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%

- Number of subjects' Lips treated with the respective device
- Number of subjects' Lips with any specific Common Treatment Response
- Mod = Moderate
- 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<sup>c</sup>	Group (N= subjects)	1-3 Days n%		4-7 Days n%		8-14 Days n%		15-30 Days n%		Last Day<sup>d</sup> n%	
1-3 Days	n%	4-7 Days	n%	8-14 Days	n%	15-30 Days	n%	Last Day	n%		

</tbl

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® 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 of 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 if determined 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  $\geq 1$ -grade point increase on the TLFS at 12 weeks when compared to pre-treatment, which should be  $\geq 70\%$ .

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 FST 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)	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 American	15 (9.8%)	2 (4.1%)	17 (8.4%)
N. Hawaiian/P. Isl. White	2 (1.3%)	0	2 (1.0%)
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			
I-III	114 (74.5%)	35 (71.5%)	149 (73.8%)
I	10 (6.5%)	7 (14.3%)	17 (8.4%)
II	46 (30.1%)	9 (18.4%)	55 (27.2%)
III	58 (37.9%)	19 (38.8%)	77 (38.2%)
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%)

<sup>a</sup> 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 $\pm$ 0.64 ml. Injection volumes into the lips tended to be lower after retreatment, with total mean injection volume being 1.03 $\pm$ 0.45 ml after retreatment. Similar mean injection volumes were used in subjects treated with the control device: 1.95 $\pm$ 0.73 ml to achieve OCR and 1.03 $\pm$ 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 of Baseline 1, 2 and/or 3.

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. GAI through 1 year as assessed by the BLE

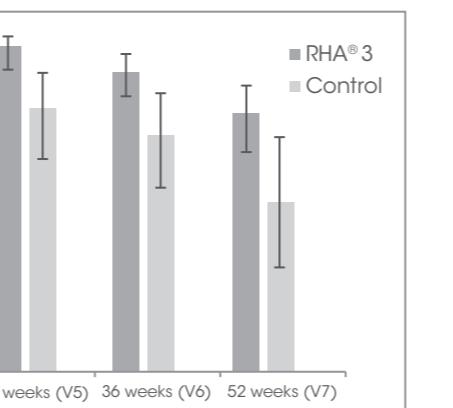


Table 8. TLFS Grade Change from Baseline as assessed by the BLE

	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 <sup>a,b</sup>	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)

<sup>a</sup> Primary effectiveness endpoint

<sup>b</sup> Estimate of difference in means RHA® 3 – control is 0.19 (-0.03, -0.42) calculated by Bootstrap estimate using 1000 samples. mITT population

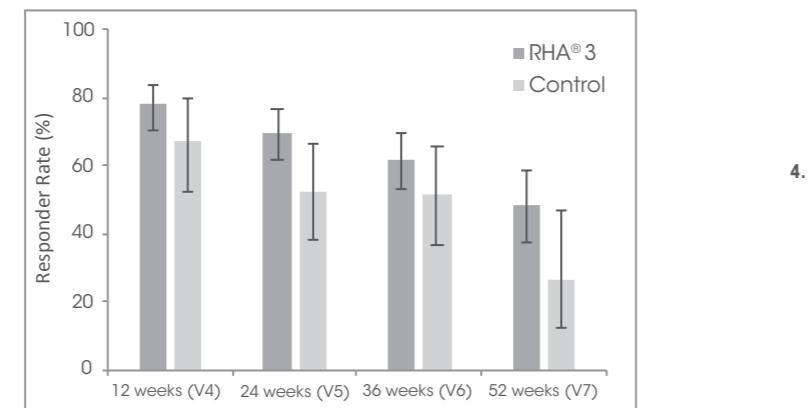
Table 9. TLFS responder rate (BLE) at Week 12 – mITT Population

