# TEOXANE RHA® Redensity

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

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

#### **DEVICE DESCRIPTION**

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

#### INTENDED USE / INDICATIONS

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

#### CONTRAINDICATIONS

- RHA® Redensity is contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.
- RHA® Redensity contains trace amounts of gram positive bacterial proteins, and is contraindicated for patients with a history of allergies to such material.
- RHA® Redensity should not be used in patients with previous hypersensitivity to local anesthetics of the amide type, such as lidocaine.
- $\bullet$  RHA  $\!\!^{\scriptscriptstyle{(\!0\!)}}$  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.
- $\bullet$  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

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

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

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

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

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

<sup>d</sup> 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 testina:

- 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 broad an authorate disreventing (CTPs).
- 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.

in subjects with higher Fitzpatrick skin types.

- 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

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		edensity 150		atment =52
Age Mean (SD) min max	61.6 38	(7.2) 81	60.7 46	(7.6) 77
Gender Female Male	147	98.0% 2.0%	51 1	98.1% 1.9%
Race White Black or African American Am.Indian/N. Alask. N. Hawaiian/P. Isl. Asian Other	143 4 1 0 2	95.3% 2.7% 0.7% 0.0% 1.3% 0.0%	52 0 0 0 0	100% 0.0% 0.0% 0.0% 0.0% 0.0%
Ethnicity Hispanic/Latino Not Hispanic/Latino	25 125	16.7% 83.3%	10 42	19.2% 80.8%
Fitzpatrick Skin Phototype I-III		147 (7	2.8%)	
    	18 37 55	12.0% 24.7% 36.7%	6 13 18	11.5% 25.0% 34.6%
IV-VI		55 (27	7.2%)	
IV V VI	29 8 3	19.3% 5.3% 2.0%	12 3 0	23.1% 5.8% 0.0%

<sup>&</sup>lt;sup>a</sup> All randomized subjects

#### 4. Treatment Characteristics

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

**b** Mod = Moderate

<sup>&</sup>lt;sup>c</sup> Sev = Severe

<sup>&</sup>lt;sup>b</sup> Number of events by maximum duration

<sup>&</sup>lt;sup>e</sup> Duration refers to number of days cited in the patient diary, irrespective of date of injection

RHA® Redensity was administered into the dermis and superficial dermis using different injection techniques to ensure a satisfactory result of the treatment of dynamic perioral rhytids.

In general, a linear threading technique combined with multiple punctures was used for 91.0% of the subjects treated with RHA® Redensity.

#### 5. Effectiveness Results

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

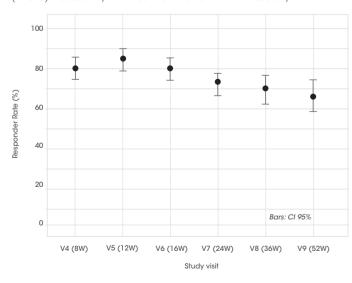
PR-SRS Responder Rate	e (BLE)	RHA® Redensity	No-Treatment	P-value <sup>b</sup>
Week 8	Na	150	51	
	Responder	121 (80.7%)	4 (7.8%)	<0.0001
	Not responder	29 (19.3%)	47 (92.2%)	
	Missing values	0	0	

<sup>a</sup> 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	156	156	147	137	131	125
(BLE assessment)	(80.4%)	(84.8%)	(80.3%)	(72.9%)	(69.7%)	(66.5%)
Not Responder	38	28	36	51	57	63
(BLE assessment)	(19.6%)	(15.2%)	(19.7%)	(27.1%)	(30.3%)	(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).

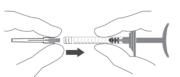
More than 78% of the subjects received repeat treatment. The effectiveness and safety profiles after repeat treatment were similar to that after initial treatment.

#### DIRECTIONS FOR ASSEMBLY OF THE NEEDLE TO THE SYRINGE

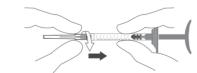
1. Remove the stopper from the syringe by pulling it off.



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.

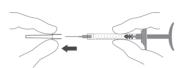


4. Continue screwing until the edge of the cap of the needle contacts the body of the syringe. There must be no space between these two parts. Failure to follow this instruction means that the needle could be ejected and/or leak at the Luer-lock.





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 antiinflammatory 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

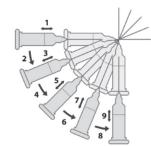
result in more discomfort for the patient due to the number of punctures.



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 auidelines 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

#### 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
- Sians 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 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® Redensity must be used prior to the expiration date printed on

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.

(Switzerland)

Revance Therapeutics, Inc.

Distributed by:

1222 Demonbreun Street, Rue de Lyon 105 CH 1203 Geneva Suite 2000 Nashville, Tennessee 37203

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

Under license U.S. Pat. Nos. 8, 450, 475; 8,822, 676; 9.089 .517 : 9.089 .518 : 9 .089 .519 : 9 .238.013 : 9.358 .322 .

#### SYMBOLS



Manufacturer's name and address



Catalog number



Lot / batch number



Consult Instructions for use

Expiration date (YYYY-MM-DD)



Single use only





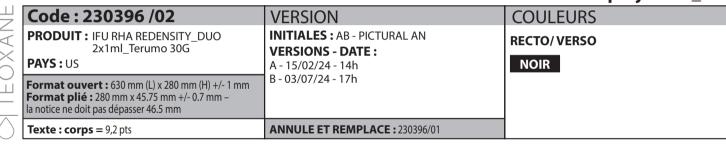


Do not use if the package is damaged





### N° projet: 24\_009





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

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

#### **DEVICE DESCRIPTION**

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

#### INTENDED USE / INDICATIONS

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

#### CONTRAINDICATIONS

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

#### WARNINGS

• RHA® 2 must not be injected into blood vessels. Introduction of product into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction. Take extra care when injecting soft tissue fillers, for example, inject the product slowly and apply the least amount of pressure necessary. Rare but serious adverse events associated with the intravascular injection of soft tissue fillers in the face have been reported and include temporary or permanent vision impairment or blindness, cerebral ischemia or cerebral hemorrhage leading to stroke, skin necrosis, and damage to underlying facial structures. Immediately stop the injection if a patient exhibits any of the following symptoms: changes in vision, signs of a stroke, blanching of the skin, or unusual pain during or shortly after the procedure. Patients should receive prompt medical attention and possibly evaluation by an appropriate health care practitioner specialist should an intravascular injection occur.

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

#### PRECAUTIONS

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

#### ADVERSE EXPERIENCES

#### 1. Clinical Evaluation of RHA® 2

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

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

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

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

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

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	тот	ALS	(1	RHA® 2 №=72 NLI	F)			ntrol Device =72 NLF)	
Responses	RHA® 2	CTRL°	Mild	Modd	Seve	Mild	Modd	Seve	
кезропзез	n⁵ %	n⁵ %	n⁵ %	n⁵ %	n⁵ %	n⁵ %	n⁵ %	n⁵ %	
Pruising	36	41	15	16	5	23	9	9	
Bruising	50.0%	56.9%	20.8%	22.2%	6.9%	31.9%	12.5%	12.5%	
Discoloration	24	27	12	7	5	14	8	5	
Discoloration	33.3%	37.5%	16.7%	9.7%	6.9%	19.4%	11.1%	6.9%	
Firmness	46	48	23	20	3	27	20	1	
Firmness	63.9%	66.7%	31.9%	27.8%	4.2%	37.5%	27.8%	1.4%	
Itching	12	15	9	3	0	10	4	1	
liciling	16.7%	20.8%	12.5%	4.2%	0.0%	13.9%	5.6%	1.4%	
Lumpa / Bumpa	38	37	21	14	3	22	13	2	
Lumps/Bumps	52.8%	51.4%	29.2%	19.4%	4.2%	30.6%	18.1%	2.8%	
Pain	19	16	13	6	0	11	5	0	
ruiii	26.4%	22.2%	18.1%	8.3%	0.0%	15.3%	6.9%	0.0%	
Redness	45	49	31	13	1	36	11	2	
Redi less	62.5%	68.1%	43.1%	18.1%	1.4%	50.0%	15.3%	2.8%	
Curallina	42	45	27	13	2	31	13	1	
Swelling	58.3%	62.5%	37.5%	18.1%	2.8%	43.1%	18.1%	1.4%	
Tenderness	44	40	34	10	0	31	9	0	
rendemess	61.1%	55.6%	47.2%	13.9%	0.0%	43.1%	12.5%	0.0%	

- <sup>a</sup> Number of subjects' NLF treated with the respective device
- <sup>b</sup> Number of subjects' NLF with any specific Common Treatment Response
- <sup>c</sup> CTRL = Control treatment
- $^{\mathbf{d}}$  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		RHA® 2 (Nº=72 NLF) Nº %				Control Device (N°=72 NLF)				
Responses		NÞ	%			NÞ	%			
Duration <sup>c</sup>	1-3	4-7	8-14	Last	1-3	4-7	8-14	Last		
Durunon	Days	Days	Days	Dayd	Days	Days	Days	Day		
Druisina	7	13	16	4	10	16	15	3		
Bruising	9.7%	18.1%	22.2%	5.6%	13.9%	22.2%	20.8%	4.2%		
Discoloration	11	4	9	3	8	10	9	3		
	15.3%	5.6%	12.5%	4.2%	11.1%	13.9%	12.5%	4.2%		
Firmness	13	11	22	14	16	13	19	12		
	18.1%	15.3%	30.6%	19.4%	22.2%	18.1%	26.4%	16.7%		
Harle Lands	5	4	3	3	9	2	4	3		
Itching	6.9%	5.6%	4.2%	4.2%	12.5%	2.8%	5.6%	4.2%		
L	11	13	14	12	14	11	12	6		
Lumps/Bumps	15.3%	18.1%	19.4%	16.7%	19.4%	15.3%	16.7%	8.3%		
Desire	11	4	4	3	7	5	4	2		
Pain	15.3%	5.6%	5.6%	4.2%	9.7%	6.9%	5.6%	2.8%		
Dodnoss	28	13	4	1	29	14	6	3		
Redness	38.9%	18.1%	5.6%	1.4%	40.3%	19.4%	8.3%	4.2%		
Curollina	19	11	12	5	22	15	8	3		
Swelling	26.4%	15.3%	16.7%	6.9%	30.6%	20.8%	11.1%	4.2%		
Tandarass	23	9	12	5	21	10	9	1		
Tenderness	31.9%	12.5%	16.7%	6.9%	29.2%	13.9%	12.5%	1.4%		

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

- <sup>e</sup> Duration refers to number of days cited in the patient diary, irrespective of date of injection
- <sup>d</sup> The CTR numbers indicated in the "Last Day" column are also included in the "8-14 Days" column.

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 seguelae.

#### 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 preinjection to 24 weeks after injection, as measured by the Blinded Live Evaluator (BLE) using a proprietary and validated 5-grade scale for scoring the severity of nasolabial folds, NLF-SRS (which for the purposes of this document will be referred to as Wrinkle Severity Rating Scale (WSRS) score.

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

#### 3. Demographics

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

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

RHA® 2 versus

Subjects' demographics are presented in Table 3.

Table 3. Demographics

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

<sup>&</sup>lt;sup>a</sup> 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 preinjection 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	Con	trol Device	
	na	WSRS	WSRS	WSRS	WSRS	
	11"	scoreb	Improvement <sup>c</sup>	scoreb	Improvement <sup>c</sup>	
Pre-treatment	67	3.45	-	3.45	-	
Week 24 <sup>d</sup>	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	

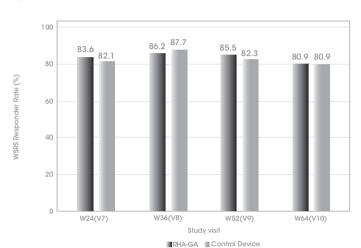
- <sup>a</sup> Number of subjects in the PP populations at the respective follow-up visits
   <sup>b</sup> Mean Wrinkle Severity Rating Scale score (higher scores mean deepest
- <sup>c</sup> Mean Wrinkle Severity Rating Scale improvement from pre-treatment (higher scores mean more improvement from pre-treatment)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

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

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

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 6
■ RHA® 2	83.6%	86.2%	85.5%	80.9%
■ Control Device	82.1%	87.7%	82.3%	80.9%

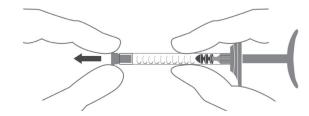
PP populations at the respective follow-up visits Rate of responders: ≥ 1 grade difference from pre-treatment on the WSRS

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.

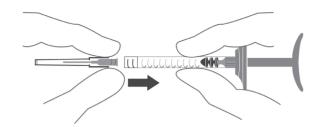
More than 78% of the subjects received repeat treatment. The effectiveness and safety profiles after repeat treatment were similar to that after initial treatment.

#### DIRECTIONS FOR ASSEMBLY OF THE NEEDLE TO THE SYRINGE

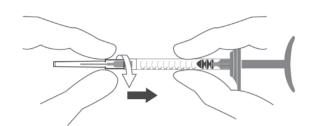
1. Remove the stopper from the syringe by pulling it off.



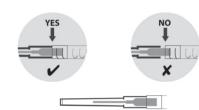
2. Insert the screw thread of the needle firmly into the syringe end-piece.



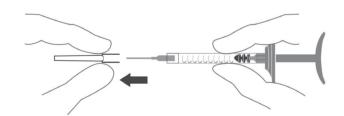
3. Screw the needle clockwise, while maintaining slight pressure between the needle and the syringe.



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 antiinflammatory 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

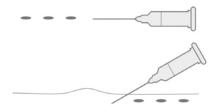
appropriate anesthetic treatment for managing comfort (e.g., topical anesthetic, local or nerve block). The patient's face should be washed with soap and water and dried with a clean towel. Cleanse the area to be treated with alcohol or another suitable antiseptic solution.

- 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.

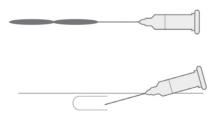
#### INJECTION TECHNIQUES

• 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.

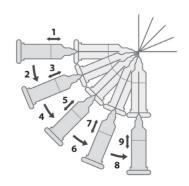
**A. Serial puncture:** consists of multiple injections, evenly and closely spaced all along wrinkles or folds. This technique is considered to be more precise, but may result in more discomfort for the patient due to the number of punctures.



**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 iniection.
- 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 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

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

#### Manufactured by:

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

Distributed by:

RHA® is a registered trademark of TEOXANE SA.

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

#### SYMBOLS



Manufacturer's name and address



Catalog number



Lot / batch number



Expiration date (YYYY-MM-DD)



Consult Instructions for use



Single use only



Sterilized using steam

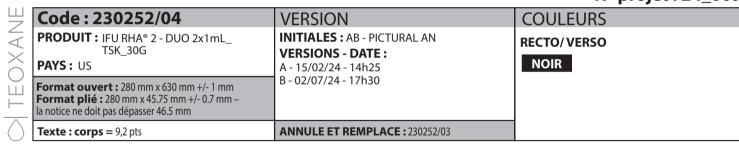


Do not use if the package is damaged





### N° projet: 24 009



## TEOXANE RHA® 3

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

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

#### DEVICE DESCRIPTION

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

#### INTENDED USE / INDICATIONS

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

RHA® 3 is indicated for injection into the vermillion body, vermillion border and oral commissure to achieve lip augmentation and lip fullness, in adults gaed 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

#### 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 fille 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
- As with all transcutaneous procedures, dermal filler implantation carries a risk of infection. Standard precautions associated with injectable materials should be followed
- The safety in patients with known susceptibility to keloid formation, hypertrophic scarring, and pigmentation disorders has not been studied.
- The safety for use in sites in the presence of other implants (including permanent implants) has not been studied
- The safety for use during pregnancy, in breastfeeding females, and in patients under
- 22 years of age has not been established. • RHA® 3 should be used with caution in patients on immunosuppressive therapy.
- Bruising or bleeding may occur at RHA® 3 injection sites. RHA® 3 should be used with caution in patients who are using substances that can prolong bleeding (such as thrombolytics, anticoagulants, or inhibitors of platelet aggregation).

