RHA® DYNAMIC VOLUME

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

BEFORE USING RHA® DYNAMIC VOLUME, PLEASE READ THE FOLLOWING INFORMATION THOROUGHLY

DEVICE DESCRIPTION

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

INTENDED USE / INDICATIONS

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

RHA® Dynamic Volume is indicated for injection into the subcutaneous to supraperiosteal layers for cheek augmentation and/or correction of age-related midface contour deficiencies, in adults aged 22 years or older.

CONTRAINDICATIONS

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

WARNINGS

- Introduction of product into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction. 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 and the Post-marketing Surveillance section for more details.
- Inflammatory reaction, anaphylactic reaction, edema, implant migration papule, acne, blisters, scarring, papules, unsatisfactory results, scarring and delayed onset of granulomas have been reported following the use of dermal fillers.

PRECAUTIONS

- In order to minimize the risks of potential complications, this product should only be used by experienced health care practitioners who have appropriate training in filler injection techniques, and who are knowledgeable about the anatomy at and around the site of injection.
- Health care practitioners are encouraged to discuss all potential risks of soft tissue injection with their patients prior to treatment and ensure that patients are aware of signs and symptoms of potential complications.
- The safety and effectiveness for the treatment of 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 for cheek augmentation have only been clinically evaluated with TSK STERiGLIDE™ cannulas that were 25G and 2 inches in length.
- As with all transcutaneous procedures, dermal filler implantation carries a risk of infection. Standard precautions associated with injectable materials should be followed.
- The safety in patients with known susceptibility to keloid formation, hypertrophic scarring, and pigmentation disorders has not been studied.
- The safety for use in sites in the presence of other implants (including permanent implants) has not been studied.
- The safety for use during pregnancy, in breastfeeding females, and in patients under 22 years of age has not been established.
- RHA® Dynamic Volume should be used with caution in patients on immunosuppressive therapy.
- Bruising or bleeding may occur at RHA® Dynamic Volume injection sites. RHA® Dynamic Volume should be used with caution in patients who are using substances that can prolong bleeding (such as thrombolytics, anticoagulants, or inhibitors

of platelet aggregation).

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

ADVERSE EXPERIENCES

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

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

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

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

1. Clinical Evaluation of RHA® 4 in the NLFs

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

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

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

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

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

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

Common Treatment Responses	TOTALS		RHA® 4 (N[a]=120 NLF)			Control Device (N[a]=120 NLF)		
	RHA® 4 n[b] (%)	CTRL[c] n[b] (%)	Mild n[b] (%)	Mod[d] n[b] (%)	Sev[e] n[b] (%)	Mild n[b] (%)	Mod[d] n[b] (%)	Sev[e] n[b] (%)
Bruising	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	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 (70.0%)	91 (75.8%)	42 (35.0%)	38 (31.7%)	4 (3.3%)	32 (26.7%)	42 (35.0%)	17 (14.2%)
Swelling	97 (80.8%)	104 (86.7%)	41 (34.2%)	44 (36.7%)	12 (10.0%)	21 (17.5%)	38 (31.7%)	45 (37.5%)
Tenderness	90 (75.0%)	95 (79.2%)	53 (44.2%)	30 (25.0%)	7 (5.8%)	23 (19.2%)	45 (37.5%)	27 (22.5%)

[a] Number of subjects' NLF treated with the respective device

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

[c] CTRL = Control treatment

[d] Mod = Moderate

[e] Sev = Severe

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

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

[a] Number of subject NLF treated with the respective device

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

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

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

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

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

2. Clinical Evaluation of RHA® Dynamic Volume 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® Dynamic Volume and was studied against the approved RHA® 4 dermal filler with lidocaine in a multicenter, controlled, randomized, double-blinded, within-subject (split-face), prospective US clinical study for the treatment of moderate to severe nasolabial folds with RHA® Dynamic Volume versus RHA® 4. Similar safety profiles between RHA® Dynamic Volume and RHA® 4 were demonstrated.

