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

ADVERSE EXPERIENCES

1. Clinical Evaluation of RHA® Redensity

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

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

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

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

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

[a] Number of subjects' who provided diary answers after V1/1b
[b] Mod = Moderate
[c] Sev = Severe

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

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

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

Lip functionality was assessed at each visit and pre- and post-injection. It included testing:
- Lip function: ability to suck liquid through a straw
- Lip sensation: ability to feel change of lip sensation with a monofilament and cotton wisp at different locations
- Lip movement: ability to pronounce specific letters and words

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

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

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

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

2. Post-marketing Surveillance

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

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

CLINICAL STUDY

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

1. Pivotal Study Design

A randomized, blinded, No-Treatment control, multicenter, prospective pivotal clinical study was conducted to evaluate the clinical safety and effectiveness of RHA® Redensity in the US and in Canada.
Subjects were randomly assigned to the RHA® Redensity treatment group or to the "No-Treatment" control group. The Treating Investigator administered the study device to the upper and lower perioral area, including as necessary, into the vermillion border of the lip. Subjects could receive a touch-up treatment 2 weeks after the initial treatment to optimize the results.
The follow-up period consisted of safety and effectiveness follow-up visits at 4, 8, 12, 16, 24, 36, and 52 weeks after the last treatment and 4 weeks after repeat treatment. The primary endpoint was at Week 8 after last treatment (initial treatment or touch-up).
Subjects were eligible for optional retreatment if necessary at Weeks 12, 16, 24 or 36. Subjects were also offered retreatment at Week 52, and were then followed for 1 month after retreatment or until all Adverse Events (AEs) resolved.
Subjects randomized to the "No-Treatment" control group received their first treatment after the primary endpoint evaluation (Week 8 after randomization) and then followed the same schedule as the initial treatment group until 52 weeks after repeat treatment.

2. Study Endpoints

The primary effectiveness endpoint was the analysis of superiority of RHA® Redensity versus the No-Treatment control, in terms of rate of responders (≥ 1 grade difference from pre-treatment on the PR-SRS) at 8 weeks after injection, as measured by the Blinded Live Evaluator (BLE) using a proprietary and validated 4-grade scale for scoring the severity of perioral rhytids, PR-SRS score.
Secondary effectiveness endpoints included Global Aesthetic Improvement (GAI), as assessed by the subject, TI and the BLE, impact and effectiveness of study treatment procedures from the subjects' perspective as assessed by the perioral rhytids domain of the FACE-Q©, subject satisfaction and an 11-point scale for Natural Look and Feel as assessed by the subjects.
Safety endpoints were evaluated throughout the study, with a 14-day subject diary capturing post-injection signs/symptoms following every study injection, and AE assessments at each visit. Injection site pain was self-assessed by the subject using a 100mm Visual Analog Scale

3. Demographics

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

Subject's demographics are presented in Table 3.

Table 3. Demographics

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

[a] All randomized subjects

4. Treatment Characteristics

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

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

5. Effectiveness Results

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

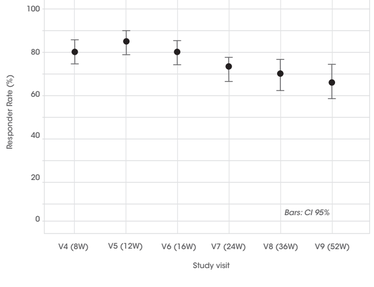
Table 4. Responder rate assessed by a Blinded Live Evaluator at primary endpoint

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

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

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

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



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

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

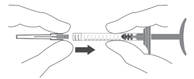
On the Global Aesthetic Improvement (GAI) scale, more than 92% of the subjects, TIs and BLEs reported that the perioral rhytids treated with RHA® Redensity were improved or very much improved at 8 weeks and this proportion remained greater than 80% up to week 52. In addition, based on the Perioral Rhytids domain of the FACE-Q© questionnaire, the subjects consistently reported improvement up to 52 weeks with a mean score change of more than 36 points from baseline throughout the follow-up period. Subjects were asked six questions within the FACE-Q© Perioral Rhytids Domain and reported being less bothered by the number and depth of lines, how noticeable lines were after treatment with RHA® Redensity. Further, based on the FACE-Q© questionnaire, subjects reported being less bothered by how perioral lines looked compared to other people their age, how old the lines made them look, and how their lines appeared when their lips are puckered.
More than 90% of the subjects reported to be satisfied or very satisfied 8 weeks after initial treatment and the rate of satisfaction remained at more than 88% at 52 weeks (the scale grades were: very satisfied, satisfied, neither satisfied nor dissatisfied, dissatisfied or very dissatisfied).

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

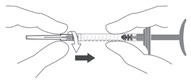
DIRECTIONS FOR ASSEMBLY OF THE NEEDLE TO THE SYRINGE

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

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

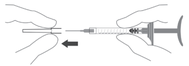


3. Screw the needle clockwise, while maintaining slight pressure between the needle and the syringe.



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

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



DIRECTION FOR INJECTIONS

Before and after treatment, health care practitioners are encouraged to conduct vision assessments, including visual acuity, extraocular motility, and visual field testing. Health care practitioners are encouraged to be prepared with the following in the event of an intravascular injection:
• ensuring supplies are immediately available, as recommended by the American Society for Dermatologic Surgery guidelines
• identifying a local ophthalmologist or ophthalmology subspecialist to be available in the event of an ophthalmic adverse event related to a dermal filler injection
• conducting a basic neurologic examination in the event of an ophthalmic adverse event due to the association of such events with central nervous system deficits.

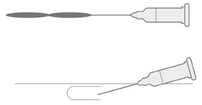
PRE-TREATMENT GUIDELINES

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

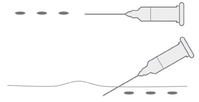
INJECTION TECHNIQUES

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

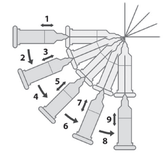
A. Preclinical testing between the following needles brands (TSK HPC, TSK PRC, Terumo TW, Terumo ETW) and the syringe has confirmed that the interoperability and compatibility is reliable and safe. **Serial puncture:** consists of multiple injections, evenly and closely spaced perpendicular to the lines.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



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



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



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

POST-TREATMENT GUIDELINES

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

STERILE NEEDLES

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

PATIENT INSTRUCTIONS

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

HOW SUPPLIED

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

SHELF-LIFE AND STORAGE

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

RxOnly

Manufactured by:

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

Distributed by:

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

SYMBOLS

Manufacturer's name and address

REF — Catalog number

LOT — Lot / batch number

Expiration date (YYYY-MM-DD)

Consult Instructions for use

Single use only

STERILE — Sterilized using steam

Do not use if the package is damaged

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

230396/01

TEOXANE

N° projet : 23_004

TEOXANE

Code : 230396/01	VERSION	COULEURS
PRODUIT : IFU RHA REDENSITY_DUO 2x1ml_Terumo 30G **PAYS :** US	**INITIALES :** NB - PICTURAL AN **VERSIONS - DATE :** 1 - 20/04/23 - 16h15 2 - 24/04/23 - 15h35	**RECTO/ VERSO** **NOIR**
Format ouvert : 630 mm (L) x 280 mm (H) +/- 1 mm **Format plié :** 280 mm x 45.75 mm +/- 0.7 mm – la notice ne doit pas dépasser 46.5 mm		
Texte : corps = 9,2 pts	**ANNULE ET REMPLACE :** 230396/00	

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 to reduce pain on injection.