- Injection of RHA® 3 into patients with a history of previous herpetic eruption may be associated with reactivation of the hernes
- 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-
- · 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-
- Severe: Great discomfort, daily activities compromised, very likely medication or make-up
- 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
- 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
- ent 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	TOT	ALS	(1	RHA® 3 (N°=75 NLF)			Control Device (N°=75 NLF)			
Responses	RHA® 3	CTRL°	Mild	Mod <sup>d</sup>	Sev <sup>e</sup>	Mild	Mod <sup>d</sup>	Sev <sup>e</sup>		
	nº %	nº %	nb %	n <sup>b</sup> %	n <sup>b</sup> %	nb %	n <sup>b</sup> %	n <sup>b</sup> %		
Bruising	42	38	20	15	7	12	20	6		
	56.0%	50.7%	26.7%	(20.0%)	9.3%	16.0%	26.7%	8.0%		
Discoloration	22	22	7	11	4	10	8	4		
	29.3%	29.3%	9.3%	14.7%	5.3%	13.3%	10.7%	5.3%		
Firmness	48	45	21	21	6	22	21	2		
	64.0%	60.0%	28.0%	28.0%	8.0%	29.3%	28.0%	2.7%		
Itching	13	11	7	4	2	5	4	2		
	17.3%	14.7%	9.3%	5.3%	2.7%	6.7%	5.3%	2.7%		
Lumps/Bumps	49	40	21	21	7	22	14	4		
	65.3%	53.3%	28.0%	28.0%	9.3%	29.3%	18.7%	5.3%		
Pain	30	23	21	6	3	18	4	1		
	40.0%	30.7%	28.0%	8.0%	4.0%	24.0%	5.3%	1.3%		
Redness	43	42	26	14	3	26	15	1		
	57.3%	56.0%	34.7%	18.7%	4.0%	34.7%	20.0%	1.3%		
Swelling	41	38	22	15	4	22	15	1		
	54.7%	50.7%	29.3%	20.0%	5.3%	29.3%	20.0%	1.3%		
Tenderness	44	37	29	12	3	26	10	1		
	58.7%	49.3%	38.7%	16.0%	4.0%	34.7%	13.3%	1.3%		

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

non Treatment Resnances after initial treatment with RHA® 3 and

<b>able 2.</b> 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		(N°=7	A® 3 5 NLF) %			Control (N°=7! n°	5 NLF)	
Duration <sup>c</sup>	1-3 Days	4-7 Days	8-14 Days	Last Day <sup>d</sup>	1-3 Days	4-7 Days	8-14 Days	Last Day <sup>d</sup>
Bruising	11 14.7%	19 25.3%	12 16.0%	4 5.3%	11 14.7%	16 21.3%	11 14.7%	1.3%

Discoloration	10	6	6	4	13	5	4	3
Discoloration	13.3%	8.0%	8.0%	5.3%	17.3%	6.7%	5.3%	4.0%
irmness	18	7	23	9	16	14	15	3
-irmness	24.0%	9.3%	30.7%	12.0%	21.3%	18.7%	20.0%	4.0%
tohina	9	4	0	0	8	3	0	0
tching	12.0%	5.3%	0.0%	0.0%	10.7%	4.0%	0.0%	0.0%
.umps/	17	11	21	12	15	13	12	6
Bumps	22.7%	14.7%	28.0%	16.0%	20.0%	17.3%	16.0%	8.0%
Darin.	21	7	2	0	18	3	2	1
Pain	28.0%	9.3%	2.7%	0.0%	24.0%	4.0%	2.7%	1.3%
) a dia a a a	27	9	7	2	27	10	5	2
Redness	36.0%	12.0%	9.3%	2.7%	36.0%	13.3%	6.7%	2.7%
Suallina	18	12	11	5	19	11	8	4
Swelling	24.0%	16.0%	14.7%	6.7%	25.3%	14.7%	10.7%	5.3%
[andarnasa	17	13	14	5	17	13	7	3
enderness	22.7%	17.3%	18.7%	6.7%	22.7%	17.3%	9.3%	4.0%
[enderness	17	13	14	5	17	13	7	3

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

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
- Proportions of subjects with at least one CTR were similar between RHA® 3 and control
- 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
- 19% of the retrieved digries (37/195) contained at least one CTR on the last day of the 30-day diary: 20% in the RHA $^{\circ}$  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-

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 digry - Safety Population

Common	тот	ALS	RHA® 3 (Nº=153)			Control (N°=49)		
Treatment	RHA® 3	Control nº %	Mild	Mod <sup>c</sup>	Sev <sup>d</sup>	Mild	Mod°	Sev <sup>d</sup>
Responses	nº %		n <sup>b</sup> %	n <sup>b</sup> %	n <sup>b</sup> %	nb %	nº %	n <sup>b</sup> %
At least 1 CTR	140	47	58	51	31	17	19	11
	95.2%	97.9%	41.4%	36.4%	22.1%	36.2%	40.4%	23.4%
Bruising	102	25	51	34	17	18	6	1
	69.4%	52.1%	50.0%	33.3%	16.7%	72.0%	24.0%	4.0%
Discoloration	65	20	39	19	7	12	7	1
	44.2%	41.7%	60.0%	29.2%	10.8%	60.0%	35.0%	5.0%
Firmness	115	38	56	47	12	17	18	3
	78.2%	79.2%	48.7%	40.9%	10.4%	44.7%	47.4%	7.9%
Itching	39	9	31	6	2	7	1	1
	26.5%	18.8%	79.5%	15.4%	5.1%	77.8%	11.1%	11.1%
Lumps/Bumps	115	38	58	46	11	24	10	4
	78.2%	79.2%	50.4%	40.0%	9.6%	63.2%	26.3%	10.5%
Pain	77	31	53	21	3	15	14	2
	52.4%	64.6%	68.8%	27.3%	3.9%	48.4%	45.2%	6.5%
Redness	81	28	49	23	9	17	9	2
	55.1%	58.3%	60.5%	28.4%)	11.1%	60.7%	32.1%	7.1%
Swelling	134	47	61	45	28	21	17	9
	91.2%	97.9%	45.5%	33.6%	20.9%	44.7%	36.2%	19.1%
Tenderness	114	38	69	35	10	17	20	1
	77.6%	79.2%	60.5%	30.7%	8.8%	44.7%	52.6%	2.6%

- a Number of subjects' Lips treated with the respective device
- <sup>b</sup> Number of subjects' Lips with any specific Common Treatment Response
- Mod = Moderate

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

CTR Duration <sup>c</sup>	Group (N°= subjects)	1-3 Days n <sup>b</sup> %	4-7 Days n <sup>b</sup> %	8-14 Days n <sup>b</sup> %	15-30 Days n <sup>b</sup> %	Last Day <sup>b</sup> n <sup>b</sup> %
At least 1 CTR	RHA® 3 (Nº=153)	111 75.5%	100 68.0%	67 45.6%	51 34.7%	30 20.4%
Alleusi i Cik	Control (N°=49)	40 83.3%	33 68.8%	11 22.9%	10 20.8%	7 14.6%
Bruising	RHA® 3 (Nº=153)	29 19.7%	34 23.1%	33 22.4%	6 4.1%	0.7%
bruising	Control (N°=49)	12 25.0%	10 20.8%	2 4.2%	1 2.1%	0
Discoloration	RHA® 3 (Nº=153)	25 17.0%	18 12.2%	15 10.2%	7 4.8%	3 2.0%
Discoloration	Control (N°=49)	13 27.1%	5 10.4%	2 4.2%	0	0
Firmness	RHA® 3 (Nº=153)	32 21.8%	26 17.7%	27 18.4%	30 20.4%	11 7.5%
11111111633	Control (N°=49)	12 25.0%	18 37.5%	4 8.3%	4 8.3%	3 6.3%
Itching	RHA® 3 (Nº=153)	22 15.0%	8 5.4%	4 2.7%	5 3.4%	0.7%
liciling	Control (N°=49)	5 10.4%	4 8.3%	0	0	0
Lumps/Bumps	RHA® 3 (Nº=153)	30 20.4%	23 15.6%	17 11.6%	45 30.6%	27 18.4%
Lumps/bumps	Control (N°=49)	13 27.1%	14 29.2%	2 4.2%	9 18.8%	7 14.6%
Pain	RHA® 3 (Nº=153)	40 27.2%	19 12.9%	10 6.8%	8 5.4%	0
ruiii	Control (N°=49)	20 41.7%	9 18.8%	2 4.2%	0	0
Redness	RHA® 3 (Nº=153)	42 28.6%	18 12.2%	15 10.2%	6 4.1%	0
Reuness	Control (N°=49)	19 39.6%	6 12.5%	3 6.3%	0	0
Swelling	RHA® 3 (Nº=153)	45 30.6%	43 29.3%	32 21.8%	14 9.5%	1 0.7%
Swelling	Control (N°=49)	25 52.1%	17 35.4%	2 4.2%	3 6.3%	0
Tondornoss	RHA® 3 (Nº=153)	37 25.2%	32 21.8%	27 18.4%	18 12.2%	3 2.0%
Tenderness	Control (N°=49)	16 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
- <sup>c</sup> 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 testina: 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 (AF) 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 AFs 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 acidbased 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 TL.
- 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 treatmentrelated 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.

assessed as Unlikely related to the study treatment or the study procedure and did not

• 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

- 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 treatmentrelated 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 compres inflammatory reaction, pain, alleraic 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

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 $^{\circ}$  3 and a control treatment in mid-

to-deep dermis for the treatment of moderate to severe nasolabial folds, or to a nontreatment 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).

condary 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

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-

#### post-injection signs/symptoms following every study injection, and AE assessments a each visit, and included self-assessment of injection site pain by the subject using a 100 mm Visual Analog Scale.

treat (ITT) population. Subjects' demographics are presented in Table 5.

#### Table 5. Demographics

umber / % of subjects	RHA® 3 ve Control D Nº=74	evice
<b>ge</b> Mean (SD) min max	55.7 26	(9.4) 77
ender Female Male	68 6	91.9% 8.1%
ace Caucasian Slack Am. Indian/N. Alask. N. Hawaiian/P. Isl. Asian Other	62 7 0 0 0 5	83.8% 9.5% 0.0% 0.0% 0.0% 6.8%

Hispanic/Latino 28.4% 71.6% Not Hispanic/Latino Fitzpatrick Skin Phototype 5.4% 28.4% 25.7% 27.0% 9.5% 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 contro 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.

DHA® 3 Control Device

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

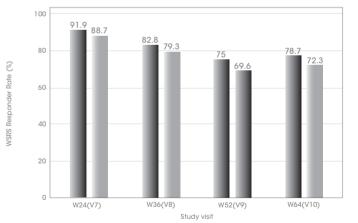
		71	na- o	Connor Device		
	nα	NLF-WS- RS score <sup>b</sup>	NLF-WSRS Improvement <sup>c</sup>	NLF-WS- RS score <sup>b</sup>	NLF-WSRS Improvement°	
Pre-treatment <sup>d</sup>	62	3.39	-	3.39	-	
Week 24	62	2.06	1.32	2.16	1.23	
Week 36	58	2.36	1.03	2.41	0.98	
Week 52	56	2.45	0.91	2.54	0.82	
Week 64	47	2.47	0.91	2.55	0.83	

- a Number of subjects in the PP populations at the respective follow-up visits
- Mean NLF-Wrinkle Severity Rating Scale score (higher scores mean deepest wrinkles) 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



■ RHA-DL ■ 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 multicente 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

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  $\geq 70\%$ .

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

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	Control	Total
	Nº=153	N°=49	Nº=202
Age Mean (SD) min max	48.8 (13.19) 22,76	48.5 (11.69) 24,68	48.7 (12.82) 22,76
Gender Female Male	151 (98.7%) 2 (1.3%)	48 (98.0%) 1 (2.0%)	199 (98.5%) 3 (1.5%)
Race Am. Indian/N. Alask. Asian Black or African American N. Hawaiian/P. Isl. White	2 (1.3%) 4 (2.6%) 15 (9.8%) 2 (1.3%) 130 (85.0%)	1 (2.0%) 1 (2.0%) 2 (4.1%) 0 45 (91.8%)	3 (1.5%) 5 (2.5%) 17 (8.4%) 2 (1.0%) 175 (86.6%)
Ethnicity Hispanic/Latino Not Hispanic/Latino Not available	32 (20.9%)	13 (26.5%)	45 (22.3%)
	118 (77.1%)	35 (71.4%)	153 (75.7%)
	3 (2.0%)	1 (2.0%)	4 (2.0%)
Fitzpatrick Skin Phototype I-III I II III III IV-VI V V	114 (74.5%)	35 (71.5%)	149 (73.8%)
	10 (6.5%)	7 (14.3%)	17 (8.4%)
	46 (30.1%)	9 (18.4%)	55 (27.2%)
	58 (37.9%)	19 (38.8%)	77 (38.2%)
	39 (25.5%)	14 (28.6%)	53 (26.2%)
	22 (14.4%)	10 (20.4%)	32 (15.8%)
	10 (6.5%)	3 (6.1%)	13 (6.4%)
	7 (4.6%)	1 (2.0%)	8 (4.0%)

Number of subjects in the safety populations

#### 4. Treatment Characteristics

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

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

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

#### 5. Effectiveness Results

The primary effectiveness endpoint was the fullness improvement from pre-injection of the lips treated with RHA® 3 compared to the improvement from pre-injection of the lip treated with the control treatment, using the TLFS, as assessed by the BLE at 12 weeks; results are presented in Table 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

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

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

#### <sup>a</sup> Primary effectiveness endpoint

<sup>b</sup> Estimate of difference in means RHA3 - control is 0.19 (-0.03, -0.42) calculated by Bootstrap estimate using 1000 samples. mITT nonulation

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

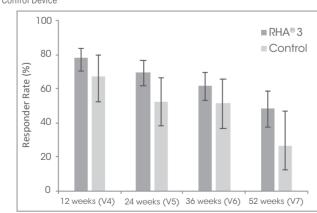
	RHA® 3	Control				
Baseline TLFS grades 1, 2 & 3	3					
N	137	44				
# of responders (%) [95% CI]	107 (78.1%) [70.5 - 84.2%]	29 (65.9%) [51.1 - 78.1%]				
Baseline TLFS grades 1 & 2						
N	68	27				
# of responders (%) [95% CI]	64 (94.1%) [85.8-97.7%]	24 (88.9%) [71.9-96.1%]				
Baseline TLFS grade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

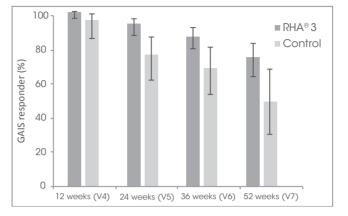
Throughout the follow-up period, the aesthetic improvement of the RHA® 3 continued to be clinically significant (≥ 1 grade difference from pre-treatment on the TLFS) for 61% (81/132) of the subjects at 36 weeks after last treatment, and for 48% (38/79) at 52 weeks after last treatment (Figure 2).

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



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).

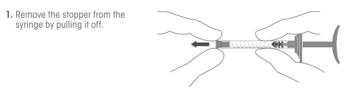
Figure 3. GAIS through 1 year as assessed by the BLE

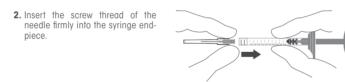


The subjects treated with RHA® 3 consistently reported improvement up to 52 weeks based on the Satisfaction with lips module of the FACE-Q® questionnaire with the mean score improving from Baseline by 51 points at Week 12 to more than 36 points throughout the follow-up period (46 at Week 24, 41 at Week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

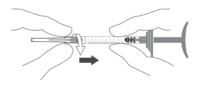
59% (90/153) of the subjects received repeat treatment. The effectiveness and safety profiles after repeat treatment were similar to that after initial treatment and touch-up.

#### DIRECTIONS FOR ASSEMBLY OF THE NEEDLE TO THE SYRINGE

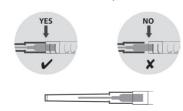




3. Screw the needle clockwise while maintaining slight pressure between the needle and the syringe.



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

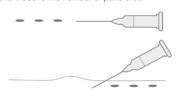


#### PRE-TREATMENT GUIDELINES

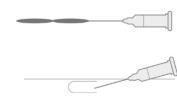
- Prior to treatment, the patient should avoid taking medications or supplements which thin the blood (e.g., aspirin, nonsteroidal anti-inflammatory medications, St. John's Wort, or high doses of Vitamin E supplements) as these agents may increase bruising and bleeding at the injection site
- Refore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

#### INJECTION TECHNIQUES

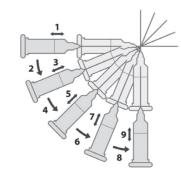
- RHA® 3 is administered by using a thin gauge needle (27 G x ½"). For the treatment of NLFs. the needle is inserted into the mid-to-deep dermis at an approximate angle of 15° to 30 parallel to the length of the wrinkle or fold. For lip augmentation, RHA® 3 is injected into the lip mucosa and/or mid 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
- 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
- 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

areater 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
- 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
- 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
- o Unusual pain during or shortly after treatment
- o Significant pain away from the injection site Signs of a stroke
- o 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
- Adverse reactions should be reported to Revance Therapeutics, Inc at 877-3REV-NOW (877-373-8669) and to Medical-us@teoxane.com.

Distributed by:

HOW SUPPLIED

RHA® 3 is supplied in individual blisters containing a 1 ml treatment syringe with two

he content of the syringe is sterile and non-pyrogenic. Do not resterilize. Do not use if

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

SHELF-LIFE AND STORAGE

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

RHA® 3 must be used prior to the expiration date printed on the package

TEOXANE S.A. Rue de Lyon 105 CH 1203 Geneva

27 G x ½" needles as indicated on the carton.

FREEZE. Do not store partially used syringes.

package is opened or damaged.

Manufactured by

(Switzerland)

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

RHA® is a registered trademark of TEOXANE SA.