RHA® Dynamic Volume is strictly identical to RHA®4 except for the small amount of anesthetic medicine: RHA® Dynamic Volume contains mepivacaine and RHA®4 contains lidocaine. Both anesthetics agents are of the same family with the same mechanisms of effect. This clinical study also serves as the support to leverage the clinical data of RHA®4 when injected into the midface for RHA® Dynamic Volume when injected into the midface.

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

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

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

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

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

Common Treatment	**TOTALS**	**RHA® Dynamic Volume (N[a]=30 NLF)**	**RHA® 4 (N[a]=30 NLF)**

Responses	RHA® Dynamic Volume n[b] (%)	RHA® 4 n[b] (%)	Mild n[b] (%)	Mod[c] n[b] (%)	Sev[d] n[b] (%)	Mild n[b] (%)	Mod[c] n[b] (%)	Sev[d] n[b] (%)
Bruising	19 (63.3%)	21 (70.0%)	7 (23.3%)	12 (40.0%)	0 (0.0%)	10 (33.3%)	11 (36.7%)	0 (0.0%)
Discoloration	11 (36.7%)	12 (40.0%)	8 (26.7%)	2 (6.7%)	1 (3.3%)	8 (26.7%)	4 (13.3%)	0 (0.0%)
Firmness	24 (80.0%)	22 (73.3%)	12 (40.0%)	10 (33.3%)	2 (6.7%)	9 (30.0%)	11 (36.7%)	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%)	2 (6.7%)
Swelling	21 (70.0%)	23 (76.7%)	11 (36.7%)	9 (30.0%)	1 (3.3%)	14 (46.7%)	9 (30.0%)	0 (0.0%)
Tenderness	24 (80.0%)	24 (80.0%)	16 (53.3%)	8 (26.7%)	0 (0.0%)	18 (60.0%)	6 (20.0%)	0 (0.0%)
Others[e]	1 (3.3%)	0 (0.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

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

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

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

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

- Both RHA® Dynamic Volume and RHA® 4 treatment groups presented with very similar adverse event profiles with an overall of 5 subjects experiencing a total of 11 treatment-related AEs.
- All treatment-related AEs were mild in severity and none were considered by Investigators to be clinically significant. All events resolved spontaneously by the time of the study exit (30 days) except the injection site mass for one subject. This event had resolved spontaneously by 46 days post-injection without the need for medical therapy.
- All treatment-related AEs experienced by both treatment groups were typical of the expected signs and symptoms observed following an injection of a hyaluronic acid-based dermal filler except one (paresthesia; mild) that was reported by the subject in the "other" category of the 30-day diary and which resolved in 2 days.
- All treatment-related AEs were based on subjects' diary entries (CTRs)
- No events were deemed to be a granuloma.
- There were no late onset treatment-related AEs.
- There were no treatment-related serious AEs.
- There were no subjects who withdrew from the study due to AEs.

Safety profile by Fitzpatrick skin type, ethnicity and age was not different.

3. Clinical Evaluation of RHA®4 for midface volume deficiency

Clinical study TEO-RHA-2004 was a multicenter, controlled, randomized, double-blinded, between-subject, prospective US study designed to compare the safety of RHA®4 versus a Control treatment for the treatment of midface volume deficiency, and demonstrated similar safety profiles. The expected signs and symptoms that occur following the injection of a hyaluronic acid-based dermal filler (i.e., CTRs) were individually assessed by subjects in a preprinted 30-day diary after each injection.

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

- Mild: Little discomfort, no effect on daily activities, no medication or make-up required
- Moderate: some discomfort, some effect on daily activities, possibly medication or make-up required

- Severe: Great discomfort, daily activities compromised, very likely medication or make-up required

CTR by severity and duration are presented respectively, in Table 5 and Table 6.