INTENDED USE / INDICATIONS

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

CONTRAINDICATIONS

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

WARNINGS

- RHA® 2 must not be injected into blood vessels. Introduction of product into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction. Take extra care when injecting soft tissue fillers, for example, inject the product slowly and apply the least amount of pressure necessary. Rare but serious adverse events associated with the intravascular injection of soft tissue fillers in the face have been reported and include temporary or permanent vision impairment or blindness, cerebral ischemia or cerebral hemorrhage leading to stroke, skin necrosis, and damage to underlying facial structures. Immediately stop the injection if a patient exhibits any of the following symptoms: changes in vision, signs of a stroke, blanching of the skin, or unusual pain during or shortly after the procedure. Patients should receive prompt medical attention and possibly evaluation by an appropriate health care practitioner specialist should an intravascular injection occur.
- Product use at specific sites in which an active inflammatory process (skin eruptions such as cysts, pimples, rashes, or hives), infection or skin injury is present should be deferred until the underlying process has been controlled.
- Treatment site reactions consist mainly of short-term inflammatory symptoms (e.g., swelling, redness, tenderness, or pain) and generally resolve within 14 days. Refer to the ADVERSE EXPERIENCES section for details.
- Inflammatory reaction, anaphylactic reaction, edema, implant migration, acne, blisters, scarring, papules and delayed onset of granulomas have been reported following the use of dermal fillers.

PRECAUTIONS

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

ADVERSE EXPERIENCES

1. Clinical Evaluation of RHA® 2

A multicenter, controlled, randomized, double-blinded, within-subject (split-face), prospective US clinical study compared the safety of RHA® 2 versus a control treatment for the treatment of moderate to severe nasolabial folds, and demonstrated similar safety profiles. The expected signs and symptoms that occur following the injection of a hyaluronic acid-based dermal filler (i.e., Common Treatment Responses; CTR) were individually assessed by subjects in a preprinted 14-day diary after each injection.
Subjects were asked to rate each CTR as None, Mild, Moderate or Severe:
- Mild: Little discomfort, no effect on daily activities, no medication or make-up required
- Moderate: some discomfort, some effect on daily activities, possibly medication or make-up required
- Severe: Great discomfort, daily activities compromised, very likely medication or make-up required

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

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

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

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

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

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

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

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

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

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

2. Post-marketing Surveillance

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

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

CLINICAL STUDY

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

1. Pivotal Study Design

A controlled, randomized, double-blinded, within-subject, multicenter, prospective pivotal clinical study was conducted to evaluate the clinical safety and efficacy of RHA® 2.
Subjects were randomly assigned to receive RHA® 2 and a control treatment in mid-to-deep dermis for the treatment of moderate to severe nasolabial folds, or to a non-treatment group. The side of the face for each device injected was assigned randomly.
If deemed necessary by the Treating Investigator, additional NLF correction was performed after 2 weeks (touch-up), with the same study device used for initial treatment.
The follow-up period consisted of safety and effectiveness follow-up visits at 4, 12, 24, 36, 52, and 64 weeks after the last treatment.
Subjects were eligible for optional retreatment if necessary at Weeks 24 or 36. Subjects were also offered retreatment at Week 52 or Week 64, and were then followed for 1 month after retreatment or until all Adverse Events (AEs) resolved. 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.

2. Study Endpoints

The primary effectiveness endpoint was the analysis of non-inferiority of RHA® 2 versus the control treatment, in terms of change from pre-injection to 24 weeks after injection, as measured by the Blinded Live Evaluator (BLE) using a proprietary and validated 5-grade scale for scoring the severity of nasolabial folds, NLF-SRS (which for the purposes of this document will be referred to as Wrinkle Severity Rating Scale (WSRS) score.
Secondary effectiveness endpoints included rates of responders (≥ 1 grade difference from pre-treatment on the WSRS), as measured by the BLE (see data in Figure 1), Global Aesthetic Improvement (GAI), as assessed by the subject and by the BLE, impact and effectiveness of study treatment procedures from the subjects' perspective as assessed by the nasolabial fold domain of the FACE-Q©, and subject satisfaction.
Safety endpoints were evaluated throughout the study, with a 14-day subject diary capturing post-injection signs/symptoms following every study injection, and AE assessments at each visit. Injection site pain was self-assessed by the subject using a 100mm Visual Analog Scale.

3. Demographics

A total of 74 subjects (34 to 79 years old) were allocated to RHA® 2 and control treatment, and 26 were allocated to untreated controls. 73 subjects were included in the ITT population.

Subjects' demographics are presented in Table 3.

Table 3. Demographics

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

[a] Number of subjects in the ITT populations

4. Treatment Characteristics

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

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

5. Effectiveness Results

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

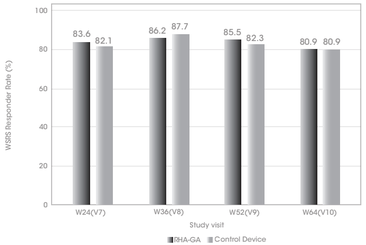
Table 4. Wrinkle Severity Rating Scale scores assessed by a Blinded Live Evaluator throughout the study

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

[a] Number of subjects in the PP populations at the respective follow-up visits
[b] Mean Wrinkle Severity Rating Scale score (higher scores mean deepest wrinkles)
[c] Mean Wrinkle Severity Rating Scale improvement from pre-treatment (higher scores mean more improvement from pre-treatment)
[d] Primary effectiveness endpoint

The results demonstrated that non-inferiority to the control was achieved for RHA® 2 at 24 weeks for the treatment of NLFs. Results also showed that RHA® 2 was non-inferior to the control treatment at all study visits.
Throughout the follow-up period, the aesthetic improvement of the RHA®2 treated NLF continued to be clinically significant (≥ 1 grade difference from pre-treatment on the WSRS) for more than 80% of the subjects at 64 weeks after initial treatment (Figure 1).

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



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

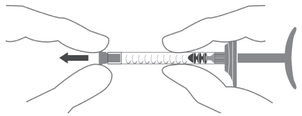
PP populations at the respective follow-up visits
Rate of responders: ≥ 1 grade difference from pre-treatment on the WSRS

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

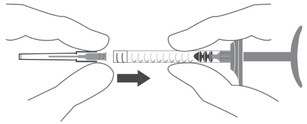
More than 78% of the subjects received repeat treatment. The effectiveness and safety profiles after repeat treatment were similar to that after initial treatment.

DIRECTIONS FOR ASSEMBLY OF THE NEEDLE TO THE SYRINGE

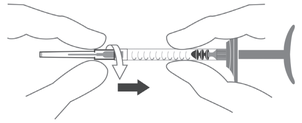
1. Remove the stopper from the syringe by pulling it off.



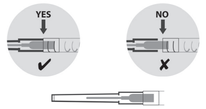
2. Insert the screw thread of the needle firmly into the syringe end-piece.



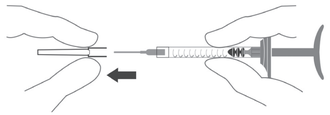
3. Screw the needle clockwise, while maintaining slight pressure between the needle and the syringe.



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



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



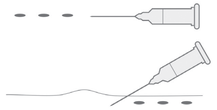
PRE-TREATMENT GUIDELINES

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

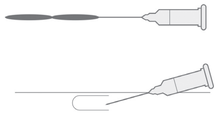
INJECTION TECHNIQUES

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

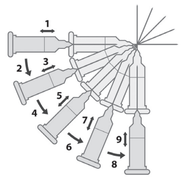
A. Serial puncture: consists of multiple injections, evenly and closely spaced all along wrinkles or folds. This technique is considered to be more precise, but may result in more discomfort for the patient due to the number of punctures.