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

#### SYMBOLS



Manufacturer's name and address



Catalog number



Lot / batch number

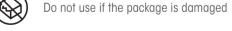


Expiration date (YYYY-MM-DD) Consult Instructions for use



Single use only

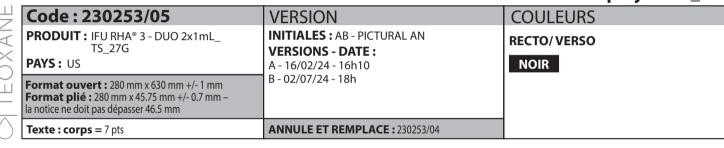








### N° projet: 24\_009





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 get implant It is produced with sodium Hyaluronic Acid (NgHA) with a concentration of 23 mg/g obtained from bacterial fermentation using the Streptococcus eaui bacterial strain, crosslinked with 1.4-butanedial dialycidyl ether (BDDE) and reconstituted in a physiological buffer (pH 7.3), RHA® 4 also contains 0.3% lidocaine hydrochloride monohydrate to reduce pain on injection.

#### INTENDED USE / INDICATIONS

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

#### CONTRAINDICATIONS

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

#### WARNINGS

- RHA® 4 must not be injected into blood vessels. Introduction of product into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction. Take extra care when injecting soft tissue fillers, for example, inject the product slowly and apply the least amount of pressure necessary. Rare but serious adverse events associated with the intravascular injection of soft tissue fillers in the face have been reported and include temporary or permanent vision impairment or blindness, cerebral ischemia or cerebral hemorrhage leading to stroke, skin necrosis, and damage to underlying facial structures. Immediately stop the injection if a patient exhibits any of the following symptoms: changes in vision, signs of a stroke, blanching of the skin, or unusual pain during or shortly after the procedure. Patients should receive prompt medical attention and possibly 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
- 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, anticoggulants 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 hernes
- If laser treatment, chemical peeling or any other procedure based on active dermal response is considered after treatment with RHA® 4, there is a possible risk of eliciting an inflammatory reaction at the implant site. This also applies if RHA® 4 is administered before the skin has healed completely after such a procedure.
- RHA® 4 is to be used as supplied. Modification or use of the product outside the Instructions for Use may adversely impact the sterility, safety, homogeneity, or performance of the product. • RHA® 4 is packaged for single-patient use. Do not reuse a syringe between two treatments and/
- or between two patients. Do not resterilize.
- Do not use if package is opened or damaged. The sterility of the product is not guaranteed in the case of failure to comply with this precaution. Failure to comply with the needle/blunt cannula attachment instructions could result in needle/blunt cannula disengagement and/or product leakage at the Luer-lock and needle/blunt cannula hub connection.
- RHA® 4 is a clear, colorless gel without particulates. In the event the contents of a syringe show signs of separation and/or appears cloudy, do not use the syringe; contact Revance Therapeutics, Inc. 877-3REV-NOW (877-373-8669).

#### ADVERSE EXPERIENCES

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

#### 1. Clinical Evaluation of RHA® 4 Into the NLFs

Clinical study TEO-RHA-1402 was a multicenter controlled randomized double-blinded withinsubject (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
- Severe: Great discomfort, daily activities compromised, very likely medication or make-up
- 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
- 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
- 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	тот	ALS	(N	RHA® 4  °=120 NL	.F)	Control Device (N°=120 NLF)		
Responses	RHA® 4	CTRL°	Mild	Mod <sup>d</sup>	Sev°	Mild	Mod <sup>d</sup>	Sev°
	nb %	nb %	n <sup>b</sup> %	n <sup>b</sup> %	nb %	n <sup>b</sup> %	n <sup>b</sup> %	nº %
Bruising	70	72	35	26	9	37	25	10
	58.3 %	60.0%	29.2%	21.7%	7.5%	30.8%	20.8%	8.3%
Discoloration	50	56	30	16	4	30	20	6
	41.7 %	46.7%	25.0%	13.3%	3.3%	25.0%	16.7%	5.0%
Firmness	91	93	36	46	9	13	50	30
	75.8%	77.5%	30.0%	38.3%	7.5%	10.8%	41.7%	25.0%
Itching	30	44	25	5	0	28	14	2
	25.0%	36.7%	20.8%	4.2%	0.0%	23.3%	11.7%	1.7%
Lumps/Bumps	81	90	36	33	12	28	37	25
	67.5%	75.0%	30.0%	27.5%	10.0%	23.3%	30.8%	20.8%
Pain	66	87	42	19	5	30	40	17
	55.0%	72.5%	35.0%	15.8%	4.2%	25.0%	33.3%	14.2%
Redness	84	91	42	38	4	32	42	17
	70.0%	75.8%	35.0%	31.7%	3.3%	26.7%	35.0%	14.2%
Swelling	97	104	41	44	12	21	38	45
	80.8%	86.7%	34.2%	36.7%	10.0%	17.5%	31.7%	37.5%
Tenderness	90	95	53	30	7	23	45	27
	75.0%	79.2%	44.2%	25.0%	5.8%	19.2%	37.5%	22.5%

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

**Duration**°

the Control Device - Safety Population

Control Device (N°=120 NLF) (N°=120 NLF) Treatment 1-3 4-7 8-14 Last 1-3 4-7 8-14 Last 18.3% | 23.3% | 16.7% | 6.7% | 30.8% | 23.3% | 5.8% | 3.3% 28 | 10 | 12 | 10 | 34 | 14 | 8 | 4 3.3% | 8.3% | 10.0% | 8.3% | 28.3% | 11.7% | 6.7% | 3.3% 3.3% | 16.7% | 45.8% | 29.2% | 10.8% | 21.7% | 45.0% | 21.7% 16.7% | 6.7% | 1.7% | 20.0% | 11.7% | 5.0% | 2.5% imps/Bumps 15.8% | 11.7% | 40.0% | 30.0% | 20.8% | 20.0% | 34.2% | 22.5% 40.0% | 10.0% | 5.0% | 2.5% | 45.0% | 20.8% | 6.7% | 1.7% 42 | 30 | 12 | 8 | 42 | 37 | 12 | 7 35.0% | 25.0% | 10.0% | 6.7% | 35.0% | 30.8% | 10.0% | 5.8%

Table 2. Duration of Common Treatment Responses after initial treatment with RHA® 4 and

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

30.0% 24.2% 26.7% 13.3% 22.5% 41.7% 22.5% 9.2%

41 22 27 14 26 39 30 8 34.2% 18.3% 22.5% 11.7% 21.7% 32.5% 25.0% 6.7%

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
- 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 NI Fs

- 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-• Severe: Great discomfort, daily activities compromised, very likely medication or make-up
- 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	тот	ALS		A® 4-canr N°=50 NL		RHA® 4-needle (N°=50 NLF)		
Treatment Responses	RHA® 4 -C nb %	RHA® 4 -N nb %	Mild n <sup>b</sup> %	Mod <sup>d</sup> n <sup>b</sup> %	Seve nb %	Mild n <sup>b</sup> %	Mod <sup>d</sup> n <sup>b</sup> %	Sev° nº %
Bruising	10	27	9	1	0	18	7	2
	20%	54%	18%	2%	0%	36%	14%	4%
Discoloration	9	16	8	1	0	10	5	1
	18%	32%	16%	2%	0%	20%	10%	2%

Firmness	40	43	23	14	3	23	17	3
	80%	86%	46%	28%	6%	46%	34%	6%
Itching	10	17	8	2	0	14	2	1
	20%	34%	16%	4%	0%	28%	4%	2%
Lumps/Bumps	33	45	24	5	4	28	12	5
	66%	90%	48%	10%	8%	56%	24%	10%
Pain	21	30	13	8	0	21	9	0
	42%	60%	26%	16%	0%	42%	18%	0%
Redness	21	33	17	4	0	26	7	0
	42%	66%	34%	8%	0%	52%	14%	0%
Swelling	36	41	25	10	1	23	16	2
	72%	82%	50%	20%	2%	46%	32%	4%
Tenderness	38	44	27	9	2	32	10	2
	76%	88%	54%	18%	4%	64%	20%	4%

- a Number of subjects' NLF treated with the respective device
- <sup>b</sup> 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	TOTAL				HA® 4-needle (N°=50 NLF) N <sup>b</sup> %							
<b>Duration</b> °	1-3	4-7	8-14	15-21	22-28	Last	1-3	4-7	8-14	15-21	22-28	Last
	d	d	d	d	d	Day	d	d	4d	d	d	Day
Bruising	3	4	3	0	0	0	8	11	5	2	1	0
	6%	8%	6%	0%	0%	0%	16%	22%	10%	4%	2%	0%
Discoloration	4	2	0	1	2	2	6	5	2	1	2	2
	8%	4%	0%	2%	4%	4%	12%	10%	4%	2%	4%	4%
Firmness	7	4	8	6	15	12	7	4	8	5	19	13
	14%	8%	16%	12%	30%	24%	14%	8%	16%	10%	38%	26%
Itching	6	4	0	0	0	0	14	2	1	0	0	0
	12%	8%	0%	0%	0%	0%	28%	4%	2%	0%	0%	0%
Lumps/Bumps	10	0	9	2	12	10	7	5	8	5	20	14
	20%	0%	18%	4%	24%	20%	14%	10%	16%	10%	40%	28%
Pain	15	2	2	1	1	1	22	6	1	0	1	0
	30%	4%	4%	2%	2%	2%	44%	12%	2%	0%	2%	0%
Redness	12	2	4	1	2	2	19	7	3	1	3	2
	24%	4%	8%	2%	4%	4%	38%	14%	6%	2%	6%	4%
Swelling	15	6	6	4	5	4	9	14	7	2	9	6
	30%	12%	12%	8%	10%	8%	18%	28%	14%	4%	18%	12%
Tenderness	16	7	6	6	3	1	19	10	9	2	4	4
	32%	14%	12%	12%	6%	2%	38%	20%	18%	4%	8%	8%

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

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 AFs were mild or moderate in severity except for only 1 subject with several severe treatment-related AFs; 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
- 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
- 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 AÉs 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, alleraic 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, antiinflammatories, 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 pasolabial 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<sup>©</sup>, 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.

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

<sup>a</sup> 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

In general, a linear threading or multiple punctate 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	<b>\® 4</b>	Control	Device
	nª	NLF-WSRS score <sup>b</sup>	NLF-WSRS Improvement	NLF-WSRS score <sup>b</sup>	NLF-WSRS Improvement
e-treatment	88	3.49	-	3.49	-
eek 24 <sup>d</sup>	88	2.15	1.34	2.33	1.16
eek 36	86	2.21	1.28	2.37	1.12
eek 52	77	2.25	1.23	2.43	1.05
eek 64	65	2.20	1.26	2.35	1.11

<sup>a</sup> a Number of subjects in the PP populations at the respective follow-up visits

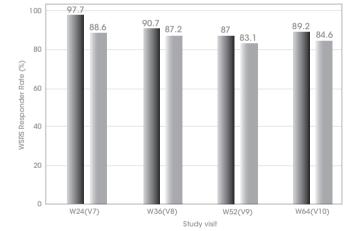
<sup>b</sup> Mean Wrinkle Severity Rating Scale score (higher scores mean deepest wrinkles) 6 Mean Wrinkle Severity Rating Scale improvement from pre-treatment (higher scores mean more improvement from pre-treatment)

<sup>d</sup> Primary effectiveness endpoint The results demonstrated that non-inferiority to the control was achieved for RHA® 4, at

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).

24 weeks for the treatment of NLFs. Results also showed that RHA® 4 was not inferior to the

**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



■RHA-UD ■ 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

#### 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 BLF.

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

#### 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<sup>©</sup>, 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 Analoa Scale.

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

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

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

#### 4. Treatment Characteristics

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

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

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.

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  $\hat{8}$ .

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

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

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

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

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

#### d Primary effectiveness endpoint

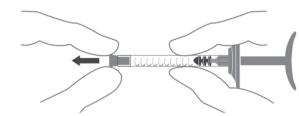
The aesthetic improvement of the RHA® 4 treated NLF with a cannula was similar to the one of the RHA® 4 treated NLF with a needle. These similar improvements were clinically significant (≥ 1 grade difference from pre-treatment on the NLF-WSRS) for 94% of the subjects at 12 weeks after initial treatment

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<sup>®</sup> 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

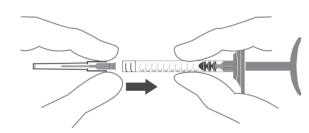
There were no differences in term of effectiveness and safety profiles between cannula brands were observed. Similar effectiveness and safety profiles were observed by age group.

#### DIRECTIONS FOR ASSEMBLY OF THE NEEDLE TO THE SYRINGE

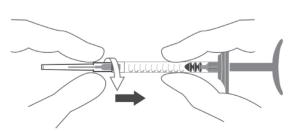
#### 1. Remove the stopper from the syringe by pulling it off.



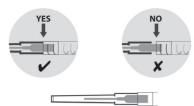
2. Insert the screw thread of the needle firmly into the syringe end-piece.



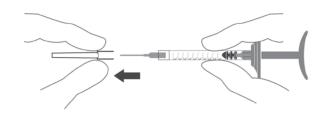
3. Screw the needle clockwise, while maintaining slight pressure between the needle and the syringe.



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.

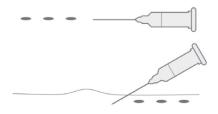


#### PRE-TREATMENT GUIDELINES

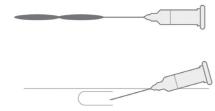
- Prior to treatment, the patient should avoid taking medications or supplements which thin the blood (e.g., aspirin, nonsteroidal anti-inflammatory medications, St. John's Wort, or high doses of Vitamin E supplements) as these agents may increase bruising and bleeding at the injection site.
- Before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

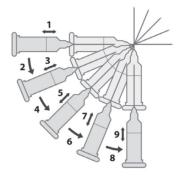
- RHA® 4 is administered by using a thin gauge needle (27 G x ½") or a blunt tip cannula (25 G x 2"). RHA® 4 is supplied with 27 G x ½" needles. The SoffFil® Precision and TSK STERIGLIDE™ cannulas were used in the clinical trials and are recommended for use with RHA® 4
- When using a needle, the needle 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 prehole needle
- ullet RHA $^{\odot}$  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



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/cannul



- 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. Fóllow 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
- · 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:

such treatment without talking with their prescribing physician.

- Changes in vision
- Unusual pain during or shortly after treatment
- Significant pain away from the injection site - Sians 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
- 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

Manufactured by:

Distributed by:

TEOXANE SA Revance Therapeutics, Inc. 1222 Demonbreun Street, Rue de Lyon, 105 CH 1203 Geneva Suite 2000 Switzerland Nashville, Tennessee 37203

RHA® is a registered trademark of TEOXANE SA.

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

#### SYMBOLS



Manufacturer's name and address



Catalog number

Lot / batch number



LOT

Expiration date (YYYY-MM-DD)



Consult Instructions for use



Sterilized using steam

Single use only

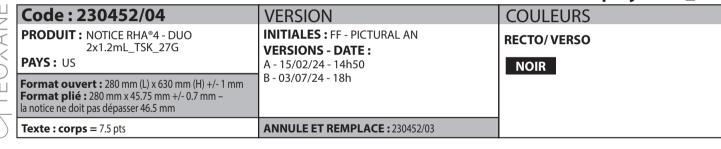


Do not use if the package is damaged





### N° projet: 24\_009



## RHA® Redensity Mepi

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

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

#### DEVICE DESCRIPTION

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

#### INTENDED USE / INDICATIONS

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

#### CONTRAINDICATIONS

- RHA® Redensity Mepi is contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.
- RHA® Redensity Mepi contains trace amounts of gram-positive bacterial proteins and in contrained for positive to with a history of allowing to wish material.
- is contraindicated for patients with a history of allergies to such material.

   RHA® Redensity Mepi should not be used in patients with previous hypersensitivity to
- local anesthetics of the amide-type, such as mepivacaine or lidocaine.

  RHA® Redensity Mepi should not be used in patients with bleeding disorders.

#### WARNINGS

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

  Inflammatory reaction, anaphylactic reaction, edema, implant migration, acne, blisters, scarring, papules and delayed onset of granulomas have been reported following the use of dermal fillers.

#### PRECAUTIONS

- In order to minimize the risks of potential complications, this product should only be
  used by experienced health care practitioners who have appropriate training in filler
  injection techniques, and who are knowledgeable about the anatomy at and around
  the site of injection.
- Health care practitioners are encouraged to discuss all potential risks of soft tissue injection with their patients prior to treatment and ensure that patients are aware of signs and symptoms of potential compilications.
- signs and symptoms of potential complications.

  The safety and effectiveness for the treatment of anatomic regions other than those described in the INTENDED USE / INDICATIONS section have not been established in controlled clinical studies.
- As with all transcutaneous procedures, dermal filler implantation carries a risk of infection. Standard precautions associated with injectable materials should be followed.
- The safety in patients with known susceptibility to keloid formation, hypertrophic scarring, and pigmentation disorders has not been studied.
- The safety for use in sites in the presence of other implants (including permanent implants) has not been studied.
- The safety for use during pregnancy, in breastfeeding females, and in patients under 22 years of age has not been established.
  The safety and effectiveness of RHA® Redensity Mepi for the correction of dynamic
- The safety and effectiveness of RHA® Redensity Mepi for the correction of dynamic perioral rhytids have not been clinically evaluated in patients with Fitzpatrick Skin Types V and VI
- RHA® Redensity Mepi should be used with caution in patients on immunosuppressive therapy.