- The most frequent CTRs were tenderness, firmness, swelling and lumps/bumps.
- Proportion of subjects experiencing at least one CTR of each category was similar between RHA®4 and Control treatment.
- The majority (68%, 87 of the 128 RHA4 subjects experiencing at least 1 CTR) of subjects had their CTRs resolved by Day 14. Similar results were observed in Control treatment group.
- The proportion of subjects reporting severe CTRs was similar in RHA®4 and Control treatment groups.
- 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 5. Common Treatment Responses by maximum severity after initial treatment with RHA®4 and the Control Device reported in subject 30-day-diary – Safety Population

Common Treatment Responses	TOTALS		RHA®4 (N[a]=152)			Control Device (N[a]=49)		
	RHA®4 n[b] %	CTRL[c] n[b] %	Mild N[c] %	Mod[e] N[c] %	Sev[f] N[c] %	Mild N[c] %	Mod[e] N[c] %	Sev[f] N[c] %
Subject with at least 1 CTR	128 90.8%	44 95.7%	69 53.9%	52 40.6%	7 5.5%	26 59.1%	15 34.1%	3 6.8%
Bruising	74 52.5%	16 34.8%	55 74.3%	17 23.0%	2 2.7%	15 93.8%	1 6.3%	0 0.0%
Discoloration	32 22.7%	6 13.0%	24 75.0%	8 25.0%	0 0.0%	6 100%	0 0.0%	0 0.0%
Firmness	108 76.6%	34 73.9%	72 66.7%	32 29.6%	4 3.7%	21 61.8%	11 32.4%	2 5.9%
Itching	17 12.1%	2 4.3%	15 88.2%	2 11.8%	0 0.0%	2 100%	0 0.0%	0 0.0%
Lumps/Bumps	77 54.6%	23 50.0%	43 55.8%	30 39.0%	4 5.2%	14 60.9%	8 34.8%	1 4.3%
Pain	70 49.6%	20 43.5%	55 78.6%	15 21.4%	0 0.0%	18 90.0%	2 10.0%	0 0.0%
Redness	61 43.3%	17 37.0%	51 83.6%	10 16.4%	0 0.0%	13 76.5%	3 17.6%	1 5.9%
Swelling	98 69.5%	28 60.9%	68 69.4%	29 29.6%	1 1.0%	24 85.7%	4 14.3%	0 0.0%
Tenderness	113 80.1%	39 84.8%	86 76.1%	26 23.0%	1 0.9%	33 84.6%	5 12.8%	1 2.6%

[a] Number of subjects' midface treated with the respective device

[b] Number of subjects' midface with any specific Common Treatment Response. All percentages are based on the number of CTR diaries retrieved by injection by subgroup in the population. In the RHA®4 group, 152 subjects were treated with initial injection and 141 CTR diaries were retrieved. In the Control treatment groups, 49 subjects were treated with initial injection and 46 CTR diaries were retrieved.

[c] Number of subjects with each specific CTR by maximum severity. All percentages are based on the number of subjects with the specific CTR by injection by subgroup in the population. In the RHA®4 group, 152 subjects were treated with initial injection and 128 subjects experienced at least 1 CTR. In Control treatment group, 49 subjects were treated with initial injection and 44 subjects experienced at least 1 CTR.

[d] CTRL = Control treatment

[e] Mod = Moderate

[f] Sev = Severe

Table 6. Duration of Common Treatment Responses after initial treatment with RHA®4 and the Control Device reported in subject 30-day-diary – Safety Population