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



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



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

POST-TREATMENT GUIDELINES

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

STERILE NEEDLES

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

PATIENT INSTRUCTIONS

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

HOW SUPPLIED

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

SHELF-LIFE AND STORAGE

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

RxOnly

Manufactured by:

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

Distributed by:

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

SYMBOLS

	Manufacturer's name and address
REF	Catalog number
LOT	Lot / batch number
	Expiration date (YYYY-MM-DD)
	Consult Instructions for use
	Single use only
STERILE	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

230252/03

TEOXANE

N° projet : 23_004

TEOXANE

Code : 230252/03	VERSION	COULEURS
PRODUIT : IFU RHA® 2 - DUO 2x1mL_ TSK_30G **PAYS :** US	**INITIALES :** NB - PICTURAL AN **VERSIONS - DATE :** 1 - 20/04/23 - 11h20 2 - 24/04/24 - 16h30	**RECTO/ VERSO** **NOIR**
Format ouvert : 280 mm x 630 mm +/- 1 mm **Format plié :** 280 mm x 45.75 mm +/- 0.7 mm – la notice ne doit pas dépasser 46.5 mm		
Texte : corps = 9,2 pts	**ANNULE ET REMPLACE :** 230252/02	

RHA® 3

TEOXANE

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 to reduce pain on injection.

INTENDED USE / INDICATIONS

RHA® 3 is indicated for injection into the mid-to-deep dermis for the correction of moderate to severe dynamic facial wrinkles and folds, such as nasolabial folds (NLFs), in adults aged 22 years or older.
RHA® 3 is indicated for injection into the 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:
  - Do not inject into blood vessels
  - Take extra care when injecting soft tissue fillers, inject the product slowly and apply the least amount of pressure necessary.

Rare but serious adverse events associated with the intravascular injection of soft tissue fillers in the face have been reported and include temporary or permanent vision impairment or blindness, cerebral ischemia or cerebral hemorrhage leading to stroke, skin necrosis, and damage to underlying facial structures. If a patient exhibits any of the following symptoms: changes in vision, signs of a stroke, blanching of the skin, or unusual pain during or shortly after the procedure, immediately stop the injection. Patients should receive prompt medical attention and possibly evaluation by an appropriate health care practitioner specialist should an intravascular injection occur.

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

PRECAUTIONS

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

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

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

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

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

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

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

Table 2. Duration of Common Treatment Responses after initial treatment with RHA® 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° %			
Duration[c]	1-3 Days	4-7 Days	8-14 Days	Last Day[d]	1-3 Days	4-7 Days	8-14 Days	Last Day[d]
Bruising	11 14.7%	19 25.3%	12 16.0%	4 5.3%	11 14.7%	16 21.3%	11 14.7%	1 1.3%
Discoloration	10 13.3%	6 8.0%	6 8.0%	4 5.3%	13 17.3%	5 6.7%	4 5.3%	3 4.0%
Firmness	18 24.0%	7 9.3%	23 30.7%	9 12.0%	16 21.3%	14 18.7%	15 20.0%	3 4.0%
Itching	9 12.0%	4 5.3%	0 0.0%	0 0.0%	8 10.7%	3 4.0%	0 0.0%	0 0.0%
Lumps/ Bumps	17 22.7%	11 14.7%	21 28.0%	12 16.0%	15 20.0%	13 17.3%	12 16.0%	6 8.0%
Pain	21 28.0%	7 9.3%	2 2.7%	0 0.0%	18 24.0%	3 4.0%	2 2.7%	1 1.3%
Redness	27 36.0%	9 12.0%	7 9.3%	2 2.7%	27 36.0%	10 13.3%	5 6.7%	2 2.7%
Swelling	18 24.0%	12 16.0%	11 14.7%	5 6.7%	19 25.3%	11 14.7%	8 10.7%	4 5.3%
Tenderness	17 22.7%	13 17.3%	14 18.7%	5 6.7%	17 22.7%	13 17.3%	7 9.3%	3 4.0%

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

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

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

2. Clinical Evaluation of RHA® 3 into the lips

The safety of the RHA® 3 indicated for lip augmentation was studied against a control treatment in a multicenter, controlled, randomized, double-blinded, between-subject, prospective U.S. clinical study. Similar safety profiles between RHA® 3 and its comparator were demonstrated.
The expected signs/symptoms that occur following the injection (i.e., CTRs) were captured by subjects in a 30-day diary. Injection sites on each side of the face were individually assessed by subjects over 30 days following study injections.
CTRs by severity and duration are presented respectively, in Table 3 and Table 4.

- The most frequent CTRs were swelling, lumps/bumps, firmness, tenderness, bruising and redness.
- Proportions of subjects with at least one CTR were similar between RHA® 3 and control treatment.
- The majority (84%, 278/329) of CTRs resolved within 14 days.
- There were no notable differences between RHA® 3 and control treatment with regard to the proportion of subjects with at least one severe CTR: 22% (31/140) for RHA® 3 against 23% (11/47) for the control. The most common CTR reported as severe was swelling. All severe CTRs did not last more than 8 days, except for 1 RHA® 3 subject who experienced severe Tenderness and severe Firmness which had a maximum duration of 14 days.
- For most of the diaries with a least one CTR reported, the maximal severit y was "Mild" or "Moderate" in both treatment groups (78%, 109/140 for RHA® 3 and 77%, 36/47 for the control).
- 19% of the retrieved diaries (37/195) contained at least one CTR on the last day of the 30-day diary: 20% in the RHA® 3 group (30/147) against 15% in the control group (7/48). All were mild in severity and not clinically significant. They were all elevated to Treatment-related AEs.

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

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

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

[a] Number of subjects' Lips treated with the respective device
[b] Number of subjects' Lips with any specific Common Treatment Response
[c] Mod = Moderate
[d] 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[c]	Group (N°= subjects)	1-3 Days n° %	4-7 Days n° %	8-14 Days n° %	15-30 Days n° %	Last Day[d] n° %
At least 1 CTR	RHA® 3 (N°=153)	111 75.5%	100 68.0%	67 45.6%	51 34.7%	30 20.4%
	Control (N°=49)	40 83.3%	33 68.8%	11 22.9%	10 20.8%	7 14.6%
Bruising	RHA® 3 (N°=153)	29 19.7%	34 23.1%	33 22.4%	6 4.1%	1 0.7%
	Control (N°=49)	12 25.0%	10 20.8%	2 4.2%	1 2.1%	0
Discoloration	RHA® 3 (N°=153)	25 17.0%	18 12.2%	15 10.2%	7 4.8%	3 2.0%
	Control (N°=49)	13 27.1%	5 10.4%	2 4.2%	0	0
Firmness	RHA® 3 (N°=153)	32 21.8%	26 17.7%	27 18.4%	30 20.4%	11 7.5%
	Control (N°=49)	12 25.0%	18 37.5%	4 8.3%	4 8.3%	3 6.3%
Itching	RHA® 3 (N°=153)	22 15.0%	8 5.4%	4 2.7%	5 3.4%	1 0.7%
	Control (N°=49)	5 10.4%	4 8.3%	0	0	0
Lumps/Bumps	RHA® 3 (N°=153)	30 20.4%	23 15.6%	17 11.6%	45 30.6%	27 18.4%
	Control (N°=49)	13 27.1%	14 29.2%	2 4.2%	9 18.8%	7 14.6%
Pain	RHA® 3 (N°=153)	40 27.2%	19 12.9%	10 6.8%	8 5.4%	0
	Control (N°=49)	20 41.7%	9 18.8%	2 4.2%	0	0
Redness	RHA® 3 (N°=153)	42 28.6%	18 12.2%	15 10.2%	6 4.1%	0
	Control (N°=49)	19 39.6%	6 12.5%	3 6.3%	0	0
Swelling	RHA® 3 (N°=153)	45 30.6%	43 29.3%	32 21.8%	14 9.5%	1 0.7%
	Control (N°=49)	25 52.1%	17 35.4%	2 4.2%	3 6.3%	0
Tenderness	RHA® 3 (N°=153)	37 25.2%	32 21.8%	27 18.4%	18 12.2%	3 2.0%
	Control (N°=49)	18 33.3%	13 27.1%	6 12.5%	3 6.3%	1 2.1%

[a] Number of subjects' Lips treated with the respective device
[b] Number of subjects' lips with each specific CTR by maximum duration
[c] Duration refers to number of days cited in the patient diary, irrespective of date of injection

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

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

All subjects were able to perform the tests successfully pre-injection and at every visit thereafter. Less than 10% of subjects had difficult sucking through a straw, feeling the mono-filament and cotton wisp, or pronouncing certain words, right after injection. All those subjects successfully completed the tests at subsequent visits.
An adverse event (AE) was defined as a treatment-related event that was not considered typical in type and/or duration and/or severity. Also, CTRs from the patient's diary that were recorded on the last day of diary were automatically elevated to the status of adverse event, regardless of severity.