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

#### ADVERSE EXPERIENCES

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

Due to the similarities in the formulation of RHA® Redensity Mepi and RHA® Redensity.

Due to the similarities in the formulation of RHA® Redensity Mepi and RHA® Redensity, the U.S. clinical evaluation of RHA® Redensity to support the indication for the correction of moderate to severe perioral rhytids provided safety and effectiveness information about RHA® Redensity Mepi for the indication for the correction of moderate to severe perioral rhytids. This safety information from this study apply to both RHA® Redensity Mepi and RHA® Redensity, and are summarized below under "Clinical Evaluation of RHA® Redensity in the perioral rhytids".

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

under "Clinical Évaluation of RHA® Redensity Mepi in the perioral rhytids".

#### 1. Clinical Evaluation of RHA® Redensity in the perioral rhytids

Clinical study TEO-RHA-1402 was a multicenter, controlled, randomized, blinded, No-Treatment control, prospective clinical study designed to compare the safety and effectiveness of RHA® Redensity versus a No-Treatment control for the treatment of moderate to severe dynamic perioral rhytids. The expected signs and symptoms that occur following the injection of a hyaluronic acid-based dermal filler (i.e., Common Treatment Responses; CTR) were individually assessed by subjects in a preprinted 14-day diary after each injection.

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

- Subjects were asked to rate each CTR as None, Mild, Moderate or Severe:
- Mild: Little discomfort, no effect on daily activities, no medication or make-up required.
   Moderate: some discomfort, some effect on daily activities, possibly medication or make-up required.
- Severe: Great discomfort, daily activities compromised, very likely medication or make-up required.
- CTRs by severity and duration are presented respectively, in Table 1 and Table 2.

   The most frequent CTRs were bruising, swelling, redness, firmness, lumps/bumps and
- 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"
- "Moderate".

   Less than 6% of each CTR was reported as "Severe" by the subjects except for
- 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	RHA® Redensity (N°=199)									
Treatment Responses	# of subjects with ≥1 CTR n <sup>b</sup> (%)	Mild n <sup>b</sup> (%)	Mod <sup>c</sup> n <sup>b</sup> (%)	Sev <sup>d</sup> n <sup>b</sup> (%)	# of subjects with no CTR n <sup>b</sup> (%)					
Redness	131	84	42	5	68					
	(65.8%)	(42.2%)	(21.1%)	(2.5%)	(34.2%)					
Pain	54	39	13	2	145					
	(27.1%)	(19.6%)	(6.5%)	(1.0%)	(72.9%)					
Tenderness	105	83	19	3	94					
	(52.8%)	(41.7%)	(9.5%)	(1.5%)	(47.2%)					

Firmness	115	79	33	3	84
	(57.8%)	(39.7%)	(16.6%)	(1.5%)	(42.2%)
Swelling	146	85	49	12	53
	(73.4%)	(42.7%)	(24.6%)	(6.0%)	(26.6%)
Lumps/Bumps	115	71	34	10	84
	(57.8%)	(35.7%)	(17.1%)	(5.0%)	(42.2%)
Bruising	154	65	65	24	45
	(77.4%)	(32.7%)	(32.7%)	(12.1%)	(22.6%)
Itching	31 (15.6%)	26 (13.1%)	3 (1.5%)	2 (1.0%)	168 (84.4%)
Discoloration	94	49	34	11	105
	(47.2%)	(24.6%)	(17.1%)	(5.5%)	(52.8%)
NI	4-1	d diam	-41/1/1-		

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

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

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

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

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

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

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

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

- All treatment-related AEs were mild or moderate in severity.
- Most of treatment-related AEs experienced were typical events following an injection
  of a hyaluronic acid-based dermal filler, such as: bruising, discoloration, erythema,
  injection site induration, irritation, swelling or pain. Other reported treatment-related
  AEs such as headache, muscle contraction or paresthesia are less typical but not
  unexpected following a dermal filler injection.
- All treatment-related AEs were temporally associated with a recent injection (no late onset).
- All treatment-related AEs were based on subjects' diary entries (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
- The duration of treatment related adverse events varied from 1 to 90 days except for two: the "Tyndall Effect" described above and there was an involuntary muscle contraction (fasciculation, left upper lip) which appeared after re-treatment at visit 9. It was mild in severity and no treatment was provided. It was persistent and had not improved at the study exit. The investigator followed up three months later and the subject stated it resolved 2 months prior.
- No events were deemed to be a granuloma or delayed inflammatory response.
- There were no events of vascular occlusion.
   There were no late onset treatment-related AEs.
- There were no treatment-related serious AEs.
- The incidence of treatment- related AE incidence rates was not different in subjects with higher Fitzpatrick skin types.

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

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

The safety of the RHA® Redensity Mepi dermal filler with mepivacaine indicated for injection into the perioral rhytids was studied against the approved RHA® Redensity dermal filler family with lidocaine in the clinical study TEO-RHA-1801, a multicenter, controlled, randomized, double-blinded, within-subject (split-face), prospective U.S. clinical study for the treatment of moderate to severe perioral rhytids with RHA® Redensity Mepi versus RHA® Redensity. Similar safety profiles between RHA® Redensity and RHA® Redensity Mepi were demonstrated.

The expected sign's/symptoms that occur following the injection (i.e., CTRs) were captured by subjects in a 30-day diary. Injection sites on each side of the face were individually assessed by subjects over 30 days following study injections. CTRs by severity and duration are presented respectively. in Table 3 and Table 4.

- The most frequent CTRs were firmness, tenderness, lumps/bumps, redness, swelling, and bruising.
- and bruising.
  Proportions of subjects experiencing at least one CTR of each category were similar between RHA® Redensity Mepi and RHA® Redensity treatments.
- The majority (97.4%) of CTRs resolved within 14 days.
- There were no notable differences between RHA® Redensity Mepi and RHA® Redensity
  with regard to the proportion of subjects (3.5%) who reported a severe CTR, the most
  common severe CTRs reported being swelling, tenderness, redness and pain.
- For nearly all CTRs (96.5%) experienced by any treatment group, the maximal severity reported was "Mild" or "Moderate".
   Importantly, on the last day of diary all ongoing CTRs (5 CTRs from 3 subjects) were

reported by the subjects mild in severity and deemed by the Investigators to be mild in severity and not clinically significant. There were all elevated to Treatment-Related AEs.

Table 3. Common Treatment Personness by maximum severity after initial treatment.

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

Oommon	TOT	ALS		=30 Perio		(Nº=30 Perioral)		
Common Treatment Responses	RHA® Redensity Mepi nb (%)	RHA® Redensity n <sup>b</sup> (%)	Mild n <sup>b</sup> (%)	Mod <sup>c</sup> n <sup>b</sup> (%)	Sev <sup>d</sup> n <sup>b</sup> (%)	Mild n <sup>b</sup> (%)	Mod <sup>c</sup> n <sup>b</sup> (%)	Sev <sup>d</sup> n <sup>b</sup> (%)
Bruising	12 (40.0%)	16 (53.3%)	9 (30.0%)	3 (10.0%)	0 (0.0%)	9 (30.0%)	6 (20.0%)	(3.3%)
Discoloration	10 (33.3%)	10 (33.3%)	8 (26.7%)	2 (6.7%)	0 (0.0%)	9 (30.0%)	(3.3%)	0 (0.0%)
Firmness	14 (46.7%)	19 (63.3%)	11 (36.7%)	3 (10.0%)	0 (0.0%)	16 (53.3%)	3 (10.0%)	0 (0.0%)
Itching	4 (13.3%)	2 (6.7%)	4 (13.3%)	0 (0.0%)	0 (0.0%)	2 (6.7%)	0 (0.0%)	0 (0.0%)
Lumps/Bumps	15 (50.0%)	17 (56.7%)	12 (40.0%)	3 (10.0%)	0 (0.0%)	10 (33.3%)	7 (23.3%)	0 (0.0%)
Pain	3 (10.0%)	4 (13.3%)	2 (6.7%)	0 (0.0%)	1 (3.3%)	3 (10.0%)	0 (0.0%)	(3.3%)
Redness	16 (53.3%)	15 (50.0%)	12 (40.0%)	3 (10.0%)	(3.3%)	9 (30.0%)	5 (16.7%)	(3.3%)
Swelling	21 (70.0%)	19 (63.3%)	16 (53.3%)	4 (13.3%)	(3.3%)	11 (36.7%)	7 (23.3%)	(3.3%)
Tenderness	13 (43.3%)	12 (40.0%)	11 (36.7%)	(3.3%)	(3.3%)	10 (3.3%)	2 (6.7%)	0 (0.0%)
Others <sup>e</sup>	(3.3%)	(3.3%)	0 (0.0%)	(3.3%)	0 (0.0%)	0 (0.0%)	(3.3%)	0 (0.0%)
Others <sup>f</sup>	(3.3%)	(3.3%)	0 (0.0%)	(3.3%)	0 (0.0%)	0 (0.0%)	(3.3%)	0 (0.0%)

- a Number of subjects' perioral rhytids treated with the respective device
- <sup>b</sup> Number of subjects' perioral rhytids with any specific Common Treatment Response
- c Mod = Moderate
- \* Sev = Severe

  One patient reported needle track marks on the corner of the mouth treated with RHA®
- Redensity Mepi dermal filler and which resolved in 2 days

  One patient reported injection site soreness on the corner of the mouth treated with RHA®
- Redensity Mepi dermal filler and which resolved in 2 days **Table 4.** Duration of Common Treatment Responses after initial treatment with

RHA® Redensity Mepi and RHA® Redensity reported in subject 30-day diary – Safety Population

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

nps/Bumps	RHA® Redensity Mepi	11 (36.7%)	3 (10.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)	(3.3%)
ірэ/випірэ	RHA® Redensity	5 (16.7%)	8 (26.7%)	3 (10.0%)	0 (0.0%)	(3.3%)	0 (0.0%)
n	RHA® Redensity Mepi	2 (6.7%)	0 (0.0%)	(3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	RHA® Redensity	3 (10.0%)	0 (0.0%)	(3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Iness	RHA® Redensity Mepi	11 (36.7%)	2 (6.7%)	3 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	RHA® Redensity	9 (30.0%)	5 (16.7%)	(3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ilina	RHA® Redensity Mepi	17 (56.7%)	2 (6.7%)	2 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
elling	RHA® Redensity	14 (46.7%)	3 (10.0%)	2 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
derness	RHA® Redensity Mepi	11 (36.7%)	2 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ucilicos	RHA® Redensity	10 (33.3%)	2 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ers <sup>e,f</sup>	RHA® Redensity Mepi	2 (6.6% <sup>e,f</sup> )	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CIS	RHA® Redensity	1 (3.3% <sup>f</sup> )	0 (0.0% <sup>e</sup> )	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

- <sup>a</sup> Number of subjects' perioral rhytids treated with the respective device
- <sup>b</sup> Number of subjects' perioral rhytids with each specific CTR by maximum duration
- <sup>e</sup> Duration refers to number of days cited in the patient diary, irrespective of date of injection
- <sup>4</sup> The CTR numbers indicated in the "Last Day" column are also included in the "22-30 Days" column one patient reported needle track marks on the corner of the mouth treated with RHA®
- Redensity Mepi dermal filler and which resolved in 2 days

  One patient reported injection site soreness on the corner of the mouth treated with RHA®
  Redensity Mepi dermal filler and which resolved in 2 days

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

• Lip function: ability to suck liquid through a straw.

• Lip movement: ability to pronounce specific letters and words.

- Lip sensation: ability to feel change of lip sensation with a monofilament and cotton wisp at different locations.
- All subjects from both groups were able to perform the tests successfully pre and postinjection and at every visit thereafter.

  Both RHA® Redensity Mepi and RHA® Redensity treatment groups presented with very similar adverse event profiles with 4 (13.3%) subjects experiencing a total of 9 treatment-related AEs. A total of 3 (10.0%) subjects in the RHA® Redensity
- treatment group experienced 4 treatment-related AEs, and 4 (13.3%) subjects in the RHA® Redensity Mepi treatment group experienced 5 treatment-related AEs.

   All treatment-related AEs were based on subjects' diary entries (CTRs)
- All treatment-related AEs were mild in severity and none were considered by Investigators to be clinically significant. All events resolved spontaneously without the pool for modified theorem.
- the need for medical therapy.

  All treatment-related AEs experienced by both treatment groups were typical of the expected signs and symptoms observed following an injection of a hyaluronic acid-based dermal filler except one (needle track marks) that was reported by the subject in the "other" category of the 30-day diary and which resolved in 3.5 days.
- In the "other" category of the 30-day diary and which resolved in 3.5 days.

  The average duration of a treatment related adverse event was 1-3.5 days except for two: an injection site mass experienced by 1 subject with only RHA® Redensity Mepi which resolved spontaneously after 35 days, and an injection site induration which was experienced by 2 (6.7%) subjects in each group. It was persistent and had not improved at the study exit for the 2 subjects. The site conducted post-exit telephone interviews with these subjects who both confirmed that the events had resolved spontaneously without intervention within 77 days post-injection.
- No events were deemed to be a granuloma.
- There were no events of vascular occlusion
- There were no late onset treatment-related AEs.
   There were no treatment-related serious AEs.
- There were no irealment-related serious AEs.
   There were no subjects who withdrew from the study due to AEs.
- Safety profile by Fitzpatrick skin type (I to IV), ethnicity, and age was not different. There were no reported cases of scarring, keloid formation or hyperpigmentation.

#### 3. Post-marketing Surveillance

Post-marketing surveillance data are based on RHA® Redensity containing lidocaine, these data are representative and applicable to RHA® Redensity Mepi.

The following adverse events were reported as part of post-marketing surveillance on the use of RHA® Redensity outside the United States with a prevalence equal or superior to 1 occurrence for 100,000 syringes: skin edema, injection site masses (lumps and bumps), skin swelling, skin induration, vascular complication (such as vessel compression/occlusion), pain, ecchymosis, erythema, skin discoloration and inflammatory reaction. Additionally, other less frequent adverse reactions have also been reported, and include dermal filler overcorrection, allergic reaction, product misplacement, inflammatory nodules (papules), skin necrosis, , granuloma, injection site movement impairment, paraesthesia, skin atrophy, injection site fibrosis, urticaria and device dislocation.

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

In many cases the symptoms resolved without any treatment. Reported treatments included the use of (in alphabetical order): analgesics, antibiotics, antihistamines, anti-inflammatories, anti-viral, corticosteroids, implant dissolution (hyaluronidase), massage, and vasodilators. Final resolution varies from ongoing to total resolution of the symptoms with or without sequelae.

#### CLINICAL STUDIES

#### CLINICAL STUDY OF RHA® REDENSITYTM

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

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

#### 1. Pivotal Study Design: Clinical Evaluation of RHA® Redensity

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 U.S. 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 offer 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. It 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 100 mm Visual Analog Scale.

#### 3. Demographics

A total of 202 subjects (38 to 81 years old) were allocated to RHA® Redensity and Notreatment control groups. 163 subjects were in the US and 39 in Canada. 199 subjects were included in the intention-to-treat (ITT) population (pooled population). Subjects' demographics are presented in Table 5.

RHA® Redensity No-Treatment

#### Table 5. Demographics

Number / % of subjects	Nº=1	50	N°=	52
Age Mean (SD) min max	61.6 38	(7.2) 81	60.7 46	(7
Gender Female Male	147 3	98.0% 2.0%	51 1	98. 1.
Race White Black or African American Am. Indian/N. Alask. N. Hawaiian/P. Isl. Asian Other	143 4 1 0 2	95.3% 2.7% 0.7% 0.0% 1.3% 0.0%	52 0 0 0 0	10/ 0./ 0./ 0./ 0./ 0./
Ethnicity Hispanic/Latino Not Hispanic/Latino	25 125	16.7% 83.3%	10 42	19.: 80.:
Fitzpatrick Skin Phototype				
-		147 (7	2.8%)	
    	18 37 55	12.0% 24.7% 36.7%	6 13 18	11. 25. 34.
IV - VI		55 (2	7.2%)	
IV V VI	29 8 3	19.3% 5.3% 2.0%	12 3 0	23. 5. 0.

#### <sup>a</sup> All randomized subjects

#### 4. Treatment Characteristics

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

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

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

initial treatment (Figure 1).