	RHA® 3	Control
<b>Baseline TLFS grades 1, 2 &amp; 3</b>		
N	137	44
# of responders (%) [95% CI]	107 (78.1%) [70.5 - 84.2%]	29 (65.9%) [51.1 - 78.1%]
<b>Baseline TLFS grades 1 &amp; 2</b>		
N	68	27
# of responders (%) [95% CI]	64 (94.1%) [85.8-97.7%]	24 (88.9%) [71.9-96.1%]
<b>Baseline TLFS grade 3</b>		
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 ( $\geq 1$  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



<sup>a</sup> 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 $\pm$ 0.64 ml. Injection volumes into the lips tended to be lower after retreatment, with total mean injection volume being 1.03 $\pm$ 0.45 ml after retreatment. Similar mean injection volumes were used in subjects treated with the control device: 1.95 $\pm$ 0.73 ml to achieve OCR and 1.03 $\pm$ 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).

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



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.

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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 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.

#### 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, any 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

# 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 (BDDG) 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 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, 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 (Softfil® 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 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/blunt cannula attachment instructions could result in needle/blunt cannula disengagement and/or product leakage of 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).

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

### 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.

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 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".

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.

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.

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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 (d) 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.

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

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

<sup>a</sup> 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

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

<sup>a</sup> Number of subjects in the PP populations

<sup>b</sup> Mean Wrinkle Severity Rating Scale score (higher scores mean deepest wrinkles)

<sup>c</sup> Mean Wrinkle Severity Rating Scale improvement from pre-treatment (higher scores mean more improvement from pre-treatment)

<sup>d</sup> Primary effectiveness endpoint

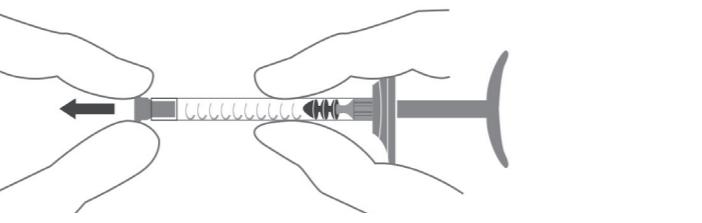
The aesthetic improvement of the RHA® 4 treated NLF with a cannula was similar to the one of the RHA® 4 treated NLF with a needle. These similar improvements were clinically significant ( $\geq 1$  grade difference from pre-treatment on the NLF-WSRS) for 94% of the subjects at 12 weeks after initial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

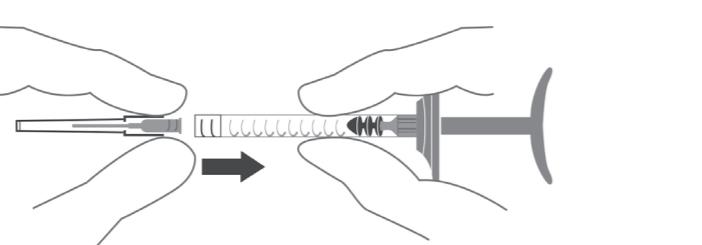
There were no differences in term of effectiveness and safety profiles between cannula brands were observed. Similar effectiveness and safety profiles were observed by age group.

## DIRECTIONS FOR ASSEMBLY OF THE NEEDLE TO THE SYRINGE

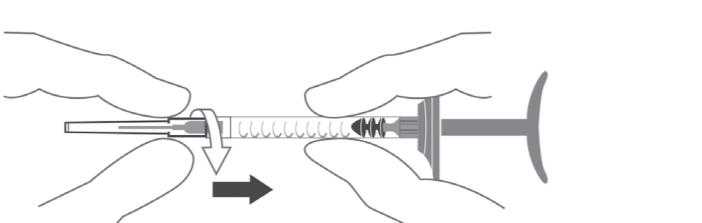
### 1. Remove the stopper from the syringe by pulling it off.



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



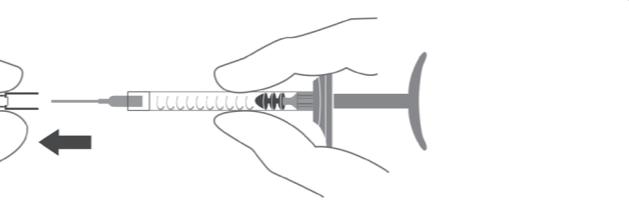
### 3. Screw the needle clockwise, while maintaining slight pressure between the needle and the syringe.