- Both RHA® 3 and control treatment groups presented with similar adverse event (AE) profiles with an overall of 64 subjects experiencing a total of 146 treatment-related AEs after initial treatment and touch-up injections.
- All treatment-related AEs were mild or moderate in severity. No severe treatment-related AEs were reported.
- Most of treatment-related AEs experienced in both treatment groups were typical of the expected signs and symptoms observed following an injection of a hyaluronic acid-based dermal filler, such as: injection site mass, injection site swelling and injection site induration. Other reported treatment-related AEs such as headache, or pruritus are less typical but not unexpected following a dermal filler injection.
- Most of treatment-related AEs were based on subjects' diary entries (CTRs): 75% (81/108) were either a CTR, or listed as Others, or from the list of pre-identified AEs on the diary and 25% (27/108) were identified by the TI.
- Most treatment-related AEs (79%, 85/108) resolved within 30 days and the proportion of subjects with reported treatment related AE was similar across the 2 treatment groups. The duration of treatment-related AEs varied from 1 to 90 days, except for 11 treatment-related AEs (with 9 of them started during the retreatment period) that were still ongoing at the end of the study (i.e., one month after retreatment). These 11 treatment-related AEs were all the typical and expected signs and symptoms observed following the injection of a dermal filler (8 Lumps/Bumps, 1 swelling, 2 firmness). All of them were mild in severity, except one moderate Lumps/Bumps, that resolved one month after injection.
- There were no treatment-related serious AEs.
- One AE of Special Interest (AESI) was reported. The subject received RHA® 3 and developed an event of Vision blurred with mild severity, the same day of the injection. The event was assessed as Unlikely related to the study treatment or the study procedure and did not motivate referral to an eye specialist. No concomitant medications were reported as being used to treat this event. The event resolved without sequelae one day later.
- No events were deemed to be a granuloma or delayed inflammatory response.
- There were no late onset treatment-related AEs.

Safety profile by Fitzpatrick skin type and ethnicity was not different. Rates of treatment-related AEs may vary according to age group without any trend identified.
There were no reported cases of scarring, keloid formation or hyperpigmentation.

3. Post-marketing Surveillance

The following adverse events were reported as part of post-marketing surveillance on the use of RHA® 3 worldwide with a prevalence equal or superior to one occurrence for 100,000 syringes: Injection site masses (lumps and bumps), skin swelling, erythema, skin induration, skin edema, vascular complication (such as vessel compression/occlusion), inflammatory reaction, pain, allergic reaction and ecchymosis.
Additionally, other less frequent adverse reactions have also been reported, and includes implant migration, granuloma, dermatitis, skin infection, blister, necrosis, fibrosis, pruritus, abscess, overcorrection, skin discoloration/Tyndall effect, telangiectasia, tenderness, urticaria, anaphylactic reaction, injection site cellulitis, influenza-like illness, keloid scarring, overcorrection, numbness, pigmentation disorder, pustules, papules, paresthesia, nerve damage, numbness, visual impairment, neuralgia, wrinkles, hyperthermia, headache, hemorrhage, herpes outbreaks, injection site movement impairment, dry skin, chapped lips, scabs, puffy skin, dizziness.
Delayed-onset inflammation near the site of dermal filler injections is one of the known adverse events associated with dermal fillers. Cases of delayed-onset inflammation have been reported to occur at the dermal filler treatment site following viral or bacterial illnesses or infections, vaccinations, or dental procedures. Typically, the reported inflammation was responsive to treatment or resolved on its own.
In many cases the symptoms resolved without any treatment. Reported treatments included the use of (in alphabetical order): analgesics, antibiotics, antihistamines, anti-inflammatories, anti-viral, corticosteroids, drainage, excision, implant dissolution (hyaluronidase), incision, massage and vasodilators. Final resolution varies from ongoing to a total resolution of the symptoms with or without sequelae.

CLINICAL TRIALS

TEO-RHA-1302 - RHA® 3 INTO THE NLFS - CLINICAL STUDY
The long-term safety and effectiveness of RHA® 3 in the correction of moderate to severe facial wrinkles and folds were evaluated in a US pivotal clinical study described hereafter.

1. Pivotal Study Design

A controlled, randomized, double-blinded, within-subject (split-face), multicenter, prospective pivotal clinical study was conducted to evaluate the clinical safety and effectiveness of RHA® 3.
Subjects were randomly assigned to receive RHA® 3 and a control treatment in mid-to-deep derma for the treatment of moderate to severe nasolabial folds, or to a non-treatment group. The side of the face for each device injected was assigned randomly.
If deemed necessary by the Treating Investigator, additional NLF correction was performed after 2 weeks (touch-up), with the same study device used for initial treatment.
The follow-up period consisted of safety and effectiveness follow-up visits at 4, 12, 24, 36, 52, and 64 weeks after the last treatment.
Subjects were eligible for optional retreatment if necessary at Weeks 24 or 36. Subjects were also offered retreatment at Week 52 or Week 64, and were then followed for 1 month after retreatment or until all Adverse Events (AEs) resolve. Retreatment on either side was provided using RHA® 3 (the control treatment was not used).
Subjects randomized to the "no treatment" control group did not receive treatment.

2. Study Endpoints

The primary effectiveness endpoint was the analysis of non-inferiority of RHA® 3 versus the control treatment, in terms of change from pre-injection to 24 weeks after injection, as measured by a Blinded Live Evaluator (BLE) using a proprietary and validated 5-grade scale for scoring the severity of nasolabial folds, NLF-WSRS (which for the purposes of this document will be referred to as Wrinkle Severity Rating Scale (NLF-WSRS) score).
Secondary effectiveness endpoints included rates of responders (≥ 1 grade difference from pre-treatment on the NLF-WSRS), as measured by the BLE (see data in Figure 1), Global Aesthetic Improvement (GAI), as assessed by the subject and by the BLE, impact and effectiveness of study treatment procedures from the subjects' perspective as assessed by the nasolabial fold domain of the FACE-Q©, and subject satisfaction.
Safety endpoints was evaluated throughout the study, with a 14-day subject diary capturing post-injection signs/symptoms following every study injection, and AE assessments at each visit, and included self-assessment of injection site pain by the subject using a 100 mm Visual Analog Scale.

3. Demographics

A total of 74 subjects (26 to 77 years old) were allocated to RHA® 3 and control treatment, and 26 were allocated to untreated controls. 74 subjects were included in the intention-to-treat (ITT) population. Subjects' demographics are presented in Table 5.

Table 5. Demographics

Number / % of subjects	RHA® 3 versus Control Device N°=74	
Age		
Mean (SD)	55.7	(9.4)
min max	26	77
Gender		
Female	68	91.9%
Male	6	8.1%
Race		
Caucasian	62	83.8%
Black	7	9.5%
Am. Indian/N. Alask.	0	0.0%
N. Hawaiian/P. Isl.	0	0.0%
Asian	0	0.0%
Other	5	6.8%
Ethnicity		
Hispanic/Latino	21	28.4%
Not Hispanic/Latino	53	71.6%
Fitzpatrick Skin Phototype		
I	4	5.4%
II	21	28.4%
III	19	25.7%
IV	20	27.0%
V	7	9.5%
VI	3	4.1%

[a] Number of subjects in the ITT populations

4. Treatment Characteristics

The study protocol allowed a maximum of 3.0 ml in a single NLF per treatment session. The overall total median volume of RHA® 3 injected to achieve optimal correction results was 1.4 ml. The proportion of subjects who received touch-up treatment with RHA® 3 at Week 2 was 67.6%.
In general, a linear threading or fan-like technique, or combination, was used for 90.3% of the subjects treated with RHA® 3.