Common Treatment Responses	RHA®4 (N[a]=152) N[b] %					Control Device (N[a]=49) N[b] %				
Duration[c]	1-3d	4-7d	8-14d	15-30d	Last Day	1-3d	4-7d	8-14d	15-30d	Last Day
Bruising	19 13.5%	28 19.9%	17 12.1%	10 7.1%	3 2.1%	5 10.9%	6 13.0%	5 10.9%	0 0%	0 0%
Discoloration	17 12.1%	5 3.5%	6 4.3%	4 2.8%	4 2.8%	3 6.5%	3 6.5%	0 0%	0 0%	0 0%
Firmness	34 24.1%	35 24.8%	19 13.5 %	20 14.2%	6 4.3%	10 21.7%	9 19.6%	5 10.9%	10 21.7%	2 4.3%
Itching	7 5.0%	3 2.1%	5 3.5%	2 1.4%	1 0.7%	2 4.3%	0 0%	0 0%	0 0%	0 0%
Lumps/ Bumps	30 21.3%	13 9.2%	12 8.5%	22 15.6%	15 10.6%	7 15.2%	5 10.9%	4 8.7%	7 15.2%	1 2.2%
Pain	39 27.7%	17 12.1%	8 5.7%	6 4.3%	1 0.7%	9 19.6%	5 10.9%	5 10.9%	1 2.2%	0 0%
Redness	41 29.1%	11 7.8%	4 2.8%	5 3.5%	2 1.4%	11 23.9%	5 10.9%	0 0%	1 2.2%	0 0%
Swelling	47 33.3%	32 22.7%	13 9.2%	6 4.3%	1 0.7%	16 34.8%	8 17.4%	1 2.2%	3 6.5%	0 0%
Tenderness	34 24.1%	39 27.7%	24 17.0 %	16 11.3%	2 1.4%	10 21.7%	15 32.6%	9 19.6%	5 10.9%	1 2.2%

[a] Number of subjects treated with the respective device

[b] Number of subjects with each specific CTR by maximum duration. All percentages are based on the number of CTR diaries retrieved by injection by subgroup in the population. In RHA®4 group 152 subjects were treated with initial injection and 141 CTR diaries were retrieved. in Control treatment group, 49 subjects were treated with initial injection and 46 CTR diaries were retrieved.

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

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

- Both RHA®4 and Control treatment groups presented with similar adverse event (AE) profiles with 36 (23.7%) subjects in the RHA®4 group experiencing a total of 67 treatment-related AEs after initial treatment and touch-up injections.
- All treatment-related AEs were mostly mild, with some that were moderate, no severe treatment-related AEs were reported after all treatments (i.e., initial, touch up and retreatment).
- Most of treatment-related AEs experienced in both treatment groups were typical of the expected signs and symptoms observed following an injection of a hyaluronic acid-based dermal filler, such as: injection site mass, injection site induration and injection site pain. Other reported treatment-related AEs such as headache, periorbital pain 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): 91% (61/67) were either a CTR, or listed as Others, or from the list of pre-identified AEs on the diary and 9% (6/67) were identified by the TI, in the in the RHA®4 group. Similar results were found in the Control treatment group.
- The proportion of subjects with reported treatment related AE was similar across the 2 treatment groups. Most treatment-related AEs (82%, 55/67) in the RHA®4 group

resolved within 14 days and was similar in Control treatment group. The duration of treatment-related AEs varied from 1 to 90 days, except for 1 treatment-related AE in the RHA®4 group. One event was an injection site mass that lasted 227 days, this event was mild in severity and resolved without sequelae. No treatment was administered for this event. These treatment-related AEs were typical and expected signs and symptoms observed following the injection of a dermal filler.

- There were no treatment-related serious AEs.
- Eleven AE of Special Interest (AESI) were reported. AESI is defined as any new vision disturbance. 10 AESIs in 5 subjects randomly assigned to RHA4 group between Visit 1 and Visit 7 and 1 AESI in 1 subject in the RHA4 group after retreatment. None of the AESIs were related to device and 2 subjects had 4 AESIs considered related to the procedure. All events were mild and none of the events fulfilled seriousness criteria. All AESI events either resolved without sequelae or were ongoing at the end of the study and Treating Investigator considered that no additional follow-up is needed.
- 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, ethnicity, age, sex, administration method and volume injected were not different between both treatment groups.