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

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

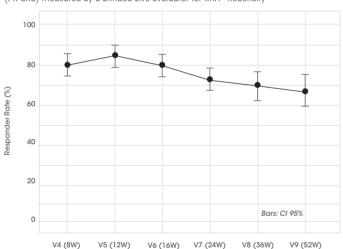
**Table 6.** Responder rate assessed by a Blinded Live Evaluator at primary endpoint

PR-SRS Responder Rate (BLE)		RHA® Redensity	No-Treatment	P-value <sup>b</sup>
Week 8	Na	150	51	
	Responder	121 (80.7%)	4 (7.8%)	< 0.0001
	Not responder		47 (92.2%)	
	Missing values	0	0	

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

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

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%)			

Study visit

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 freated 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® auestionnaire, the subjects consistently reported improvement up to 52 weeks with a mean score change of more than 36 points from baseline throughout the followup period. Subjects were asked six questions within the FACE-Q<sup>©</sup> 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<sup>©</sup> 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, atisfied 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.

The safety and effectiveness of the RHA® Redensity Mepi in the correction of moderate to severe perioral rhytids were evaluated in comparison to RHA® Redensity (lidocaine) in a U.S. pivotal clinical study described hereafter.

The purpose of this short-term clinical study was to compare RHA® Redensity Mepi containing mepivacaine with RHA® Redensity containing lidocaine in terms of reducing pain during injection into the perioral rhytids. The duration of the effectiveness of the anesthetic agent (mepiyacaine or lidocaine) is less than a day.

#### 1. Pivotal Study Design

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

Subjects were treated RHA® Redensity Mepi with mepivacaine in a randomly selected sequence (first or second injection) into the perioral rhytids in one side of the face and RHA® 1` with into the contralateral perioral rhytids. RHA® Redensity Mepi and RHA® Redensity were administered into the dermis and superficial dermis for the treatment of moderate to severe perioral rhytids

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

#### 2. Study Endpoints

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

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

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

Secondary effectiveness endpoints included change in the severity of the perioral rhytids as measured by the TI using the PR-SRS, the rates of responders ( $\geq$  1-grade difference from pre-treatment on the PR-SRS), as measured by the TI, Global Aesthetic Improvement (GAI), as assessed by the subject and by the TL impact and effectiveness of study treatment procedures from the subjects' perspective as assessed by the nasolabial fold domain of the FACE-Q<sup>©</sup>, and subject satisfaction.

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

#### 3. Demographics

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

Table 7. Demographics

Number / % of subjects	RHA® Redensity N RHA® Rede N°=30	nsity
Age Mean (SD) min max	64.3 48	(8.2 7
Gender Female Male	30 0	100.09
Race Caucasian Black Am. Indian/N. Alask. N. Hawaiian/P. Isl. Asian Other	30 0 0 0 0	100.09 0.09 0.09 0.09 0.09
Ethnicity Hispanic/Latino Not Hispanic/Latino	11 19	36.79 63.39
Fitzpatrick Skin Phototype I-III I II III III IV-VI V	23 1 11 11 7 7 7 0	76.79 3.39 36.79 36.79 23.39 0.09 0.09

Number of subjects in the ITT population

#### 4. Treatment Characteristics

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

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

The primary effectiveness endpoint was met for RHA® Redensity Mepi

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

For both treatment groups, the level of pain decreased over time with no statistically significant difference at all time points (at 15, 30, 45, and 60 minutes post-injection) he injection pain was reduced to 6.8 mm for RHA® Redensity Mepi and 6.3 mm RHA® Redensity after 15 minutes and gone (0.0 mm) after 60 minutes post-injection.

Finally, the duration of anesthetic effect was also reported by the subject to be similar between treatment groups, lasting around 3.6 hours for the side treated with RHA® Redensity Mepi (with mepivacaine) and 3 hours for the side treated with RHA® Redensity (with lidocaine) Results are presented in Table 8 and Table 9.

**Table 8.** Injection Site Pain during injection – ITT population

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

a Number of subjects in the ITT population

Table 9. Injection Site Pain after injection – ITT population

VAS pain (mm) Mean (SD)	RHA® Redensity Mepi N°=30	RHA® Redensity N°=30	VAS Difference (mm) N°=30
Time point:			
- 15 Min	6.8 (13.72)	6.3 (12.29)	-0.6 (2.16)
- 30 Min	1.0 (4.19)	1.0 (4.03)	-0.0 (0.18)
- 45 Min	0.4 (2.37)	0.3 (1.83)	-0.1 (0.55)
- 60 Min	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)

Number of subjects in the ITT population

Secondary endpoints demonstrated no difference between RHA® Redensity Mepi and

A similar improvement in the PR-SRS scores was observed one month post-injection with a score improvement of 1.5 points in both RHA® Redensity Mepi and RHA® Redensity treatment aroups. Responder rate was nearly similar after the injection, with 93.3% of treated subjects

with RHA® Redensity Mepi versus 96.7% with RHA® Redensity. Responder rate was similar for both treatment groups one-month post-injection, with 96.7% of treated On GAI scale, RHA® Redensity Mepi and RHA® Redensity demonstrated identical GAI

scores as assessed by both TIs and subjects. 100% of the subjects were deemed by the TI to have their perioral rhytids treated improved or very much improved at one-month post-injection. 100% of the subjects reported having their perioral rhytids treated improved or very much improved.

The subjects also reported similar improvement based on the Perioral Rhytids domain of the FACE-Q<sup>®</sup> questionnaire with the mean score increasing by 64.7 and 60.9 points in the RHA® Redensity Mepi and RHA® Redensity treatment group, respectively

More than 96% of the subjects reported being satisfied or very satisfied one month after their treatment with no distinction between the treatment groups. Similar effectiveness and safety profiles were observed by Fitzpatrick skin type (I to IV),

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

#### DIRECTIONS FOR ASSEMBLY OF THE NEEDLE TO THE SYRINGE

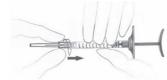
1. Remove the stopper from the syringe by pulling it off.

ethnicity and age groups.



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





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 even 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 freatment, 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
- Prior to treatment with RHA® Redensity Mepi the patient should be assessed for appropriate anesthetic treatment for managing comfort (e.g., topical anesthetic, local or nerve block). The patient's face should be washed with soap and water and dried with a clean towel. Cleanse the area to be treated with alcohol or another suitable antiseptic solution.
- Sterile gloves are recommended while injecting RHA® Redensity Mepi.
   Before injecting, prime the needle by carefully pressing the syringe plunger until a
- small droplet of the gel is visible at the tip of the needle.

#### INJECTION TECHNIQUES

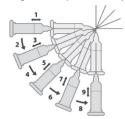
- RHA® Redensity Mepi can be administered by using a thin gauge needle (30 G x ½") and with a number of different techniques that depend on the injector's experience and preference, and patient characteristics.
- A. Preclinical testing between the following needles brands (TSK HPC, TSK PRC, Terumo TW, Terumo ETW) and the syringe has confirmed that the interoperability and compatibility is reliable and safe. Serial puncture: consists of multiple injections evenly and closely spaced perpendicular to the lines. This technique is considered to be more precise, but may result in more discomfort for the patient due to the number of punctures



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

#### POST-TREATMENT GUIDELINES

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

#### STERILE NEEDLES

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

#### PATIENT INSTRUCTIONS

- A patient information brochure is available on request, or via the website www.revance.com.
- It is recommended that the following information be shared with patients:
- Patients should be advised not to wear make-up during 12 hours following injection.

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

#### HOW SUPPLIED

RHA® Redensity Mepi are supplied in individual blisters containing a 1 mL treatment syringe with two 30 G x 1/2" needles as indicated on the carton. The content of the syringe is sterile and non-pyrogenic. Do not re-sterilize. Do not use if package is opened or damaged

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

#### SHELF-LIFE AND STORAGE

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

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

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

#### SYMBOLS



Manufacturer's name and address



LOT Lot / batch number

Catalog number



Consult Instructions for use

Expiration date (YYYY-MM-DD)



Single use only



Do not use if the package is damaged





## RHA® 2 Mepi

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

#### DEVICE DESCRIPTION

RHA® 2 Mepi is a viscoelastic, sterile, non-pyrogenic, clear, colorless, homogeneous and biodegradable gel implant. It is produced with sodium Hyaluronic Acid (NaHA) with a concentration of 23 mg/g obtained from bacterial fermentation using the Streptococcus equi bacterial strain, crosslinked with 1.4-butanedial dialycidyl ether (BDDE), and reconstituted in a physiological buffer (pH 7.3). RHA® 2 Mepi also contains 0.3% mepivacaine hydrochloride to reduce pain on injection.

#### INTENDED USE / INDICATIONS

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

#### CONTRAINDICATIONS

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

#### WARNINGS

- Introduction of product into the vasculature may lead to embolization occlusion of the vessels, ischemia, or infarction. To avoid this:
- Do not inject into blood vessels
- Take extra care when injecting soft-tissue fillers, inject the product slowly and apply the least amount of pressure necessary.
- Rare but serious adverse events associated with the intravascular injection of softtissue 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
- 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
- As with all transcutaneous procedures, dermal filler implantation carries a risk of infection. Standard precautions associated with injectable materials should be
- The safety in patients with known susceptibility to keloid formation, hypertrophic scarring, and pigmentation disorders has not been studied. • The safety for use in sites in the presence of other implants (including permanent
- implants) has not been studied.
- The safety for use during pregnancy, in breastfeeding females, and patients under 22 years of age has not been established.
- RHA® 2 Mepi should be used with caution in patients on immunosuppressive therapy. Bruising or bleeding may occur at RHA® 2 Mepi injection sites. RHA® 2 Mepi should be used with caution in patients who are using substances that can prolong bleeding

(such as thrombolytics, anticoagulants, or inhibitors of platelet aggregation).

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

#### ADVERSE EXPERIENCES

RHA® 2 Mepi and RHA® 2 have the same formulation except for a difference in the anesthetic agent: RHA® 2 Mepi contains mepivacaine (0.3% w/w), while RHA® 2 contains lidocaine (0.3% w/w). Mepivacaine and lidocaine have many similar and equivalent physico-chemical characteristics and properties, they are also harmacologically related.

Due to the similarities in the formulation of RHA® 2 Mepi and RHA® 2, the U.S. clinical evaluation of RHA® 2 to support the indication for the correction of moderate to severe dynamic wrinkles and folds, such as NLF, provided safety and effectiveness information about RHA® 2 Mepi for the indication for the correction of moderate to severe dynamic wrinkles and folds, such as NLF. This safety information from this long-term study apply to both RHA® 2 Mepi and RHA® 2, and are summarized below under "Clinical Evaluation of RHA® 2 in the NLFs"

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

#### 1. Clinical Evaluation of RHA® 2 in the NLFs

Clinical study TEO-RHA-1302 was a multicenter, controlled, randomized, doubleblinded, within-subject (split-face), prospective US study designed to compare the safety of RHA® 2 versus a control treatment for the treatment of moderate to severe nasolabial folds and demonstrated similar safety profiles. The expected signs and symptoms that occur following the injection of a hyaluronic acid-based dermal filler (i.e., Common Treatment Responses; CTR) were individually assessed by subjects in a reprinted 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
- Severe: Great discomfort, daily activities compromised, very likely medication or
- 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 bruisina.
- 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

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

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

ommon reatment	TOT	ALS	(N°=72 NLF)			(N°=72 NLF)		
esponses	RHA® 2 nb (%)	CTRL° nº (%)	Mild nb (%)	Mod <sup>d</sup> n <sup>b</sup> (%)	Seve nb (%)	Mild nb (%)	Mod <sup>d</sup> n <sup>b</sup> (%)	Seve nb (%)
ruising	36 (50.0%)	41 (56.9%)	15 (20.8%)	16 (22.2%)	5 (6.9%)	23 (31.9%)	9 (12.5%)	9 (12.5%)
iscoloration	24 (33.3%)	27 (37.5%)	12 (16.7%)	7 (9.7%)	5 (6.9%)	14 (19.4%)	8 (11.1%)	5 (6.9%)
irmness	46 (63.9%)	48 (66.7%)	23 (31.9%)	20 (27.8%)	3 (4.2%)	27 (37.5%)	20 (27.8%)	1 (1.4%)
ching	12 (16.7%)	15 (20.8%)	9 (12.5%)	3 (4.2%)	0 (0.0%)	10 (13.9%)	4 (5.6%)	1 (1.4%)
umps/ 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%)
ain	19 (26.4%)	16 (22.2%)	13 (18.1%)	6 (8.3%)	0 (0.0%)	11 (15.3%)	5 (6.9%)	0 (0.0%)
edness	45 (62.5%)	49 (68.1%)	31 (43.1%)	13 (18.1%)	1 (1.4%)	36 (50.0%)	11 (15.3%)	2 (2.8%)
welling	42 (58.3%)	45 (62.5%)	27 (37.5%)	13 (18.1%)	2 (2.8%)	31 (43.1%)	13 (18.1%)	1 (1.4%)
enderness	44 (61.1%)	40 (55.6%)	34 (47.2%)	10 (13.9%)	0 (0.0%)	31 (43.1%)	9 (12.5%)	0 (0.0%)

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

- <sup>b</sup> Number of subjects' NLF with any specific Common Treatment Response
- c CTRL = Control treatment
- e Sev Severe

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

ommon eatment esponses		(N°=7	\® 2 2 NLF) (%)		Control Device (N°=72 NLF) n <sup>b</sup> (%)			
uration <sup>c</sup>	1-3	4-7	8-14	Last	1-3	4-7	8-14	Last
	Days	Days	Days	Day <sup>d</sup>	Days	Days	Days	Day <sup>d</sup>
uising	7	13	16	4	10	16	15	3
	(9.7%)	(18.1%)	(22.2%)	(5.6%)	(13.9%)	(22.2%)	(20.8%)	(4.2%)
scoloration	11	4	9	3	8	10	9	3
	(15.3%)	(5.6%)	(12.5%)	(4.2%)	(11.1%)	(13.9%)	(12.5%)	(4.2%)
mness	13	11	22	14	16	13	19	12
	(18.1%)	(15.3%)	(30.6%)	(19.4%)	(22.2%)	(18.1%)	(26.4%)	(16.7%)
hing	5 (6.9%)	4 (5.6%)	3 (4.2%)	3 (4.2%)	9 (12.5%)	2 (2.8%)	4 (5.6%)	3 (4.2%)
mps/ Bumps	11	13	14	12	14	11	12	6
	(15.3%)	(18.%)	(19.4%)	(16.7%)	(19.4%)	(15.3%)	(16.7%)	(8.3%)
iin	11	4	4	3	7	5	4	2
	(15.3%)	(5.6%)	(5.6%)	(4.2%)	(9.7%)	(6.9%)	(5.6%)	(2.8%)
edness	28 (38.9%)	13 (18.1%)	4 (5.6%)	1 (1.4%)	29 (40.3%)	14 (19.4%)	6 (8.3%)	3 (4.2%)
velling	19	11	12	5	22	15	8	3
	(26.4%)	(15.3%)	(16.7%)	(6.9%)	(30.6%)	(20.8%)	(11.1%)	(4.2%)
nderness	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

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

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-
- All treatment-related AEs were temporally associated with a recent device (RHA® 2 or control treatment) injection (no late onset).
- All treatment-related AEs were based on subjects' diary entries (CTRs) except one (injection site bruising; mild) that was reported by the Treating Investigator at time of initial injection and which resolved in 12 days.
- No events were deemed to be a granuloma.
- There were no late onset treatment-related AFs
- There were no treatment-related serious AEs.

#### 2. Clinical Evaluation of RHA® Mepi in the NLFs

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

The expected signs/symptoms that occur following the injection (i.e., CTRs) were captured by subjects in a 30-day diary. Injection sites on each side of the face were individually assessed by subjects over 30 days following study injections. CTRs by severity and duration are presented respectively, in Table 3 and Table 4.