5. Effectiveness Results

The primary effectiveness endpoint was met for RHA® 3. The primary effectiveness endpoint was the aesthetic improvement from pre-injection of the NLF treated with RHA® 3 compared to the improvement from pre-injection of the NLF treated with the control treatment, as assessed (using the Nasolabial Folds Wrinkle Severity Rating Scale NLF-WSRS) by the BLE at 24 weeks after baseline; results are presented in Table 6.

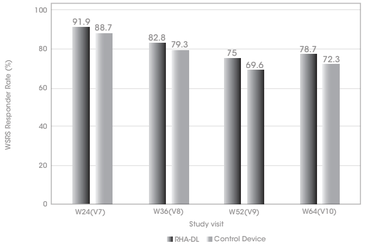
Table 6. Wrinkle Severity Rating Scale scores assessed by a Blinded Live Evaluator throughout the study

	n°	RHA® 3		Control Device	
		NLF-WS-RS score[b]	NLF-WSRS Improvement[c]	NLF-WS-RS score[b]	NLF-WSRS Improvement[c]
Pre-treatment[d]	62	3.39	-	3.39	-
Week 24	62	2.06	1.32	2.16	1.23
Week 36	58	2.36	1.03	2.41	0.98
Week 52	56	2.45	0.91	2.54	0.82
Week 64	47	2.47	0.91	2.55	0.83

[a] Number of subjects in the PP populations at the respective follow-up visits
[b] Mean NLF-Wrinkle Severity Rating Scale score (higher scores mean deepest wrinkles)
[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® 3 at 24 weeks for the treatment of NLFs. Results also showed that RHA® 3 was not inferior to the control treatment at all study visits.
Throughout the follow-up period, the aesthetic improvement of the RHA® 3 treated NLF continued to be clinically significant (≥ 1 grade difference from pre-treatment on the NLF-WSRS) for more than 78% 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® 3 and the Control Device



	Week 24	Week 36	Week 52	Week 64
RHA® 3	91.9%	82.8%	75.0%	78.7%
Control Device	88.7%	79.3%	69.6%	72.3%

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

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

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

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

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

1. Pivotal Study Design

A prospective, double-blinded, randomized, controlled, between-subject, multicenter clinical study was conducted to evaluate the clinical safety and effectiveness of RHA® 3 versus control for injection into the lips (vermilion body, vermilion border, and oral commissures) for lip augmentation.

A total of 202 subjects were randomized and underwent treatment with either RHA® 3 (N = 153) or control (N = 49) in the vermilion border, vermilion body and oral commissure for the lip augmentation and lip fullness. 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 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 Fulness Scale (TLFS). The co-primary endpoint was the proportion of responders with a ≥1-grade point increase on the TLFS at 12 weeks when compared to pretreatment, which should be ≥ 70%.

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

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

3. Demographics

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

Table 7. Demographics

Number / % of subjects	RHA® 3 N[a]=153	Control N[a]=49	Total N[a]=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%)	1 (2.0%)	5 (2.5%)
Black or African American	15 (9.8%)	2 (4.1%)	17 (8.4%)
N. Hawaiian/P. Isl.	2 (1.3%)	0	2 (1.0%)
White	130 (85.0%)	45 (91.8%)	175 (86.6%)
Ethnicity			
Hispanic/Latino	32 (20.9%)	13 (26.5%)	45 (22.3%)
Not Hispanic/Latino	118 (77.1%)	35 (71.4%)	153 (75.7%)
Not available	3 (2.0%)	1 (2.0%)	4 (2.0%)
Fitzpatrick Skin Phototype			
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%)

[a] Number of subjects in the safety populations

4. Treatment Characteristics

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

The proportion of subjects who received touch-up treatment at Week 4 was lower with RHA® 3 (58.2%, 89/153) than with control (73.5%, 36/49).

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

5. Effectiveness Results

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

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

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

[a] Primary effectiveness endpoint

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

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

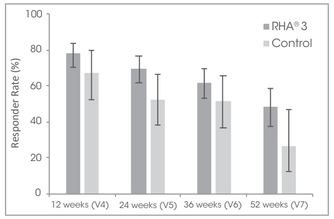
	RHA® 3	Control
Baseline TLFS grades 1, 2 & 3		
N	137	44
# of responders (%) [95% CI]	107 (78.1%) [70.5 - 84.2%]	29 (65.9%) [51.1 - 78.1%]
Baseline TLFS grades 1 & 2		
N	68	27
# of responders (%) [95% CI]	64 (94.1%) [85.8-97.7%]	24 (88.9%) [71.9-96.1%]
Baseline TLFS grade 3		
N	69	17
# of responders (%)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

mITT population

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

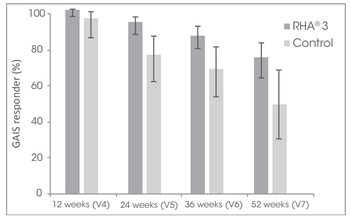
Throughout the follow-up period, the aesthetic improvement of the RHA® 3 continued to be clinically significant (≥ 1 grade difference from pre-treatment on the TLFS) for 61% (81/132) of the subjects at 36 weeks after last treatment, and for 48% (38/79) at 52 weeks after last treatment (Figure 2).

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



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

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



The subjects treated with RHA® 3 consistently reported improvement up to 52 weeks based on the Satisfaction with lips module of the FACE-Q© questionnaire with the mean score improving from Baseline by 51 points at Week 12, to more than 36 points throughout the follow-up period (46 at Week 24, 41 at Week 36 and 36 at Week 52). Similar results were found with the Satisfaction with outcomes module of the FACE-Q© questionnaire.

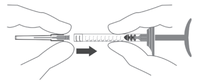
84% (113/135) of the subjects reported to be satisfied or very satisfied 12 weeks after treatment and the rate of satisfaction was 83% (67/81) at 52 weeks (the scale grades were: very satisfied, satisfied, neither satisfied nor dissatisfied, dissatisfied, or very dissatisfied).

59% (90/153) of the subjects received repeat treatment. The effectiveness and safety profiles after repeat treatment were similar to that after initial treatment and touch-up.

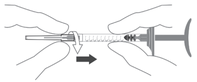
DIRECTIONS FOR ASSEMBLY OF THE NEEDLE TO THE SYRINGE

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

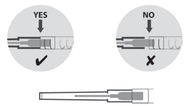
2. Insert the screw thread of the needle firmly into the syringe end-piece.



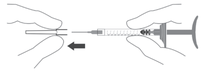
3. Screw the needle clockwise, while maintaining slight pressure between the needle and the syringe.



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



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



PRE-TREATMENT GUIDELINES

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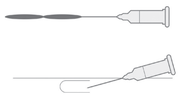
- Before injecting, prime the needle by carefully pressing the syringe plunger until a small droplet of the gel is visible at the tip of the needle.