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

4. Post-marketing Surveillance

Post-marketing surveillance data are based on RHA® 4 containing lidocaine, these data are representative and applicable to RHA® Dynamic Volume.

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: skin edema/skin swelling, injection site masses (inflammatory or non-inflammatory nodules), skin induration, injection site inflammation, pain, erythema, granuloma, vascular complication, ecchymosis, skin infection and tenderness.
Additionally, other less frequent adverse reactions have also been reported, and includes implant migration, allergic reaction, skin discoloration/Tyndall effect, abscess, overcorrection, pruritus, anaphylactic reaction, skin necrosis, urticaria, blister, scab, angioedema, chapped lips, dermatitis, dry skin, fibrosis, herpes breakout, 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, antihistamines, anti-inflammatories, anti-viral, drainage, excision, implant dissolution (hyaluronidase), incision, massage and vasodilators.

CLINICAL STUDIES

CLINICAL STUDY OF RHA® 4 INTO THE NLFS

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

The long-term safety and effectiveness of RHA® 4 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 into the NLFs

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) resolved. 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 (≥ 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 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, 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 7.

Table 7. Demographics

Number / % of subjects	**RHA® 4 versus Control Device** N[a]=118	
Age		
Mean (SD)	57.4	(10.0)
min max	27	86
Gender		
Female	106	89.8%
Male	12	10.2%
Race		
Caucasian	97	82.2%
Black	19	16.1%
Am. Indian/N. Alask.	1	0.9%
N. Hawaiian/P. Isl.	0	0.0%
Asian	1	0.9%
Other	0	0.0%
Ethnicity		
Hispanic/Latino	30	25.4%
Not Hispanic/Latino	88	74.6%
Fitzpatrick Skin Phototype		
I	4	3.4%
II	21	17.8%
III	40	33.9%
IV	31	26.3%
V	14	11.9%
VI	8	6.8%

[a] Number of subjects in the ITT populations

4. Treatment Characteristics

The study protocol allowed a maximum of 3.0 mL in a single NLF per treatment session. The overall total median volume of RHA® 4 injected to achieve optimal correction results was 1.7 mL. The proportion of subjects who received touch-up treatment with RHA® 4 at Week 2 was 27.1%.

In general, a linear threading or multiple 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 Nasolabial Folds Wrinkle Severity Rating Scale, NLF-WSRS) by the BLE at 24 weeks after baseline, and results are presented in Table 8.

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

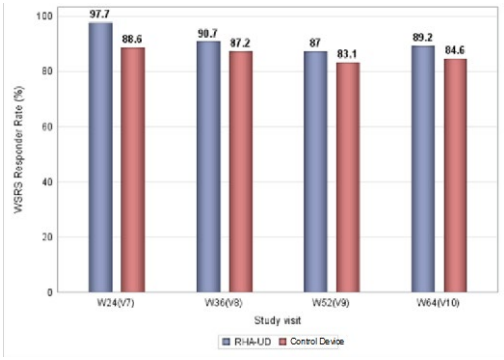
		RHA® 4		**Control Device**	
	n[a]	NLF-WSRS score[b]	NLF-WSRS Improvement[c]	NLF-WSRS score[b]	NLF-WSRS Improvement[c]
Pre-treatment	88	3.49	-	3.49	-
Week 24[d]	88	2.15	1.34	2.33	1.16
Week 36	86	2.21	1.28	2.37	1.12
Week 52	77	2.25	1.23	2.43	1.05
Week 64	65	2.20	1.26	2.35	1.11

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

The results demonstrated that non-inferiority to the control was achieved for RHA® 4 at 24 weeks for the treatment of NLFs. Results also showed that RHA® 4 was non-inferior to the control treatment at all study visits.

Throughout the follow-up period, the aesthetic improvement of the RHA® 4 treated NLF continued to be clinically significant (≥ 1 grade difference from pre-treatment on the NLF-WSRS) for more than 89% of the subjects at 64 weeks after initial treatment (Figure 1).