## 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.

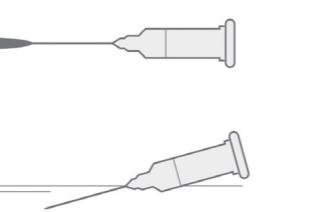
## INJECTION TECHNIQUES

- 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 Softfil® 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.

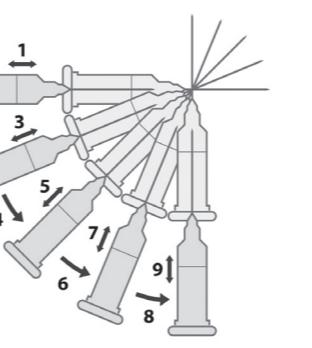
**A. Serial puncture:** (only recommended for needle): consists of multiple injections, evenly and closely spaced all along wrinkles or folds. This technique is considered to be more precise, but may result in more discomfort for the patient due to the number of punctures.



## 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 (regrograde) or pushing (antegrade) the needle/cannula.

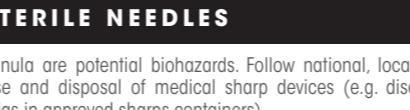


## C. Fanning technique: the needle/cannula is introduced as for the Linear threading technique, and the product is injected along several closely spaced lines, by changing the direction of the needle/cannula, all using the same puncture site (the needle/cannula is not withdrawn).



## 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 cannulae are potential biohazards. Follow national, local, or institutional guidelines for use and disposal of medical sharp devices (e.g. discard uncapped needles and cannulae 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/cannulae 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/cannulae. 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 of 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 Demonbreu Street,  
Suite 2000  
Nashville, Tennessee 37203

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

TEOXANE

# TEOXANE

## 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 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.
- 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 dynamic perioral rhytids. This safety information from this study apply to both RHA® Redensity Mepi and RHA® Redensity, and are summarized below **"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.

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 of 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.

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%)

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 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	RHA® Redensity (N=199)					
	1-3 Days n° (%)	4-7 Days n° (%)	8-14 Days n° (%)	Last Day <sup>a</sup> 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%)	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%)		

<sup>a</sup> Number of subjects' who provided diary answers after V1/1b

<sup>b</sup> Number of subjects' perioral rhytids with any specific Common Treatment Response

<sup>c</sup> Mod = Moderate

<sup>d</sup> Sev = Severe

**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

<sup>a</sup>

<sup>b</sup>

<sup>c</sup>

<sup>d</sup>

<sup>e</sup>

<sup>f</sup>

<sup>g</sup>

<sup>h</sup>

<sup>i</sup>

<sup>j</sup>

<sup>k</sup>

<sup>l</sup>

<sup>m</sup>

<sup>n</sup>

<sup>o</sup>

<sup>p</sup>

<sup>q</sup>

<sup>r</sup>

<sup>s</sup>

<sup>t</sup>

<sup>u</sup>

<sup>v</sup>

<sup>w</sup>

<sup>x</sup>

<sup>y</sup>

<sup>z</sup>

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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; 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