INJECTION TECHNIQUES

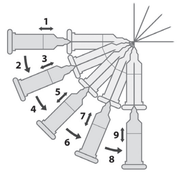
- RHA® 3 is administered by using a thin gauge needle (27 G x ½"). For the treatment of NLFs, the needle is inserted into the mid-to-deep dermis at an approximate angle of 15° to 30° parallel to the length of the wrinkle or fold. For lip augmentation, RHA® 3 is injected into the lip mucosa and/or mid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

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

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



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



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

POST-TREATMENT GUIDELINES

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

STERILE NEEDLES

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

PATIENT INSTRUCTIONS

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

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

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

RxOnly

HOW SUPPLIED

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

SHELF-LIFE AND STORAGE

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

Manufactured by:

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

Distributed by:

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

SYMBOLS

- Manufacturer's name and address
- REF — Catalog number
- LOT — Lot / batch number
- Expiration date (YYYY-MM-DD)
- Consult Instructions for use
- Single use only
- STERILE — 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

23025304

TEOXANE

N° projet : 23_004

TEOXANE

Code : 230253/03	VERSION	COULEURS
PRODUIT : IFU RHA® 3 - DUO 2x1mL_ TSK_27G **PAYS :** US	**INITIALES :** NB - PICTURAL AN **VERSIONS - DATE :** 1 - 22/04/23 - 13h30	**RECTO/ VERSO** **NOIR**
Format ouvert : 280 mm x 630 mm +/- 1 mm **Format plié :** 280 mm x 45.75 mm +/- 0.7 mm – la notice ne doit pas dépasser 46.5 mm		
Texte : corps = 9,2 pts	**ANNULE ET REMPLACE :** 230253/02	

RHA® 4

TEOXANE

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

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

DEVICE DESCRIPTION

RHA® 4 is a viscoelastic, sterile, non-pyrogenic, clear, colorless, homogeneous and biodegradable gel implant. It is produced with sodium Hyaluronic Acid (NaHA) with a concentration of 23 mg/g obtained from bacterial fermentation using the *Streptococcus equi* bacterial strain, crosslinked with 1,4-butanediol diglycidyl ether (BDDE) and reconstituted in a physiological buffer (pH 7.3). RHA® 4 also contains 0.3% lidocaine hydrochloride 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 resterilize.
- Do not use if package is opened or damaged. The sterility of the product is not guaranteed in the case of failure to comply with this precaution. Failure to comply with the needle/blunt cannula attachment instructions could result in needle/blunt cannula disengagement and/or product leakage at the Luer-lock and needle/blunt cannula hub connection.
- RHA® 4 is a clear, colorless gel without particulates. In the event the contents of a syringe show signs of separation and/or appears cloudy, do not use the syringe; contact Renexus Therapeutics, Inc. 877-3REV-NOW (877-373-8669).

ADVERSE EXPERIENCES

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

1. Clinical Evaluation of RHA® 4 Into the NLFs

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

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

Common Treatment Responses	TOTALS		RHA® 4 (N°=120 NLF)			Control Device (N°=120 NLF)		
	RHA® 4 n° %	CTRL[c] n° %	Mild n° %	Mod[d] n° %	Sev[e] n° %	Mild n° %	Mod[d] n° %	Sev[e] n° %
Bruising	70 58.3 %	72 60.0%	35 29.2%	26 21.7%	9 7.5%	37 30.8%	25 20.8%	10 8.3%
Discoloration	50 41.7 %	56 46.7%	30 25.0%	16 13.3%	4 3.3%	30 25.0%	20 16.7%	6 5.0%
Firmness	91 75.8%	93 77.5%	36 30.0%	46 38.3%	9 7.5%	13 10.8%	50 41.7%	30 25.0%
Itching	30 25.0%	44 36.7%	25 20.8%	5 4.2%	0 0.0%	28 23.3%	14 11.7%	2 1.7%
Lumps/Bumps	81 67.5%	90 75.0%	36 30.0%	33 27.5%	12 10.0%	28 23.3%	37 30.8%	25 20.8%
Pain	66 55.0%	87 72.5%	42 35.0%	19 15.8%	5 4.2%	30 25.0%	40 33.3%	17 14.2%
Redness	84 70.0%	91 75.8%	42 35.0%	38 31.7%	4 3.3%	32 26.7%	42 35.0%	17 14.2%
Swelling	97 80.8%	104 86.7%	41 34.2%	44 36.7%	12 10.0%	21 17.5%	38 31.7%	45 37.5%
Tenderness	90 75.0%	95 79.2%	53 44.2%	30 25.0%	7 5.8%	23 19.2%	45 37.5%	27 22.5%

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

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

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

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

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

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

Clinical study TEO-RHA-2001 was a multicenter, controlled, single-blinded, within-subject (split-face), prospective study to evaluate the effectiveness and safety of using RHA® 4 injected with a blunt cannula (25G x 2") or with a sharp needle (27G x ½") for the treatment of moderate to severe nasolabial folds. The expected signs and symptoms that occur following the injection of a hyaluronic acid-based dermal filler (i.e., Common Treatment Responses; CTR) were individually assessed by subjects in a preprinted 28-day diary after each injection. Subjects were asked to rate each CTR as None, Mild, Moderate or Severe:
- Mild: Little discomfort, no effect on daily activities, no medication or make-up required
- Moderate: some discomfort, some effect on daily activities, possibly medication or make-up required
- Severe: Great discomfort, daily activities compromised, very likely medication or make-up required

CTR by severity and duration are presented respectively, in Table 3 and Table 4.
- The most frequent CTRs were firmness, swelling, tenderness, lumps/bumps, redness, pain and bruising.
- Proportions of subjects experiencing at least one CTR of each category was similar between RHA® 4 injected with a cannula and between RHA® 4 injected with a needle.
- When analyzed for each individual sign or symptom, the number of subjects who experienced at least 1 CTR was consistently and markedly lower in the RHA® 4-cannula group, with a significant difference between treatment groups for bruising, lumps/bumps, redness, itching, and pain.
- The majority (73%) of CTRs had resolved by Day 14.
- For nearly all CTRs (more than 80%) experienced by any treatment group (initial treatment or touch-up treatment), the maximal severity reported was "Mild" or "Moderate".
- There were approximately the same number of subjects who reported severe CTR with RHA® 4 injected with a cannula (10%) as RHA® 4 injected with a needle (14%).

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

Common Treatment Responses	TOTALS		RHA® 4-cannula (N°=50 NLF)			RHA® 4-needle (N°=50 NLF)		
	RHA® 4 -C nb %	RHA® 4 -N nb %	Mild n° %	Mod[d] n° %	Sev[e] n° %	Mild n° %	Mod[d] n° %	Sev[e] n° %
Bruising	10 20%	27 54%	9 18%	1 2%	0 0%	18 36%	7 14%	2 4%
Discoloration	9 18%	16 32%	8 16%	1 2%	0 0%	10 20%	5 10%	1 2%
Firmness	40 80%	43 86%	23 46%	14 28%	3 6%	23 46%	17 34%	3 6%
Itching	10 20%	17 34%	8 16%	2 4%	0 0%	14 28%	2 4%	1 2%
Lumps/Bumps	33 66%	45 90%	24 48%	5 10%	4 8%	28 56%	12 24%	5 10%
Pain	21 42%	30 60%	13 26%	8 16%	0 0%	21 42%	9 18%	0 0%
Redness	21 42%	33 66%	17 34%	4 8%	0 0%	26 52%	7 14%	0 0%
Swelling	36 72%	41 82%	25 50%	10 20%	1 2%	23 46%	16 32%	2 4%
Tenderness	38 76%	44 88%	27 54%	9 18%	2 4%	32 64%	10 20%	2 4%

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

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

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

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

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

3. Post-marketing Surveillance

The following adverse events were reported as part of post-marketing surveillance on the use of RHA® 4 worldwide with a prevalence equal or superior to one occurrence for 100,000 syringes: Injection site masses (lumps and bumps), skin swelling, firmness, edema, inflammatory reaction, erythema, pain, granuloma, vascular complication, skin infection and bruising.
Additionally, other less frequent adverse reactions have also been reported, and includes implant migration, allergic reaction, skin discoloration/Tyndall effect, tenderness, abscess, overcorrection, pruritus, anaphylactic reaction, pigmentation disorder, skin necrosis, urticaria, angioedema, chapped lips, dermatitis, fibrosis, herpes breakout, influenza-like illness, numbness, pustules, telangiectasia and visual impairment.
Delayed-onset inflammation near the site of dermal filler injections is one of the known adverse events associated with dermal fillers. Cases of delayed-onset inflammation have been reported to occur at the dermal filler treatment site following viral or bacterial illnesses or infections, vaccinations, or dental procedures. Typically, the reported inflammation was responsive to treatment or resolved on its own.
In many cases the symptoms resolved without any treatment. Reported treatments included the use of (in alphabetical order): analgesics, antibiotics, anti-histamines, anti-inflammatories, anti-viral, drainage, excision, implant dissolution (hyaluronidase), incision, massage and vasodilatators.