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

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

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

Common	TOT	ALS		RHA® Mep N°=30 NLI		RHA® (Nº=30 NLF)		
Treatment Responses	RHA® Mepi n <sup>b</sup> (%)	RHA® nb (%)	Mild n <sup>b</sup> (%)	Mod <sup>c</sup> n <sup>b</sup> (%)	Sev <sup>d</sup> n <sup>b</sup> (%)	Mild n <sup>b</sup> (%)	Mod <sup>c</sup> n <sup>b</sup> (%)	Sev <sup>d</sup> n <sup>b</sup> (%)
Bruising	19 (63.3%)	21 (70.0%)	7 (23.3%)	12 (40.0%)	0 (0.0%)	10 (33.3%)	11 (36.7%)	0 (0.0%)
Discoloration	11 (36.7%)	12 (40.0%)	8 (26.7%)	2 (6.7%)	(3.3%)	8 (26.7%)	4 (13.3%)	0 (0.0%)
Firmness	24 (80.0%)	22 (73.3%)	12 (40.0%)	10 (33.3%)	2 (6.7%)	9 (30.0%)	11 (36.7%)	2 (6.7%)
Itching	7 (23.3%)	6 (20.0%)	7 (23.3%)	0 (0.0%)	0 (0.0%)	6 (20.0%)	0 (0.0%)	0 (0.0%)
Lumps/ Bumps	22 (73.3%)	21 (70.0%)	10 (33.3%)	11 (36.7%)	1 (3.3%)	10 (33.3%)	11 (36.7%)	0 (0.0%)
Pain	12 (40.0%)	9 (30.0%)	10 (33.3%)	11 (36.7%)	0 (0.0%)	10 (33.3%)	11 (36.7%)	0 (0.0%)
Redness	21 (70.0%)	20 (66.7%)	12 (40.0%)	6 (20.0%)	3 (10.0%)	14 (46.7%)	4 (13.3%)	(6.7%)
Swelling	21 (70.0%)	23 (76.7%)	11 (36.7%)	9 (30.0%)	1 (3.3%)	14 (46.7%)	9 (30.0%)	0 (0.0%)
Tenderness	24 (80.0%)	24 (80.0%)	16 (53.3%)	8 (26.7%)	0 (0.0%)	18 (60.0%)	6 (20.0%)	0 (0.0%)
Otherse	1 (3.3%)	0 (0.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

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

CTP Group 1-3 4-7 8-14 15-21 22-30 Last David

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

Ouration <sup>c</sup>	(N°= 30 NLF)	Days n <sup>b</sup> (%)	nº (%)				
) ruining	RHA® Mepi	8 (26.7%)	5 (16.7%)	5 (16.7%)	(3.3%)	0 (0.0%)	0 (0.0%)
Bruising	RHA®	9 (30.0%)	8 (26.7%)	4 (13.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Discoloration	RHA® Mepi	6 (20.0%)	5 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Discoloration	RHA®	7 (23.3%)	3 (10.0%)	2 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
irmness	RHA® Mepi	5 (16.7%)	4 (13.3%)	9 (30.0%)	(3.3%)	5 (16.7%)	3 (10.0%)
·immess	RHA®	2 (6.7%)	6 (20.0%)	6 (20.0%)	6 (20.0%)	2 (6.7%)	4 (13.3%)
tching	RHA® Mepi	5 (16.7%)	(3.3%)	(3.3%)	0 (0.0%)	0 (0.0%)	(3.3%)
ioning	RHA®	4 (13.3%)	(3.3%)	(3.3%)	0 (0.0%)	0 (0.0%)	(3.3%)
.umps/ Bumps	RHA® Mepi	8 (26.7%)	2 (6.7%)	9 (30.0%)	(3.3%)	2 (6.7%)	(3.3%)
umps/ bumps	RHA®	5 (16.7%)	4 (13.3%)	6 (20.0%)	5 (16.7%)	1 (3.3%)	0 (0.0%)
Pain	RHA® Mepi	9 (30.0%)	3 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ulli	RHA®	7 (23.3%)	2 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Redness	RHA® Mepi	12 (40.0%)	7 (23.3%)	2 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
teuriess	RHA®	13 (43.3%)	6 (20.0%)	(3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Swelling	RHA® Mepi	9 (30.0%)	7 (23.3%)	5 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
weiling	RHA®	10 (33.3%)	8 (26.7%)	4 (13.3%)	(3.3%)	0 (0.0%)	0 (0.0%)
enderness	RHA® Mepi	10 (33.3%)	8 (26.7%)	4 (13.3%)	(3.3%)	1 (3.3%)	0 (0.0%)
endemess	RHA®	12 (40.0%)	8 (26.7%)	3 (10.0%)	(3.3%)	0 (0.0%)	0 (0.0%)
)thores	RHA® Mepi	(3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Otherse	RHA®	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

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

- Number of subject NLF with each specific ČTR by maximum duration
   Duration refers to number of days cited in the patient diary, irrespective of date of injection
- <sup>d</sup>The CTR numbers indicated in the "Last Day" column are also included in the
- "22-30 Days" column One patient reported mild paresthesia on the corner of the mouth treated with RHA® Mepi dermal filler and which resolved in 2 days

• Both RHA® Mepi and RHA® treatment groups presented with very similar adverse event profiles with an overall of 5 subjects experiencing a total of 11 treatment-

- All treatment-related AFs were mild in severity and none were considered by Investigators to be clinically significant. All events resolved spontaneously by the time of the study exit (30 days) except the injection site mass for one subject. This event had resolved spontaneously by 46 days post-injection without the need for
- All treatment-related AEs experienced by both treatment groups were typical of the expected signs and symptoms observed following an injection of a hyaluronic acidbased dermal filler except one (paresthesia: mild) that was reported by the subject in the "other" category of the 30-day diary and which resolved in 2 days.
- All treatment-related AEs were based on subjects' diary entries (CTRs).
- · No events were deemed to be a granuloma
- There were no late onset treatment-related AEs.
- There were no treatment-related serious AEs.
- There were no subjects who withdrew from the study due to AEs. Safety profile by Fitzpatrick skin type, ethnicity and age was not different.

#### 3. Post-marketing Surveillance

Post Marketing surveillance data are based on RHA® 2 containing lidocaine, these data are representative and applicable to RHA® 2 Mepi.

The following adverse events were reported as part of postmarketing surveillance on the use of RHA® 2 worldwide with a prevalence equal or superior to 1 occurrence for 100.000 syringes: Injection site masses (lumps and bumps), skin edema, skin swelling, vascular complication (such as vessel compression/occlusion), skin discoloration ecchymosis, erythema, inflammatory reaction, allergic reaction, pain and skin

Additionally, other less frequent adverse reactions have also been reported and included dermatitis, granuloma, skin necrosis, implant migration, skin discoloration/ Tyndall effect, skin infection, herpes breakout, pruritus, paresthesia, abscess, acne, anajoedema, blister, scabs, fainting, product misplacement, puffiness, tenderness, injection site movement impairment, papules, pustules, dry skin, scabs, syncope and telanaiectasia.

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, 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

#### CLINICAL STUDIES

#### CLINICAL STUDY OF RHA® 2

RHA® 2 Mepi is strictly identical to RHA® 2 except for the small amount of anesthetic medicine: RHA® 2 Mepi contains mepivacaine and RHA® 2 contains lidocaine. Both anesthetics agents are of the same family with the same mechanisms of effect. RHA® 2 Mepi and RHA® 2 have the same indication. The long-term safety and effectiveness of RHA® 2 Mepi were evaluated in a clinical study using RHA® 2.

The long-term safety and effectiveness of RHA® 2 in the correction of moderate to severe facial wrinkles and folds were evaluated in a U.S. pivotal clinical study described

#### 1. Pivotal Study Design: Clinical Evaluation of RHA® 2

A controlled, randomized, double-blinded, within-subject (split-face), multicenter prospective pivotal clinical study was conducted to evaluate the clinical safety and

Subjects were randomly assigned to receive RHA® 2 and a control treatment in midto-deep dermis for the treatment of moderate to severe nasolabial folds, or to a nontreatment 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

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

100 mm Visual Analog Scale.

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-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-freatment 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 RLE impact and effectiveness of study treatment procedures from the subjects' perspective as assessed by the nasolabial fold domain of the FACE-Q<sup>©</sup>, 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 AÉ assessments at each visit. Injection site pain was self-assessed by the subject using a

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 Subjects' demographics are presented in Table 5.

Table 5. Demographics

nber / % of subjects	RHA® 2 versus Control device Nº=73				
ean (SD) n max	55.5 34	(10.9) 79			
nder male ale	62 11	84.9% 15.1%			
ve ucasian ick I. Indian/N. Alask. Hawaiian/P. Isl. ian her	59 9 0 0 2 3	80.8% 12.3% 0.0% 0.0% 2.7% 4.1%			
n <b>icity</b> spanic/Latino t Hispanic/Latino	21 52	28.8% 71.2%			
patrick Skin Phototype	1 24 20 17 7 4	1.4% 32.9% 27.4% 23.3% 9.6% 5.5%			
nher of subjects in the ITT populations					

Number of subjects in the ITT population:

#### 4. Treatment Characteristics

The study protocol allowed a maximum of 3.0 ml in a single NLF per treatment session. The 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 Nasolabial Folds Wrinkle Severity Rating Scale NLF-WSRS) by the BLE at 24 weeks after baseline; results are presented in

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

		R	HA® 2	Conti	rol Device
	nª	NLF-WSRS   NLF-WSRS   Improvement		NLF-WSRS score <sup>b</sup>	NLF-WSRS Improvement <sup>c</sup>
Pre-treatment	67	3.45	-	3.45	-
Week 24 <sup>d</sup>	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

<sup>a</sup> Number of subjects in the PP populations at the respective follow-up visits <sup>b</sup> Mean NLF-Wrinkle Severity Rating Scale score (higher scores mean deepest wrinkles) • Mean NLF-Wrinkle Severity Rating Scale improvement from pre-treatment (higher scores mean

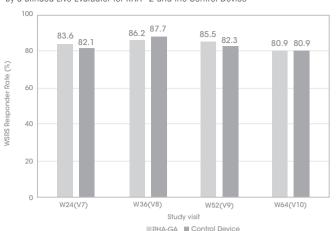
more improvement from pre-treatment)

d Primary effectiveness endpoint

The results demonstrated that non-inferiority to the control was achieved for RHA® 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 NLF-WSRS) for more than 80% of the subjects at 64 weeks after initial treatment

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



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

PP populations at the respective follow-up visits

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

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

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

#### **CLINICAL STUDY of RHA® MEPI**

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

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

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

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

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

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

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

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

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

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

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

Subjects' demographics are presented in Table 7.

#### Table 7. Demographics

Number / % of subjects	RHA® Mepi versus RHA® N°=30			
Age Mean (SD) min max	57 33	(9.7 7		
Gender Female Male	27	90.09 10.09		
Race Caucasian Black Am. Indian/N. Alask. N. Hawaiian/P. Isl. Asian Other	27 3 0 0 0	90.09 10.09 0.09 0.09 0.09 0.09		
Ethnicity Hispanic/Latino Not Hispanic/Latino	12 18	40.0% 60.0%		
Fitzpatrick Skin Phototype I II II II V V	1 8 10 8 0 3	3.39 26.79 33.39 26.79 0.09 10.09		

Number of subjects in the ITT population

#### 4. Treatment Characteristics

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

In general, a linear threading, fan-like technique, or a combination of linear threading with multiple punctuate pools, was used for 96.6% of the subjects treated with

#### 5. Effectiveness Results

The primary effectiveness endpoint was met for RHA® Mepi

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

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

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

**Table 8.** Injection Site Pain during injection – PP population

VAS pain (mm)	S pain (mm) RHA® Mepi N°=30		VAS Difference (mm) N°=30
Mean (SD)	17.1 (18.38)	16.3 (18.89)	-0.8 (8.09)
Min, Max	0,55	0,70	-20, 20

a Number of subjects in the PP population

Table 9. Injection Site Pain after injection – ITT population

VAS pain (mm)	RHA® Mepi	RHA®	VAS Difference (mm)
Mean (SD)	N°=30	N°=30	N°=30
Time point: - 15 Min - 30 Min - 45 Min - 60 Min	4.9 (12.33)	5.1 (15.94)	0.2 (6.81)
	2.0 (5.66)	3.1 (12.30)	1.1 (10.36)
	0.0 (0.00)	2.1 (11.68)	2.1 (11.68)
	0.0 (0.00)	1.9 (10.22)	1.9 (10.22)

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

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

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

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

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

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

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

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

#### DIRECTIONS FOR ASSEMBLY OF THE NEEDLE TO THE SYRINGE

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



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



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



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



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

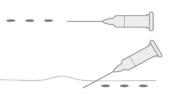


#### PRE-TREATMENT GUIDELINES

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

#### INJECTION TECHNIQUES

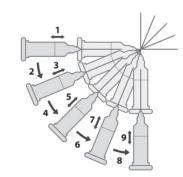
- RHA® 2 Mepi is administered by using a thin gauge needle (30 G x ½"). The needle is inserted into the mid-to-deep dermis at an approximate angle of 15° to 30° parallel to the length of the wrinkle or fold.
- RHA® 2 Mepi can be injected by a number of different techniques that depend on the injector's experience and preference, and patient characteristics.
- A. Serial puncture: consists of multiple injections, evenly and closely spaced all along wrinkles or folds. This technique is considered to be more precise, but may result in more discomfort for the patient due to the number of punctures.



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



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



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

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

#### POST-TREATMENT GUIDELINES

- When the injection is completed, the treated site may be gently massaged so that it conforms to the contour of the surrounding tissues. If an overcorrection has occurred, massage the area firmly between your fingers or against an underlying area to obtain
- 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 container
- 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
- RHA® 2 Mepi is provided with 2 needles that do not contain engineered injury. protection. Administration of RHA® 2 Mepi requires direct visualization and complete and gradual insertion of the needle making engineered protection devices not feasible. To avoid needle stick injury and sharp exposure, take care to inject in
- Obtain prompt medical attention if injury with used needle occurs.

#### PATIENT INSTRUCTIONS

Patient information brochure is available on request, or via the website

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

#### HOW SUPPLIED

RHA® 2 Mepi is supplied in individual blisters containing a 1 ml treatment syringe with two 30 G x ½" needles as indicated on the carton.

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

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

#### SHELF-LIFE AND STORAGE

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

## RxOnlv

Manufactured by:

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Distributed by:

RHA® is a registered trademark of TEOXANE SA.

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

#### SYMBOLS



Manufacturer's name and address



LOT Lot / batch number

Catalog number



Consult Instructions for use



Single use only



Do not use if the package is damaged







## RHA® 3 Mepi

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

#### DEVICE DESCRIPTION

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

#### INTENDED USE / INDICATIONS

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

#### CONTRAINDICATIONS

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

#### WARNINGS

- Introduction of product into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction. To avoid this:
- Do not inject into blood vessels.
- -Take extra care when injecting soft tissue fillers, inject the product slowly and apply the least amount of pressure necessary. Rare but serious adverse events associated with the intravascular injection of soft-
- tissue fillers in the face have been reported and include temporary or permanent vision impairment or blindness, cerebral ischemia or cerebral hemorrhage leading to stroke, skin necrosis, and damage to underlying facial structures. If a patient exhibits any of the following symptoms: changes in vision, signs of a stroke, blanching of the skin, or unusual pain during or shortly after the procedure, immediately stop the injection. Patients should receive prompt medical attention and possibly evaluation by an appropriate health care practitioner specialist should an intravascular injection
- 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
- · 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
- 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
- RHÁ® 3 Mepi should be used with caution in patients on immunosuppressive therapy.

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

#### ADVERSE EXPERIENCES

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

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

A second U.S. study was conducted for the indication for the correction of moderate to severe dynamic wrinkles and folds, such as NLFs to evaluate the safety of RHA® 3 Mepi when compared to RHA® 3. The safety information from this clinical study is summarized below under "Clinical Evaluation of RHA® Mepi in the NLFs".

#### 1. Clinical Evaluation of RHA® 3 in the NLFs

Clinical study TEO-RHA-1302 was a multicenter, controlled, randomized, doubleblinded, 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,
- 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"
- 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	TOTALS		RHA® 3 (Nº=75 NLF)			Control Device (N°=75 NLF)		
Responses	RHA® 3 n <sup>b</sup> (%)	CTRL° n° (%)	Mild n <sup>b</sup> (%)	Mod <sup>d</sup> n <sup>b</sup> (%)	Sev <sup>e</sup> n <sup>b</sup> (%)	Mild n <sup>b</sup> (%)	Mod <sup>d</sup> n <sup>b</sup> (%)	Sev <sup>e</sup> n <sup>b</sup> (%)
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	38	22	15	4	22	15	1
Swelling	(54.7%)	(50.7%)	(29.3%)	(20.0%)	(5.3%)	(29.3%)	(20.0%)	(1.3%)
Tenderness	44	37	29	12	3	26	10	1
rendemess	(58.7%)	(49.3%)	(38.7%)	(16.0%)	(4.0%)	(34.7%)	(13.3%)	(1.3%)

- Number of subjects' NLF treated with the respective device.
- <sup>b</sup> 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		(N°=7	4® 3 5 NLF) (%)		Control Device (N°=75 NLF) nb (%)			
Duration	1-3 Days	4-7 Days	8-14 Days	Last Day <sup>d</sup>	1-3 Days	4-7 Days	8-14 Days	Last Day <sup>d</sup>
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%)

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

An adverse event (AF) 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-
- 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® Mepi in the NLFs

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

The expected signs/symptoms that occur following the injection (i.e., CTRs) were captured by subjects in a 30-day diary. Injection sites on each side of the face were individually assessed by subjects over 30 days following study injections. CTRs by severity and duration are presented respectively, in Table 3 and Table 4.