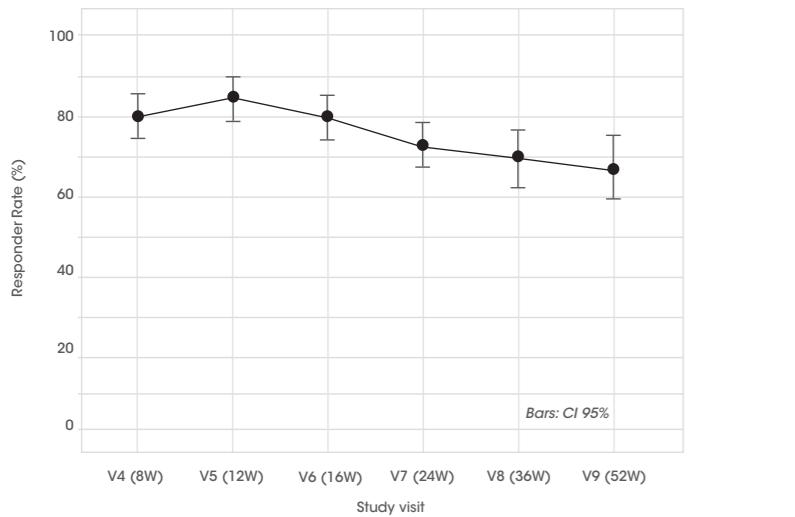
PR-SRS Responder Rate (BLE)	RHA® Redensity	No-Treatment	P-value *
Week 8	N=150	51	
Responder	121 (80.7%)	4 (7.8%)	<0.0001
Not responder	29 (19.3%)	47 (92.2%)	
Missing values	0	0	

\* ITT population – BLE assessment – Last Observation Carried Forward (LOCF)

† 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% of 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 MEDI

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 US 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 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, the rates of responders (≥ 1-grade difference from pre-treatment on 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 nasal/oblique fold domain of the FACE-Q®, and subject satisfaction.

**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	64.3 (8.2)
Mean (SD)	48
min max	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%
Fitpatrick 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%

\* 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 punctate 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

\* 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)

\* 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.

\* 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 1/2") 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.

\* 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.

## 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

# 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 resterilize.
- 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. 877-373-8669.
- 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.
- 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 <sup>c</sup> n° (%)	Mild n° (%)	Mod <sup>d</sup> n° (%)	Sev <sup>e</sup> n° (%)	Mild n° (%)	Mod <sup>d</sup> n° (%)	Sev <sup>e</sup> 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 (9.7%)	7 (9.6%)	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%)	4 (2.0%)	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%)	30 (6.6%)	18 (1.1%)	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%)	15 (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%)

- 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® 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 <sup>f</sup>	
Bruising	19 (63.3%)	21 (70.0%)	7 (23.3%)	12 (40.0%)	0 (0%)
Discoloration	11 (36.7%)	12 (40.0%)	8 (26.7%)	2 (6.7%)	1 (3.3%)
Firmness	24 (80.0%)	22 (73.3%)	12 (40.0%)	10 (33.3%)	9 (30.0%)
Itching	7 (23.3%)	6 (20.0%)	3 (12.5%)	0 (0.0%)	0 (0.0%)
Lumps/ Bumps	22 (73.3%)	21 (70.0%)	10 (33.3%)	11 (36.7%)	8 (33.3%)
Pain	12 (40.0%)	9 (30.0%)	10 (33.3%)	11 (36.7%)	0 (0%)
Redness	21 (70.0%)	20 (66.7%)	12 (40.0%)	6 (20.0%)	3 (10.0%)
Swelling	21 (70.0%)	23 (67.7%)	11 (36.7%)	9 (30.0%)	4 (14.3%)
Tenderness	24 (80.0%)	24 (80.0%)	16 (53.3%)	8 (26.7%)	0 (0.0%)
Others <sup>g</sup>	1 (3.3%)	0 (0.0%)	1 (3.3%)	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

<sup>f</sup> One patient reported mild paresthesia on the corner of the mouth treated with RHA® Mepi