CLINICAL TRIALS

A. Pivotal STUDY for RHA® 4 into the NLFs

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

1. Pivotal Study Design

A controlled, randomized, double-blinded, within-subject, multicenter, prospective pivotal clinical study was conducted to evaluate the clinical safety and effectiveness of RHA® 4.
Subjects were randomly assigned to receive RHA® 4 and a control treatment in deep dermis to superficial subcutaneous for the treatment of moderate to severe nasolabial folds, or to a non-treatment group.The side of the face for each device injected was assigned randomly.
If deemed necessary by the Treating Investigator, additional NLF correction was performed after 2 weeks (touch-up), with the same study device used for initial treatment.
The follow-up period consisted of safety and effectiveness follow-up visits at 4, 12, 24, 36, 52, and 64 weeks after the last treatment.
Subjects were eligible for optional retreatment if necessary at Weeks 24 or 36. Subjects were also offered retreatment at Week 52 or Week 64, and were then followed for 1 month after retreatment or until all Adverse Events (AEs) resolve. Retreatment on either side was provided using RHA® 4 (the Control treatment was not used).
Subjects randomized to the "no treatment" control group did not receive treatment.

2. Study Endpoints

The primary effectiveness endpoint was the analysis of non-inferiority of RHA® 4 versus the Control treatment, in terms of change from pre-injection to 24 weeks after injection, as measured by the Blinded Live Evaluator (BLE) using a proprietary and validated 5-grade scale for scoring the severity of nasolabial folds, NLF-WSRS (which for the purposes of this document will be referred to as NLF-Wrinkle Severity Rating Scale (WSRS) score.
Secondary effectiveness endpoints included rates of responders (≥ 1 grade difference from pre-treatment on the NLF-WSRS), as measured by the BLE (see data in Figure 1), Global Aesthetic Improvement (GAI), as assessed by the subject and by the BLE, impact and effectiveness of study treatment procedures from the subjects' perspective as assessed by the nasolabial fold domain of the FACE-Q©, and subject satisfaction.
Safety endpoints was evaluated throughout the study, with a 14-day subject diary capturing post-injection signs/symptoms following every study injection, and AE assessments at each visit, and included self-assessment of injection site pain by the subject using a Visual Analog Scale.

3. Demographics

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

Table 5. Demographics

Number / % of subjects	RHA® 4 versus Control Device N°=118
Age	
Mean (SD)	57.4 (10.0)
min max	27 86
Gender	
Female	106 89.8%
Male	12 10.2%
Race	
Caucasian	97 82.2%
Black	19 16.1%
Am. Indian/N. Alask.	1 0.9%
N. Hawaiian/P. Isl.	0 0.0%
Asian	1 0.9%
Other	0 0.0%
Ethnicity	
Hispanic/Latino	30 24.5%
Not Hispanic/Latino	88 74.6%
Fitzpatrick Skin Phototype	
I	4 3.4%
II	21 17.8%
III	40 33.9%
IV	31 26.3%
V	14 11.9%
VI	8 6.8%

[a] Number of subjects in the ITT populations

4. Treatment Characteristics

The study protocol allowed a maximum of 3.0 ml in a single NLF per treatment session.The overall total median volume of RHA® 4 injected to achieve optimal correction results was 1.7 ml. The proportion of subjects who received touch-up treatment with RHA® 4 at Week 2 was 27.1%.
In general, a linear threading or multiple puncture pools technique, or combination, was used for 84.7% of the subjects treated with RHA® 4.

5. Effectiveness Results

The primary effectiveness endpoint was met for RHA® 4.The primary effectiveness endpoint was the aesthetic improvement from pre-injection of the NLF treated with RHA® 4 compared to the improvement from pre-injection of the NLF treated with the Control treatment, as assessed (using the NLF-WSRS) by the BLE at 24 weeks after baseline, and results are presented in Table 6.

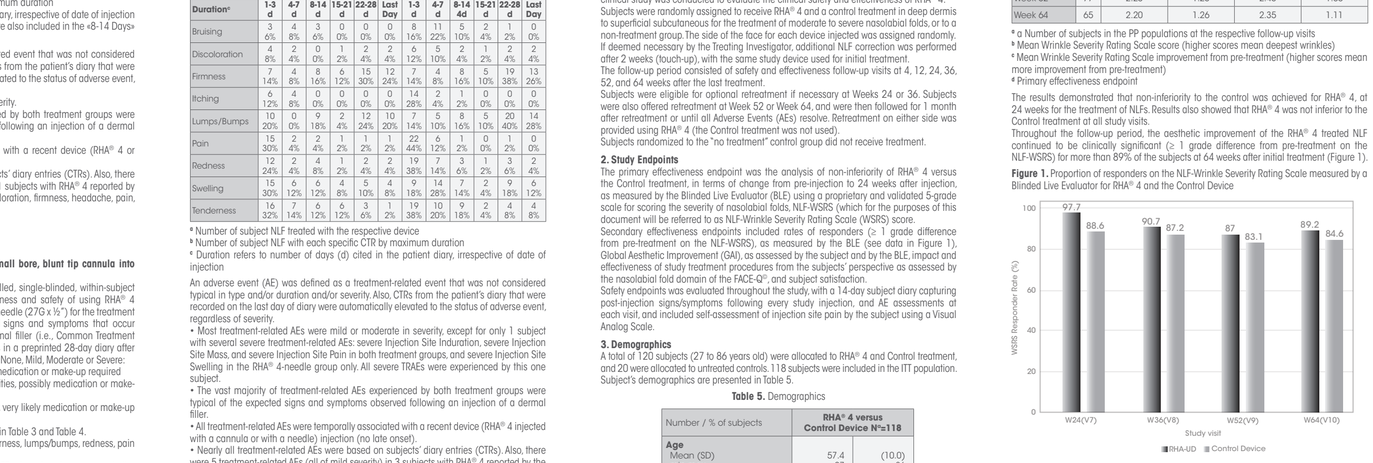
Table 6. NLF - Wrinkle Severity Rating Scale scores assessed by a Blinded Live Evaluator throughout the study

		RHA® 4		Control Device	
	n[a]	NLF-WSRS score[b]	NLF-WSRS Improvement[c]	NLF-WSRS score[b]	NLF-WSRS Improvement[c]
Pre-treatment	88	3.49	-	3.49	-
Week 24[d]	88	2.15	1.34	2.33	1.16
Week 36	86	2.21	1.28	2.37	1.12
Week 52	77	2.25	1.23	2.43	1.05
Week 64	65	2.20	1.26	2.35	1.11

[a] Number of subjects in the PP populations at the respective follow-up visits
[b] Mean Wrinkle Severity Rating Scale score (higher scores mean deepest wrinkles)
[c] Mean Wrinkle Severity Rating Scale improvement from pre-treatment (higher scores mean more improvement from pre-treatment)
[d] Primary effectiveness endpoint

The results demonstrated that non-inferiority to the control was achieved for RHA® 4, at 24 weeks for the treatment of NLFs. 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 the RHA® 4 treated NLF continued to be clinically significant (≥ 1 grade difference from pre-treatment on the NLF-WSRS) for more than 89% of the subjects at 64 weeks after initial treatment (Figure 1).