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

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

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

Common	TOT	ALS		RHA® Mep N°=30 NLI		RHA® (N°=30 NLF)		
Treatment Responses	RHA® Mepi n <sup>b</sup> (%)	RHA® nb (%)	Mild n <sup>b</sup> (%)	Mod <sup>c</sup> n <sup>b</sup> (%)	Sev <sup>d</sup> n <sup>b</sup> (%)	Mild n <sup>b</sup> (%)	Mod <sup>c</sup> n <sup>b</sup> (%)	Sev <sup>d</sup> n <sup>b</sup> (%)
Bruising	19 (63.3%)	21 (70.0%)	7 (23.3%)	12 (40.0%)	0 (0.0%)	10 (33.3%)	11 (36.7%)	0 (0.0%)
Discoloration	11 (36.7%)	12 (40.0%)	8 (26.7%)	2 (6.7%)	(3.3%)	8 (26.7%)	4 (13.3%)	0 (0.0%)
Firmness	24 (80.0%)	22 (73.3%)	12 (40.0%)	10 (33.3%)	2 (6.7%)	9 (30.0%)	11 (36.7%)	2 (6.7%)
Itching	7 (23.3%)	6 (20.0%)	7 (23.3%)	0 (0.0%)	0 (0.0%)	6 (20.0%)	0 (0.0%)	0 (0.0%)
Lumps/ Bumps	22 (73.3%)	21 (70.0%)	10 (33.3%)	11 (36.7%)	(3.3%)	10 (33.3%)	11 (36.7%)	0 (0.0%)
Pain	12 (40.0%)	9 (30.0%)	10 (33.3%)	11 (36.7%)	0 (0.0%)	10 (33.3%)	11 (36.7%)	0 (0.0%)
Redness	21 (70.0%)	20 (66.7%)	12 (40.0%)	6 (20.0%)	3 (10.0%)	14 (46.7%)	4 (13.3%)	2 (6.7%)
Swelling	21 (70.0%)	23 (76.7%)	11 (36.7%)	9 (30.0%)	(3.3%)	14 (46.7%)	9 (30.0%)	0 (0.0%)
Tenderness	24 (80.0%)	24 (80.0%)	16 (53.3%)	8 (26.7%)	0 (0.0%)	18 (60.0%)	6 (20.0%)	0 (0.0%)
Otherse	(3.3%)	0 (0.0%)	(3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

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

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

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

- a Number of subject NLF treated with the respective device <sup>b</sup> Number of subject NLF with each specific CTR by maximum duration
- <sup>e</sup> Duration refers to number of days cited in the patient diary, irrespective of date of injection
- <sup>4</sup>The CTR numbers indicated in the "Last Day" column are also included in the "22-30 Days"
- \* One patient reported mild paresthesia on the corner of the mouth treated with RHA® Mepi dermal filler and which resolved in 2 days

• Both RHA® Mepi and RHA® treatment groups presented with very similar adverse event profiles with an overall of 5 subjects experiencing a total of 11 treatment-

- All treatment-related AEs were mild in severity and none were considered by Investigators to be clinically significant. All events resolved spontaneously by the time of the study exit (30 days) except the injection site mass for one subject. This event had resolved spontaneously by 46 days post-injection without the need for medical therapy.
- All treatment-related AEs experienced by both treatment groups were typical of the expected signs and symptoms observed following an injection of a hyaluronic acidbased dermal filler except one (paresthesia: mild) that was reported by the subject in the "other" category of the 30-day diary and which resolved in 2 days.
- All treatment-related AEs were based on subjects' diary entries (CTRs)
- No events were deemed to be a granuloma There were no late onset treatment-related AFs.
- There were no treatment-related serious AFs
- There were no subjects who withdrew from the study due to AEs.
- 3. Post-marketing Surveillance

Post-marketing surveillance data are based on RHA® 3 containing lidocaine, these data are representative and applicable to RHA® 3 Mepi.

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 discolouration/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, neuralaia, 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 total resolution of the symptoms with or without sequelae.

#### CLINICAL STUDIES

#### RHA® 3 CLINICAL STUDY- of RHA® 3

RHA® 3 Mepi is strictly identical to RHA® 3 except for the small amount of anesthetic medicine: RHA® 3 Mepi contains mepivacaine and RHA® 3 contains lidocaine. Both anesthetics agents are of the same family with the same mechanisms of effect RHA® 3. Meni and RHA® 3 have the same indication. The long-term safety and effectiveness of RHA® 3 Mepi were evaluated in a clinical study using RHA® 3.

The long-term safety and effectiveness of RHA® 3 in the correction of moderate to severe facial wrinkles and folds were evaluated in a US pivotal clinical study described

#### 1. Pivotal Study Design: Clinical Evaluation of RHA® 3

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 midto-deep dermis for the treatment of moderate to severe nasolabial folds, or to a nontreatment 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

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 endnoints 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<sup>®</sup>, 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) min max	55.7 26	(9.4) 77					
<b>Gender</b> Female Male	68 6	91.9% 8.1%					
Race Caucasian Black Am. Indian/N. Alask. N. Hawaiian/P. Isl. Asian Other	62 7 0 0 0 5	83.8% 9.5% 0.0% 0.0% 0.0% 6.8%					
Ethnicity Hispanic/Latino Not Hispanic/Latino	21 53	28.4% 71.6%					
Fitzpatrick Skin Phototype 	4 21 19 20 7 3	5.4% 28.4% 25.7% 27.0% 9.5% 4.1%					
Number of subjects in the ITT no	Number of subjects in the ITT populations						

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

		R	HA® 3	Contr	rol Device	
	nª	NLF-WSRS score <sup>b</sup>	NLF-WSRS Improvement°	NLF-WSRS score <sup>b</sup>	NLF-WSRS Improvement°	
re-treatment <sup>d</sup>	62	3.39	-	3.39	-	
Veek 24	62	2.06	1.32	2.16	1.23	
Veek 36	58	2.36	1.03	2.41	0.98	
Veek 52	56	2.45	0.91	2.54	0.82	
Veek 64	47	2.47	0.91	2.55	0.83	

<sup>a</sup> Number of subjects in the PP populations at the respective follow-up visits

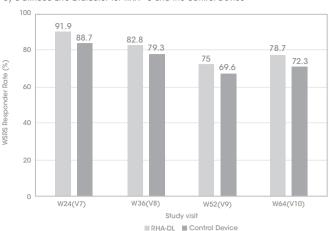
<sup>b</sup> Mean NLF-Wrinkle Severity Rating Scale score (higher scores mean deepest wrinkles) Mean NLF-Wrinkle Severity Rating Scale improvement from pre-treatment (higher scores mean

<sup>d</sup> 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 non-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. Proportion of responders on the NLF-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 NLF-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<sup>©</sup> 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

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

#### CLINICAL STUDY of RHA® Mepi

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

The results of this clinical study are applicable to RHA® 3 Mepi as both RHA® 4 Mepi and RHA® 3 Mepi are from the same family of products, with similar physico-chemical characteristics and with the same indication. RHA® 4 Mepi was considered worst case of the RHA® family of products for this indication (including RHA® 3 Mepi) as it was injected into the deeper layers of the dermis (deep dermis to subcutaneous)

#### 1. Pivotal Study Design

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

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

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

#### 2. Study Endpoints

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

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

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

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

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

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

RHA® Mepi versus

Subjects' demographics are presented in Table 7.

Table 7. Demographics

Number / % of subjects	RHA® Nº=30		
Age Mean (SD) min max	57 33	(9.7 79	
Gender Female Male	27 3	90.0%	
Race Caucasian Black Am. Indian/N. Alask. N. Hawaiian/P. Isl. Asian Other	27 3 0 0 0	90.0% 10.0% 0.0% 0.0% 0.0% 0.0%	
Ethnicity Hispanic/Latino Not Hispanic/Latino	12 18	40.0%	
Fitzpatrick Skin Phototype I II III IV V VI	1 8 10 8 0 3	3.3% 26.7% 33.3% 26.7% 0.0%	

Number of subjects in the ITT population

#### 4 Treatment Characteristics

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

In general, a linear threading, fan-like technique, or a combination of linear threading with multiple punctuate pools, was used for 96.6% of the subjects treated with

#### 5. Effectiveness Results

The primary effectiveness endpoint was met for RHA® Mepi.

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

For both treatment groups, the level of pain decreased over time with no statistically significant difference at all time points (at 15, 30, 45, and 60 minutes post-injection) The injection pain was reduced to 4.9 mm for RHA® Mepi and 5.1 mm for RHA® after 5 minutes and almost gone after 60 minutes post-injection

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

**Table 8.** Injection Site Pain during injection – PP population

VAS pain (mm)	RHA® Mepi	RHA®	VAS Difference (mm)
	N°=30	Nº=30	N°=30
Mean (SD)	17.1 (18.38)	16.3 (18.89)	-0.8 (8.09)
Min, Max	0,55	0,70	-20, 20

a Number of subjects in the PP population

Table 9. Injection Site Pain after injection – ITT population

VAS pain (mm)	RHA® Mepi	RHA®	VAS Difference (mm)
Mean (SD)	N°=30	N°=30	N°=30
Time point: - 15 Min - 30 Min - 45 Min - 60 Min	4.9 (12.33) 2.0 (5.66) 0.0 (0.00) 0.0 (0.00)	5.1 (15.94) 3.1 (12.30) 2.1 (11.68) 1.9 (10.22)	0.2 (6.81) 1.1 (10.36) 2.1 (11.68) 1.9 (10.22)

<sup>&</sup>lt;sup>a</sup> Number of subjects in the ITT population

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

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

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

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

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

More than 96% of the subjects reported being satisfied or very satisfied one month after their treatment with no distinction between the treatment groups. Similar effectiveness and safety profiles were observed by Fitzpatrick skin type, ethnicity

Results of RHA® 3 long term safety and effectiveness are applicable to RHA® 3 Mepi.

#### **DIRECTIONS FOR ASSEMBLY** OF THE NEEDLE TO THE SYRINGE

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



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



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



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



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



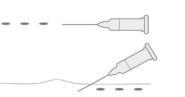
#### PRE-TREATMENT GUIDELINES

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

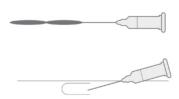
#### INJECTION TECHNIQUES

- RHA® 3 Mepi is administered by using a thin gauge needle (27 G x ½"). 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® 3 Mepi can be injected by a number of different techniques that depend on the injector's experience and preference, and patient characteristics.

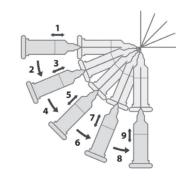
A. Serial puncture: consists of multiple injections, evenly and closely spaced all along wrinkles or folds. This technique is considered to be more precise, but may result in more discomfort for the patient due to the number of punctures.



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



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



- RHA® 3 Mepi is injected slowly into the mid-to-deep dermis. If the injection is made too deeply, i.e. into sub-cutaneous tissue, the correction may not be as expected. It is possible to tell when an injection is being made too deeply because subcutaneous tissue 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® 3 Mepi, the same procedure should be repeated until a satisfactory result is obtained.

#### POST-TREATMENT GUIDELINES

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

#### STERILE NEEDLES

- After use, needles are potential biohazards, Follow national, local, or institutional guidelines for use and disposal of medical sharp devices (e.g. discard uncapped needles in approved sharps containers
- Disposal should be in accordance with accepted medical practice and applicable local, State and Federal requirements.
- To help avoid needle breakage, do not attempt to straighten a bent needle, discard it and complete the procedure with a replacement needle.
- Do not recap needles. Recapping by hand is a hazardous practice and should be
- RHA® 3 Mepi is provided with 2 needles that do not contain engineered injury protection. Administration of RHA® 3 Mepi requires direct visualization and complete and gradual insertion of the needle making engineered protection devices not feasible. To avoid needle stick injury and sharp exposure, take care to inject in
- 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
- Sians of a stroke
- o 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® 3 Mepi is supplied in individual blisters containing a 1ml 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

#### SHELF-LIFE AND STORAGE

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

## RxOnlv

Manufactured by:

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

Revance Therapeutics, Inc. 1222 Demonbreun Street. Suite 2000

Nashville, Tennessee 37203

Distributed by:

RHA® is a registered trademark of TEOXANE SA.

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

#### SYMBOLS



Manufacturer's name and address



Lot / batch number

Cataloa number



LOT

Expiration date (YYYY-MM-DD)



Consult Instructions for use



STERILE Sterilized using steam

Single use only



Do not use if the package is damaged





## RHA® 4 Mepi

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

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

#### DEVICE DESCRIPTION

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

#### INTENDED USE / INDICATIONS

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

#### CONTRAINDICATIONS

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

#### WARNINGS

- Introduction of product into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction. To avoid this:
- Do not inject into blood vessels.
- Take extra care when injecting soft tissue fillers, inject the product slowly and apply the least amount of pressure necessary.
- Rare but serious adverse events associated with the intravascular injection of soft tissue fillers in the face have been reported and include temporary or permanent vision impairment or blindness, cerebral ischemia or cerebral hemorrhage leading to stroke, skin necrosis, and damage to underlying facial structures. If a patient exhibits any of the following symptoms: changes in vision, signs of a stroke, blanching of the skin, or unusual pain during or shortly after the procedure, immediately stop the injection. Patients should receive prompt medical attention and possibly evaluation by an appropriate health care practitioner specialist should an intravascular injection
- 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.
- 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 gae has not been established.

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

#### ADVERSE EXPERIENCES

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

Due to the similarities in the formulation of RHA® 4 Mepi and RHA® 4, the U.S. clinical evaluation of RHA® 4 to support the indication for the correction of moderate to severe dynamic wrinkles and folds, such as NLF, provided safety and effectiveness information about RHA® 4 Mepi for the indication for the correction of moderate to severe dynamic wrinkles and folds, such as NLF. This safety information from this long-term study applies to both RHA® 4 Mepi and RHA® 4, and is summarized below under **"Clinical Evaluation of RHA® 4 in the NLFs"**.

A second U.S. study was conducted for the indication for the correction of moderate to severe dynamic wrinkles and folds, such as NLF, to evaluate the safety of RHA® 4 Mepi when compared to RHA® 4. The safety information from this clinical study are summarized below under "Clinical Evaluation of RHA® 4 Mepi in the NLFs".

#### 1. Clinical Evaluation of RHA® 4 in the NLFs

make-up required.

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
- Severe: Great discomfort, daily activities compromised, very likely medication or make-up required.
- CTRs by severity and duration are presented respectively, in Table 1 and Table 2.
- The most frequent CTRs were swelling, firmness, tenderness, redness, lumps/bumps, pain, and bruising.
- 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 reported in subject 14-day diary – Safety Population

Common Treatment	TOTALS		(1)	RHA® 4 (N°=120 NLF)			Control Device (N°=120 NLF)		
Responses	RHA® 4 nb (%)	CTRL° nº (%)	Mild nb (%)	Mod <sup>d</sup> n <sup>b</sup> (%)	Seve nb (%)	Mild n <sup>b</sup> (%)	Mod <sup>d</sup> n <sup>b</sup> (%)	Seve nb (%)	
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	91	42	38	4	32	42	17
	(70.0%)	(75.8%)	(35.0%)	(31.7%)	(3.3%)	(26.7%)	(35.0%)	(14.2%)
Swelling	97	104	41	44	12	21	38	45
	(80.8%)	(86.7%)	(34.2%)	(36.7%)	(10.0%)	(17.5%)	(31.7%)	(37.5%)
Tenderness	90	95	53	30	7	23	45	27
	(75.0%)	(79.2%)	(44.2%)	(25.0%)	(5.8%)	(19.2%)	(37.5%)	(22.5%)

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

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

Common Treatment Responses		(N°=12	\® 4 20 NLF) (%)		Control Device (N°=120 NLF) N° (%)			
Duration	1-3	4-7	8-14	Last	1-3	4-7	8-14	Last
	Days	Days	Days	Day <sup>d</sup>	Days	Days	Days	Day <sup>d</sup>
Bruising	22	28	20	8	37	28	7	4
	(18.3%)	(23.3%)	(16.7%)	(6.7%)	(30.8%)	(23.3%)	(5.8%)	(3.3%)
Discoloration	28	10	12	10	34	14	8	4
	(23.3%)	(8.3%)	(10.0%)	(8.3%)	(28.3%)	(11.7%)	(6.7%)	(3.3%)
Firmness	16	20	55	35	13	26	54	26
	(13.3%)	(16.7%)	(45.8%)	(29.2%)	(10.8%)	(21.7%)	(45.0%)	(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	14	48	36	25	24	41	27
	(15.8%)	(11.7%)	(40.0%)	(30.0%)	(20.8%)	(20.0%)	(34.2%)	(22.5%)
Pain	48 (40.0%)	12 (10.0%)	6 (5.0%)	3 (2.5%)	54 (45.0%)	25 (20.8%)	8 (6.7%)	2 (1.7%)
Redness	42 (35.0%)	30 (25.0%)	12 (10.0%)	8 (6.7%)	42 (35.0%)	37 (30.8%)	12 (10.0%)	7 (5.8%)
Swelling	36	29	32	16	27	50	27	11
	(30.0%)	(24.2%)	(26.7%)	(13.3%)	(22.5%)	(41.7%)	(22.5%)	(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
- <sup>b</sup> Number of subject NLF with each specific CTR by maximum duration
- Duration refers to number of days cited in the patient diary, irrespective of date of injection
   The CTR numbers indicated in the "Last Day" column are also included in the "8-14 Days"

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 Mepi in the NLFs

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

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

   The most frequent CTRs were firmness, tenderness, lumps/bumps, redness, swelling,
- and bruising.