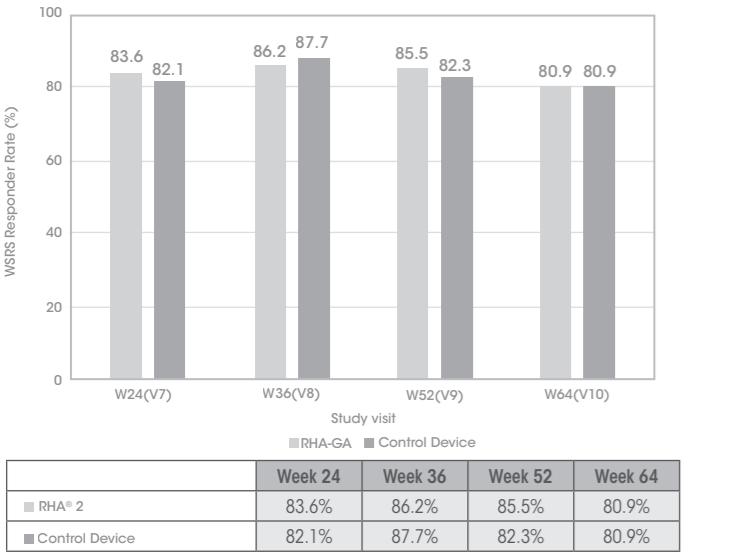
<sup>g</sup> Duration refers to number of days cited in the patient diary, irrespective of date of injection

<sup>h</sup> The CTR numbers indicated in the "Last Day" column are also included in the "8-14 Days" column

**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 <sup>d</sup> n° (%)	Sev <sup>e</sup> n° (%)	Mild n° (%)	Mod <sup>d</sup> n° (%)	Sev <sup>e</sup> n° (%)
Bruising	19 (63.3%)	21 (70.0%)	7 (23.3%)	12 (40.0%)	0 (0%)	10 (33.3%)	11 (36.7%)	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%)
Firmness	24 (80.0%)	22 (73.3%)	12 (40.0%)	10 (33.3%)	2 (6.7%)	9 (30.0%)	11 (36.7%)	2 (6.7%)
Itching	7 (23.3%)	6 (20.0%)	3 (12.5%)	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%)	9 (30.0%)	0 (0%)
Pain	12 (40.0%)	9 (30.0%)	10 (33.3%)	0 (0.0%)	0 (0.0%)	11 (36.7%)	9 (30.0%)	0 (0%)
Redness	21 (70.0%)	20 (66.7%)	12 (40.0%)	10 (33.3%)	1 (3.3%)	14 (46.7%)	13 (43.3%)	0 (0%)
Swelling	21 (70.0%)	20 (66.7%)	11 (36.7%)	10 (33.3%)	0 (0.0%)	14 (46.7%)		

**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



PP populations at the respective follow-up visits  
Rate of responders:  $\geq 1$  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 ( $\geq 1$ -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 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 <0.001).

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) 0.55	16.3 (18.89) 0.70	-0.8 (8.09) -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.

#### 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.

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 color 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  $\frac{1}{2}$ " 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  
1222 Demonbreu Street,  
Suite 2000  
Nashville, Tennessee 37203

##### Distributed by:

Revance Therapeutics, Inc.  
1222 Demonbreu 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)



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 was 96% at week 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® 3 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 effect of the anesthetic agent (mepivacaine or lidocaine) is less than a day. The results of the clinical study are applicable to RHA® 3 Mepi as both RHA® 4 Mepi and RHA® 3 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 to compare the level of pain using the dermato-sympathetic technique of the level of pain using the VAS pain score (VAS) in the correction of moderate to severe facial wrinkles and folds. The 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 with the control/dermal lidocaine fold. RHA® 3 Mepi and RHA® 4 were administered in 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 Endpoint**  
The primary endpoint was the analysis of the non-inferiority of the injection site pain felt during injection assessed by the subjects 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 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 endpoints demonstrated no difference between RHA® 3 Mepi 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 9 points in the RHA® 3 Mepi treatment group and 18 points in the RHA® 4 treatment group. Results were very similar for both treatment groups in the improvement, with 100% of treated subjects, and 100% with RHA® 3 Mepi versus 64.7% with RHA® 4 at month post-injection.

On GAI scale, RHA® 3 Mepi and RHA® 4 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 improving by 63.8 and 64.2 points in the RHA® 3 Mepi and RHA® 4 treatment groups, respectively.

More than 95% 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-1802 - 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 vermillion body, vermillion border and oral commissure 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 US pivotal clinical study described hereafter.