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



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

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

On the Global Aesthetic Improvement (GAI) scale, more than 87% of the subjects reported that the NLF treated with RHA® 4 was improved or very much improved from week 24 to week 64.The subjects consistently reported improvement up to 64 weeks based on the NLF module of the FACE-Q© questionnaire with the mean score improving from 24 to more than 70 throughout the follow-up period. More than 93% of the subjects reported to be satisfied or very satisfied from week 24 to week 64 (the scale grades were: very satisfied, satisfied, neither satisfied nor dissatisfied, dissatisfied or very dissatisfied).
More than 75% of the subjects received repeat treatment. The effectiveness and safety profiles after repeat treatment were similar to that after initial treatment.

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

1. Clinical Study Design

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

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

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

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

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

2. Study Endpoints

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

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

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

3. Demographics

A total of 50 subjects (42 to 77 years old) were injected with RHA® 4 into their NLFs with a cannula on one side of the face, and with a sharp needle on the other side.

Subject's demographics are presented in Table 7.

Table 7. Demographics

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

[a] 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[a]	NLF-WSRS score[b]	NLF-WSRS Improvement[c]	WSRS score[b]	WSRS Improvement[c]
Pre-treatment	46	3.3	-	3.3	-
Week 12[d]	46	1.7	1.61	1.7	1.65

[a] Number of subjects in the PP populations
[b] Mean Wrinkle Severity Rating Scale score (higher scores mean deepest wrinkles)
[c] Mean Wrinkle Severity Rating Scale improvement from pre-treatment (higher scores mean more improvement from pre-treatment)
[d] Primary effectiveness endpoint

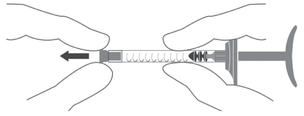
The aesthetic improvement of the RHA® 4 treated NLF with a cannula was similar to the one of the RHA® 4 treated NLF with a needle. These similar improvements were clinically significant (≥ 1 grade difference from pre-treatment on the NLF-WSRS) for 94% of the subjects at 12 weeks after initial treatment.

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

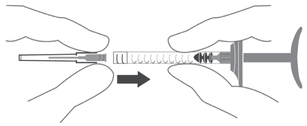
There were no differences in term of effectiveness and safety profiles between cannula brands were observed. Similar effectiveness and safety profiles were observed by age group.

DIRECTIONS FOR ASSEMBLY OF THE NEEDLE TO THE SYRINGE

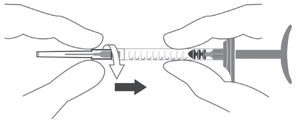
1. Remove the stopper from the syringe by pulling it off.



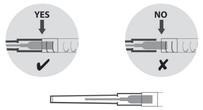
2. Insert the screw thread of the needle firmly into the syringe end-piece.



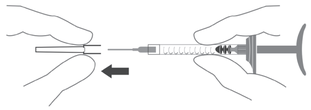
3. Screw the needle clockwise, while maintaining slight pressure between the needle and the syringe.



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



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



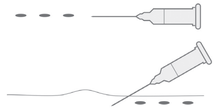
PRE-TREATMENT GUIDELINES

• Prior to treatment, the patient should avoid taking medications or supplements which thin the blood (e.g., aspirin, nonsteroidal anti-inflammatory medications, St. John's Wort, or high doses of Vitamin E supplements) as these agents may increase bruising and bleeding at the injection site.
• Before starting treatment, a complete medical history should be taken from the patient and the patient should be counseled on appropriate indications, risks, and should be informed about the expected treatment results, and expected responses. The patient should be advised of the necessary precautions before commencing the procedure.
• Prior to treatment with RHA® 4 the patient should be assessed for appropriate anesthetic treatment for managing comfort (e.g., topical anesthetic, local or nerve block). The patient's face should be washed with soap and water and dried with a clean towel. Cleanse the area to be treated with alcohol or another suitable antiseptic solution.
• Sterile gloves are recommended while injecting RHA® 4.
• Before injecting, prime the needle by carefully pressing the syringe plunger until a small droplet of the gel is visible at the tip of the needle.

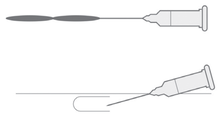
INJECTION TECHNIQUES

• RHA® 4 is administered by using a thin gauge needle (27 G x ½") or a blunt tip cannula (25 G x 2"). RHA® 4 is supplied with 27 G x ½" needles. The 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.

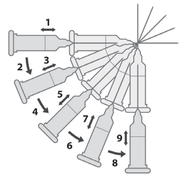
A. Serial puncture: (only recommended for needle): consists of multiple injections, evenly and closely spaced all along wrinkles or folds. This technique is considered to be more precise, but may result in more discomfort for the patient due to the number of punctures.



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 (retrograde) or pushing (antegrade) the needle/cannula.



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



• RHA® 4 is injected slowly into the deep dermis to superficial subcutaneous.
• If the color of the needle/cannula can be seen through the skin during injection, this means that the injection is too superficial. This should be avoided as the results of the correction could be irregular.
• The injection should be stopped before pulling the syringe out of the skin, to prevent product from leaking out, or product misplacement (too superficially in the skin).
• The volume to be injected depends on the corrections to be performed, but it is important to not overcorrect. Based on the US clinical study, patients should be limited to 6.0 ml per patient per treatment session in wrinkles and folds such as NLFs. The safety of injecting greater amounts has not been established.
• If blanching is observed (e.g., the overlying skin turns a whitish color), the injection should be stopped immediately and the area massaged until it returns to a normal color. Blanching may represent a vessel occlusion. If normal skin coloring does not return, do not continue with the injection. Treat in accordance with American Society for Dermatologic Surgery guidelines, which include hyaluronidase injection.
• If the wrinkles need further treatment with RHA® 4, the same procedure should be repeated until a satisfactory result is obtained.

POST-TREATMENT GUIDELINES

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

STERILE NEEDLES

• After use, needles and cannula are potential biohazards. Follow national, local, or institutional guidelines for use and disposal of medical sharp devices (e.g. discard uncapped needles and cannulas in approved sharps containers).
• Disposal should be in accordance with accepted medical practice and applicable local, State and Federal requirements.
• Obtain prompt medical attention if injury with used needles/cannulas occurs.
• To help avoid needle breakage, do not attempt to straighten a bent needle. Discard it and complete the procedure with a replacement needle.
• Do not recap needles/cannulas. Recapping by hand is a hazardous practice and should be avoided.

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

PATIENT INSTRUCTIONS

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

HOW SUPPLIED

RHA® 4 is supplied in individual blisters containing a 1.2 ml treatment syringe with two 27 G x ½" needles as indicated on the carton.
The content of the syringe is sterile and non-pyrogenic. Do not resterilize. Do not use if package is opened or damaged.
Each syringe is packaged into a blister with two unique device identifier traceability labels.

SHELF-LIFE AND STORAGE

RHA® 4 must be used prior to the expiration date printed on the package.
Store at room temperature (up to 25°C/77°F). Do not expose to direct sunlight. DO NOT FREEZE.

RxOnly

TEOXANE

Manufactured by:

TEOXANE SA
Rue de Lyon, 105
CH 1203 Geneva
Switzerland

Distributed by:

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

SYMBOLS

Manufacturer's name and address

REF — Catalog number

LOT — Lot / batch number

Expiration date (YYYY-MM-DD)

Consult Instructions for use

Single use only

STERILE — 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

230452/03

N° projet : 23_008

TEOXANE

Code : 230452/03	VERSION	COULEURS
PRODUIT : NOTICE RHA®4 - DUO 2x1.2mL_TSK_27G **PAYS :** US	**INITIALES :** NB - PICTURAL AN **VERSIONS - DATE :** 1 - 12/06/23 - 11h10 2 - 06/07/23 - 14h10 3 - 11/07/23 - 14h30 4 - 19/07/23 - 11h45 5 - 19/07/23 - 13h50	**RECTO/ VERSO** **NOIR**
Format ouvert : 280 mm (L) x 630 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 = 7.5 pts	**ANNULE ET REMPLACE :** 230452/02	