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

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

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

TOTALS RHA® 4 Mepi RHA® 4

ommon	101	ALU	(N°=30 NLF)			(N°=30 NLF)			
eatment esponses	RHA® 4 Mepi n <sup>b</sup> (%)	RHA® 4 nº (%)	Mild n <sup>b</sup> (%)	Mod <sup>c</sup> n <sup>b</sup> (%)	Sev <sup>d</sup> n <sup>b</sup> (%)	Mild n <sup>b</sup> (%)	Mod <sup>c</sup> n <sup>b</sup> (%)	Sev <sup>d</sup> n <sup>b</sup> (%)	
uising	19 (63.3%)	21 (70.0%)	7 (23.3%)	12 (40.0%)	0 (0.0%)	10 (33.3%)	11 (36.7%)	0 (0.0%)	
scoloration	11 (36.7%)	12 (40.0%)	8 (26.7%)	2 (6.7%)	(3.3%)	8 (26.7%)	4 (13.3%)	0 (0.0%)	
mness	24 (80.0%)	22 (73.3%)	12 (40.0%)	10 (33.3%)	2 (6.7%)	9 (30.0%)	11 (36.7%)	2 (6.7%)	
hing	7 (23.3%)	6 (20.0%)	7 (23.3%)	0 (0.0%)	0 (0.0%)	6 (20.0%)	0 (0.0%)	0 (0.0%)	
mps/ Bumps	22 (73.3%)	21 (70.0%)	10 (33.3%)	11 (36.7%)	(3.3%)	10 (33.3%)	11 (36.7%)	0 (0.0%)	
in	12 (40.0%)	9 (30.0%)	10 (33.3%)	11 (36.7%)	0 (0.0%)	10 (33.3%)	11 (36.7%)	0 (0.0%)	
dness	21 (70.0%)	20 (66.7%)	12 (40.0%)	6 (20.0%)	3 (10.0%)	14 (46.7%)	4 (13.3%)	2 (6.7%)	
velling	21 (70.0%)	23 (76.7%)	11 (36.7%)	9 (30.0%)	(3.3%)	14 (46.7%)	9 (30.0%)	0 (0.0%)	
nderness	24 (80.0%)	24 (80.0%)	16 (53.3%)	8 (26.7%)	0 (0.0%)	18 (60.0%)	6 (20.0%)	0 (0.0%)	
herse	1 (3.3%)	0 (0.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	

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

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

c (N°= Days Days Days Days Days Days

Ouration <sup>c</sup>	30 NLF)	n <sup>b</sup> (%)					
\t_t	RHA® 4 Mepi	8 (26.7%)	5 (16.7%)	5 (16.7%)	(3.3%)	0 (0.0%)	0 (0.0%)
Bruising	RHA® 4	9 (30.0%)	8 (26.7%)	4 (13.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Diagola setion	RHA® 4 Mepi	6 (20.0%)	5 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Discoloration	RHA® 4	7 (23.3%)	3 (10.0%)	2 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	RHA® 4 Mepi	5 (16.7%)	4 (13.3%)	9 (30.0%)	(3.3%)	5 (16.7%)	3 (10.0%)
Firmness	RHA® 4	2 (6.7%)	6 (20.0%)	6 (20.0%)	6 (20.0%)	2 (6.7%)	4 (13.3%)
tohina	RHA® 4 Mepi	5 (16.7%)	(3.3%)	(3.3%)	0 (0.0%)	0 (0.0%)	(3.3%)
tching	RHA® 4	4 (13.3%)	(3.3%)	(3.3%)	0 (0.0%)	0 (0.0%)	(3.3%)
45	RHA® 4 Mepi	8 (26.7%)	(6.7%)	9 (30.0%)	(3.3%)	(6.7%)	(3.3%)
umps/ Bumps	RHA® 4	5 (16.7%)	4 (13.3%)	6 (20.0%)	5 (16.7%)	1 (3.3%)	0 (0.0%)
V*	RHA® 4 Mepi	9 (30.0%)	3 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pain	RHA® 4	7 (23.3%)	2 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
N. d	RHA® 4 Mepi	12 (40.0%)	7 (23.3%)	2 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Redness	RHA® 4	13 (43.3%)	6 (20.0%)	(3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Vuollina	RHA® 4 Mepi	9 (30.0%)	7 (23.3%)	5 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Swelling	RHA® 4	10 (33.3%)	8 (26.7%)	4 (13.3%)	(3.3%)	0 (0.0%)	0 (0.0%)
andornos	RHA® 4 Mepi	10 (33.3%)	8 (26.7%)	4 (13.3%)	(3.3%)	1 (3.3%)	0 (0.0%)
enderness	RHA® 4	12 (40.0%)	8 (26.7%)	3 (10.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)
Dil 9	RHA® 4 Mepi	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Otherse	RHA® 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Number of subject NLF treated with the respective device.

- <sup>b</sup> Number of subject NLF with each specific CTR by maximum duration
- Duration refers to number of days cited in the patient diary, irrespective of date of injection
   The CTR numbers indicated in the "Last Day» column are also included in the "22-30 Days"
- One patient reported mild paresthesia on the corner of the mouth treated with RHA® 4 Mepi dermal filler and which resolved in 2 days

• Both RHA® 4 Mepi and RHA® 4 treatment groups presented with very similar adverse event profiles with an overall of 5 subjects experiencing a total of 11 treatment-related AEs.

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

#### 3. Post-marketing Surveillance

Post-marketing surveillance data are based on RHA $^{\circ}$  4 containing lidocaine, these data are representative and applicable to RHA $^{\circ}$  4 Mepi.

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, skin induration, skin edema, inflammatory reaction, erythema, pain, granuloma, vascular complication (such as vessel compression/occlusion), skin infection, allergic reaction, tenderness, skin discoloration, device dislocation and ecchymosis.

Additionally, other less frequent adverse reactions have also been reported, and includes injection site movement impairment, paresthesia "puffy skin, "skin discoloration/Tyndall effect, tenderness, abscess, overcorrection, pruritus, anaphylactic reaction, pigmentation disorder, skin necrosis, urticaria, angioedema, chapped lips, dermatitis, fibrosis, herpes breakout, blister, cellulitis, influenza-like illness, headache, hemorrhage, numbness, pustules, papules, blanching, fainting, hyperthermia, telangiectasia and visual impairment, neuralgia, wrinkles, 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 total resolution of the symptoms with or without sequelae.

#### CLINICAL STUDIES

#### CLINICAL STUDY of RHA® 4

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

The long-term safety and effectiveness of RHA $^{\otimes}$  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: Clinical Evaluation of RHA® 4

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 Wrinkle Severity Rating Scale (NLF-WSRS)) score.

Secondary effectiveness endpoints included rates of responders ( $\geq 1$  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 nosolabial fold domain of the FACE-Q $^{\circ}$ , 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 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 intention-to-treat (ITT) population

Subject's demographics are presented in Table 5.

#### Table 5. Demographics

RHA® 4 versus Control device №=118			
57.4	(10.0)		
27	86		
106	89.8%		
12	10.2%		
97 19 1 0 1	82.2% 16.1% 0.9% 0.0% 0.9% 0.0%		
30	25.4%		
88	74.6%		
4	3.4%		
21	17.8%		
40	33.9%		
31	26.3%		
14	11.9%		
8	6.8%		
	Control de N°=11  57.4 27  106 12  97 19 1 0 30 88  4 21 40 31 14		

<sup>a</sup> 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 punctate 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 $^{\odot}$  4. The primary effectiveness endpoint was the aesthetic improvement from pre-injection of the NLF treated with RHA $^{\odot}$  4 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, and results are presented in Table 4.

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

		R	HA® 4	Control Device			
	nª	NLF-WSRS score <sup>b</sup>	NLF-WSRS Improvement°				
re-treatment	88	3.49	-	3.49	-		
Veek 24 <sup>d</sup>	88	2.15	1.34	2.33	1.16		
Veek 36	86	2.21	1.28	2.37	1.12		
Veek 52	77	2.25	1.23	2.43	1.05		
Veek 64	65	2.20	1.26	2.35	1.11		

<sup>a</sup> Number of subjects in the PP populations at the respective follow-up visits

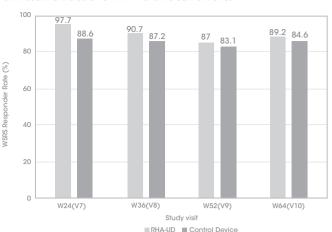
Mean NLF-Wrinkle Severity Rating Scale score (higher scores mean deepest wrinkles)
 Mean NLF-Wrinkle Severity Rating Scale improvement from pre-treatment (higher scores mean more improvement from pre-treatment)

In Primary effectiveness endpoint
The results demonstrated that non-inferiority to the control was achieved for RHA® 4 at

24 weeks for the treatment of NLFs. Results also showed that RHA® 4 was non-inferior to the control treatment at all study visits. Throughout the follow-up period, the aesthetic improvement of the RHA® 4 treated NLF continued to be clinically significant ( $\geq 1$  grade difference from pre-treatment on

NLF continued to be clinically significant (> 1 grade difference from pre-treatment on the NLF-WSRS) for more than 89% of the subjects at 64 weeks after initial treatment (Figure 1).

**Figure 1.** Proportion of responders on the Wrinkle Severity Rating Scale measured by a Blinded Live Evaluator for RHA $^{\circ}$  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 NLF-WSRS

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

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

#### CLINICAL STUDY OF RHA® 4 Mepi

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

#### 1. Pivotal Study Design

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

Subjects were treated RHA® 4 Mepi with mepivacaine in a randomly selected sequence (first or second injection) into the nasolabial fold in one side of the face and RHA® 4 with into the contradateral nasolabial fold. RHA® 4 Mepi and RHA® 4 were administered into deep dermis to superficial subcutaneous tissue for the treatment of moderate to severe nasolabial folds.

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

#### 2. Study Endpoints

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

was prohibited.

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

sensation commencing 60 minutes post-injection.

Secondary effectiveness endpoints included change in the severity of the NLF as measured by the TI using the WSRS, the rates of responders (≥ 1-grade difference from pre-treatment on the NLF-WSRS), as measured by the TI, Global Aesthetic Improvement (GAI), as assessed by the subject and by the TI, impact and effectiveness of study

pre-freatment on the NLF-WSRS), as measured by the TI, Global Aesthetic Improvement (GAI), as assessed by the subject and by the TI, impact and effectiveness of study treatment procedures from the subjects' perspective as assessed by the nasolabial fold domain of the FACE-QP, and subject satisfaction.

Safety endpoints were evaluated throughout the study, with a 30-day subject diary

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

#### 3. Demographics

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

DIIA® 4 Mani waran

Subjects' demographics are presented in Table 7.

#### Table 7. Demographics

RHA® 4 Mepi versus RHA® 4 Nº=30		
57	(9.7	
33	7	
27	90.09	
3	10.09	
27 3 0 0 0	90.09 10.09 0.09 0.09 0.09 0.09	
12	40.09	
18	60.09	
1	3.39	
8	26.79	
10	33.39	
8	26.79	
0	0.09	
3	10.09	
	RHA® N°=3i 57 33 27 3 0 0 0 0 12 18 1 8 10 8 0	

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

#### 4. Treatment Characteristics

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

In general, a linear threading, fan-like technique, or a combination of linear threading with multiple punctuate pools, was used for 96.6% of the subjects treated with RHA® 4 Mani

#### 5. Effectiveness Results

The primary effectiveness endpoint was met for RHA® 4 Mepi.

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

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

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

#### **Table 8.** Injection Site Pain during injection – PP population

VAS pain (mm)	RHA® 4 Mepi N°=30	RHA® 4 Nº=30	VAS Difference (mm) N°=30
Mean (SD)	17.1 (18.38)	16.3 (18.89)	-0.8 (8.09)
Min, Max	0,55	0,70	-20, 20

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

Table 9. Injection Site Pain after injection – ITT population

VAS pain (mm)	RHA® 4 Mepi	RHA® 4	VAS Difference (mm)
Mean (SD)	Nº=30	Nº=30	N°=30
Time point: - 15 Min - 30 Min - 45 Min - 60 Min	4.9 (12.33) 2.0 (5.66) 0.0 (0.00) 0.0 (0.00)	5.1 (15.94) 3.1 (12.30) 2.1 (11.68) 1.9 (10.22)	0.2 (6.81) 1.1 (10.36) 2.1 (11.68) 1.9 (10.22)

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

Secondary endpoints demonstrated no difference between RHA® 4 Mepi and RHA® 4 regarding clinical performance.

A similar improvement in the NLF-WSRS scores was observed one month post-injection, with a score improvement of 1.9 points in the RHA $^{\oplus}$  4 Mepi treatment group and 1.8 points in the RHA $^{\oplus}$  4 treatment group.

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

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

The subjects also reported similar improvement based on the NLF module of the FACE-Q $^{\circ}$  questionnaire with the mean score increasing by 63.8 and 64.2 points in the RHA $^{\circ}$  4 Mepi and RHA $^{\circ}$  4 treatment groups, respectively.

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

Similar effectiveness and safety profiles were observed by Fitzpatrick skin type, ethnicity and age groups.

## Results of RHA® 4 long term safety and effectiveness are applicable to RHA® 4 Mepi. DIRECTIONS FOR ASSEMBLY

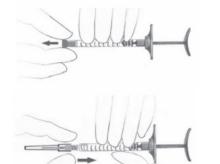
OF THE NEEDLE TO THE SYRINGE

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

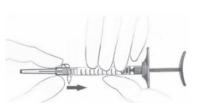
2. Insert the screw thread of the

needle firmly into the syringe

end-piece.



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



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



**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

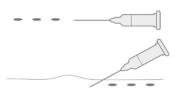
 Prior to treatment, the patient should avoid taking medications or supplements which thin the blood (e.g., aspirin, nonsteroidal anti-inflammatory medications, St. John's Wort, or high doses of Vitamin E supplements) as these agents may increase bruising and bleeding at the injection site.

- 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
- Prior to treatment with RHA® 4 Mepi the patient should be assessed for appropriate
  anesthetic treatment for managing comfort (e.g., topical anesthetic, local or nerve
  block). The patient's face should be washed with soap and water and dried with
  a clean towel. Cleanse the area to be treated with alcohol or another suitable
  antiseptic solution.
- Sterile gloves are recommended while injecting RHA® 4 Mepi.
- Before injecting, prime the needle by carefully pressing the syringe plunger until a small droplet of the gel is visible at the tip of the needle.

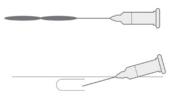
#### INJECTION TECHNIQUES

- RHA® 4 Mepi is administered by using a thin gauge needle (27 G x ½"). 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.
- RHA® 4 Mepi can be injected by a number of different techniques that depend on the injector's experience and preference, and patient characteristics.

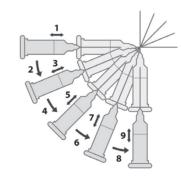
**A. Serial puncture:** consists of multiple injections, evenly and closely spaced all along wrinkles or folds. This technique is considered to be more precise, but may result in more discomfort for the patient due to the number of punctures.



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



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



- RHA® 4 Mepi is injected slowly into the deep dermis to superficial subcutaneous.
- 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® 4 Mepi, the same procedure should be repeated until a satisfactory result is obtained.

#### POST-TREATMENT GUIDELINES

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

#### STERILE NEEDLES

- After use, needles are potential biohazards. Follow national, local, or institutional guidelines for use and disposal of medical sharp devices (e.g. discard uncapped needles in approved sharps containers).
- Disposal should be in accordance with accepted medical practice and applicable local, State and Federal requirements.
   To help avoid needle breakage, do not attempt to straighten a bent needle, discard it
- and complete the procedure with a replacement needle.

   Do not recap needles. Recapping by hand is a hazardous practice and should be
- RHA® 4 Mepi is provided with 2 needles that do not contain engineered injury protection. Administration of RHA® 4 Mepi requires direct visualization and complete and gradual insertion of the needle making engineered protection devices not

feasible. To avoid needle stick injury and sharp exposure, take care to inject in

appropriate conditions.Obtain prompt medical attention if injury with used needle occurs.

#### PATIENT INSTRUCTIONS

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

- It is recommended that the following information be shared with patients:
- Patients should be advised not to wear make-up during 12 hours following injection.
   Patient should be advised not to take high-dose Vitamin E, aspirin, anti-inflammatories or anti-coagulants during the week prior to the injection. Patients must not discontinue such treatment without talking with their prescribing physician.
- Patients should minimize exposure of the treated area to excessive sun, UV lamp exposure and extreme temperatures (e.g. cold weather, sauna) at least within the first 24 hours, or until initial swelling and redness 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:
- o Changes in vision
- Unusual pain during or shortly after treatment
- Significant pain away from the injection site
- o 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 Mepi is supplied in individual blisters containing a 1.2 ml treatment syringe with two 27 G x  $\frac{1}{2}$ " needles as indicated on the carton.

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

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

#### SHELF-LIFE AND STORAGE

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

## RxOnly

Manufactured by: Distributed by:

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

 $\ensuremath{\mathsf{RHA}}^{\ensuremath{\$}}$  is a registered trademark of TEOXANE SA.

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

#### SYMBOLS



Manufacturer's name and address



LOT

Lot / batch number

Catalog number



Sterilized using steam

Expiration date (YYYY-MM-DD)

Consult Instructions for use



Single use only



Do not use if the package is damaged