**1. TEO-RHA-1804 - Pivotal Study Design: Clinical Evaluation of RHA® 3 into the Lips**  
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 commissure) for lip augmentation.

A total of 202 subjects were randomized and underwent treatment with either RHA® 3 (N = 153) or control (N = 49) for the injection into the vermillion border, vermillion body and oral commissure for the lip augmentation. 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. Retreatment was provided using RHA® 3 (the control device was not used).

**2. Study Endpoint**  
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  $\geq 1$ -grade point increase on the TLFS at 12 weeks when compared to pre-treatment, which should be  $\geq 70\%$ .

Secondary effectiveness endpoints included TLFS change from Baseline and rates of responders, as assessed by the BLE at each study visit (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 treatments from the subjects' perspective as assessed by the TLFS 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 of 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 30 subjects (33 to 79 years old) were enrolled and randomized, these 30 subjects were included in the intent-to-treat (IT) population (and per protocol (PP) population). Subjects' demographics are presented in Table 9.

**Table 9. Demographics**

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

\* Number of subjects in the ITT population

**4. Treatment Characteristics**  
The primary 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® 3 Mepi 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 punctuate pools, was used for 95.6% 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 <0.001).

For both treatment groups, the level of pain decreased over time with no statistically significant difference at all time points (at 1, 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® 4 at 15 minutes and almost gone after 60 minutes post-injection.

Finally, the relative anesthetic effect was also reported by the subject to be similar between treatment groups, testing 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. 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.	2 (1.3%)	1 (2.0%)	3 (1.5%)
Asian	4 (2.6%)	5 (10.2%)	5 (2.5%)
Black or African	15 (9.8%)	2 (4.1%)	17 (8.4%)
American	2 (1.3%)	0	2 (1.0%)
N. Hawaiian/P. Isl.	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%)

Results are presented in Table 10 and Table 11.

**Table 11. Injection Site Pain after injection – ITT 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 12. Injection Site Pain during injection – PP population**

VAS pain (mm)	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

**Table 13. GAI through 52 weeks as assessed by the BLE**

Fitzpatrick Skin Phototype	RHA® 3 Mepi N=30	RHA® N=30	VAS Difference (mm) N=30
I-III	114 (74.5%)	35 (71.5%)	149 (73.8%)
IV-VI	39 (25.5%)	14 (28.6%)	53 (26.2%)
VI	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

**Table 14. Treatment Characteristics**

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 51 points at Week 12, to more than 36 points throughout the follow-up period (at 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% (93/113) of the subjects were very satisfied or satisfied 12 weeks after treatment and the rate of satisfaction was 63% (67/103) at 52 weeks (the scale grades were: very satisfied, satisfied, neither satisfied nor dissatisfied, dissatisfied or very dissatisfied).

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-treatment. 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 improving by 63.8 and 64.2 points in the RHA® 3 Mepi and RHA® 4 treatment groups, respectively.

More than 95% 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.

**Table 15. TLFS Grade Change from Baseline as assessed by the BLE**

RHA® 3 (N=137)	Control (N=44)



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# 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 (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® 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 supraperitoneal 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. 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 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 provider who 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 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 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 nonocular 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 STERIGUIDE™ 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 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® 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 sterility, 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 reseal.
- 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. 877-3REVA-NOW (877-373-8669).
- Failure to comply with the needle/blunt cannula attachment instructions could result in needle/blunt cannula disengagement and/or product leakage of 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/v), while RHA® 4 contains lidocaine (0.3% w/v). 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® 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 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 is 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".

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

##### 1. Clinical Evaluation of RHA® 4

1. Clinical Evaluation of RHA®

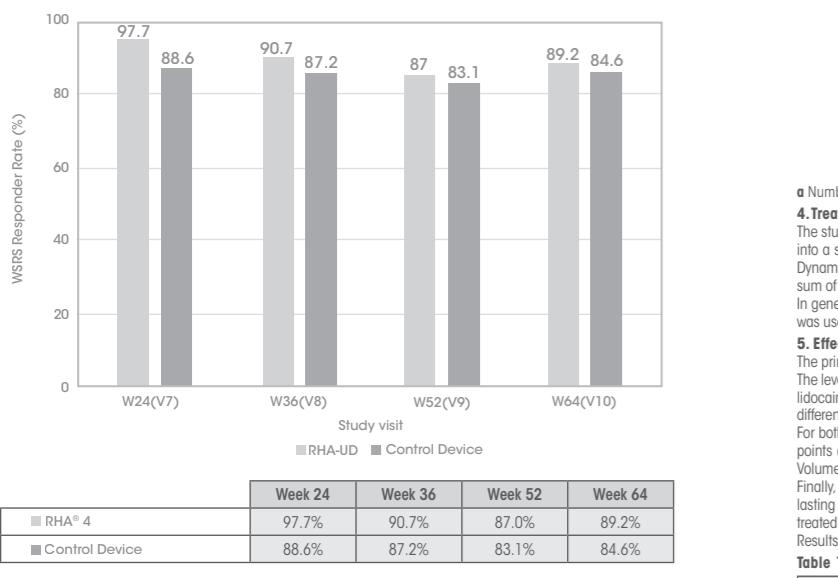
c Mean NLF-Wrinkle Severity Rating Scale improvement from pre-treatment (higher scores mean more improvement from pre-treatment)

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 ( $\geq 1$  grade difference from pre-treatment on the NLF-WRS) 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



PP populations at the respective follow-up visits  
Rate of responders:  $\geq 1$  grade difference from pre-treatment on the NLF-WRS

On the Global Aesthetic Improvement (GAI) scale, the scale included the following grades: 1-Much improved (improved 3+ change) to Worse 5-Much worse than 87% of the subjects and the BLE reported that the NLF treated with RHA® 4 were 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 compare the level of pain using the dermal filler 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 in one side of the face and RHA® 4 with 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 Analog 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 ( $\geq 1$  grade difference from pre-treatment on the NLF-WRS), 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 (IT) 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) min max	57 (9.7) 33 79
Gender	
Female Male	27 90.0% 3 10.0%

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, at 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. Retreatment was 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 of each study visits (see data in Table 13 and Figure 2). Global Aesthetic Improvement (GAI), as assessed by the subject, TI and BLE, impact and effectiveness of study treatment procedures from the subjects' perspective as

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%
<b>Ethnicity</b>			
Hispanic/Latino		12	40.0%
Not Hispanic/Latino		18	60.0%
<b>Fitzpatrick Skin Phototype</b>			
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 puncture 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 after the subject was treated with RHA® 4 were improved or very much improved from week 24 to week 64. 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 1, 15, 30, 45, and 60 minutes post-injection). The injection pain was reduced to 4 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) Min, Max	17.1 (18.38) 0.55	16.3 (18.89) 0.70	-0.8 (6.09) -20,20

a Number of subjects in the PP population

**Table 11.** Injection Site Pain after injection – ITT population

VAS pain (mm) Mean	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-WRS 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 of one-month post-injection.

**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*	-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 IT 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 ( $\geq 1$  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 ( $\geq 1$ -grade improvement from Baseline) on the TMVDS measured by the BLE for RHA® 4 and the Control device

**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, at 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. Retreatment was 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 of each study visits (see data in Table 13 and Figure 2). Global Aesthetic Improvement (GAI), 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 of each visit, and included self-assessment of injection site pain by the subject using a 100mm Visual Analog Scale.

#### 3. Demographics

A total of 201 subjects 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
</tbl



**Code : 230695/01**

**PRODUIT :** IFU\_RHA Dynamic Volume

**PAYS :** USA

**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

**VERSION**

**INITIALES :** AB - PICTURAL MB

**VERSIONS - DATE :**

1 - 16/06/25 - 15h

2 - 16/06/25 - 09h30

3 - 08/10/25 - 11h00

4 - 13/10/25 - 15h55

**COULEURS**

**RECTO/VERSO**



**NOIR**

**ANNULE ET REMPLACE :** 230695/00 (AC-21-009)