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



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

PP populations 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, (the scale included the following grades: 1-Much improved 2-Improved 3-No change 4-Worse 5-Much worse) more than 87% of the subjects and the BLE reported that the NLF treated with RHA® 4 was improved or very much improved from week 24 to week 64. The subjects consistently reported improvement up to 64 weeks based on the NLF module of the FACE-Q© questionnaire with the mean score improving from 24 to more than 70 throughout the follow-up period. More than 93% of the subjects reported to be satisfied or very satisfied from week 24 to week 64 (the scale grades were: very satisfied, satisfied, neither satisfied nor dissatisfied, dissatisfied or very dissatisfied).

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

CLINICAL STUDY OF RHA® DYNAMIC VOLUME into the NLFs

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

1. Pivotal Study Design

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

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

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

2. Study Endpoints

The primary endpoint was the analysis of the non-inferiority of the injection site pain felt during injection assessed by the subject immediately following injection with RHA® Dynamic Volume (using a 100 mm Visual 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 treatment procedures from the subjects' perspective as assessed by the nasolabial fold domain of the FACE-Q©, and subject satisfaction.

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

3. Demographics

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

Subjects' demographics are presented in Table 9.

Table 9. Demographics

Number / % of subjects	**RHA® Dynamic Volume versus RHA® 4** Nª=30	
Age		
Mean (SD)	57	(9.7)
min max	33	79
Gender		
Female	27	90.0%
Male	3	10.0%
Race		
Caucasian	27	90.0%
Black	3	10.0%
Am. Indian/N. Alask.	0	0.0%
N. Hawaiian/P. Isl.	0	0.0%
Asian	0	0.0%
Other	0	0.0%
Ethnicity		
Hispanic/Latino	12	40.0%
Not Hispanic/Latino	18	60.0%
Fitzpatrick Skin Phototype		
I	1	3.3%
II	8	26.7%

Number / % of subjects	RHA® Dynamic Volume versus RHA® 4 Nª=30	
III	10	33.3%
IV	8	26.7%
V	0	0.0%
VI	3	10.0%

ª Number of subjects in the ITT population

4. Treatment Characteristics

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

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

5. Effectiveness Results

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

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

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

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

Results are presented in Table 10 and Table 11.

Table 10. Injection Site Pain during injection – PP population

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

ª Number of subjects in the PP population

Table 11. Injection Site Pain after injection – ITT population

VAS pain (mm) Mean (SD)	RHA® Dynamic Volume Nª=30	RHA® 4 Nª=30	VAS Difference (mm) Nª=30
Time point:			
- 15 Min	4.9 (12.33)	5.1 (15.94)	0.2 (6.81)
- 30 Min	2.0 (5.66)	3.1 (12.30)	1.1 (10.36)
- 45 Min	0.0 (0.00)	2.1 (11.68)	2.1 (11.68)
- 60 Min	0.0 (0.00)	1.9 (10.22)	1.9 (10.22)

ª Number of subjects in the ITT population

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

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

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

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

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

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

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

Results of RHA® 4 long term safety and effectiveness are applicable to RHA® Dynamic Volume.

Pivotal STUDY of RHA®4 for midface volume deficiency

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

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

1. Pivotal Study Design

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

A total of 201 subjects were randomized and underwent treatment with either RHA® 4 (N = 152) or Control treatment (N = 49) in the midface area for cheek augmentation and/or correction of age-related midface contour deficiencies. Injection was performed with a needle and/or cannula. If deemed necessary to achieve optimal correction, additional midface correction was performed after 4 weeks (touch-up), with the same study device used for initial treatment.
The follow-up period consisted of safety and effectiveness follow-up visits at 2, 4, 8, 16, 24, 36, and 52 weeks after the last treatment.
Subjects were eligible for optional retreatment if necessary, at Weeks 52, and were then followed for 3 months after retreatment or until all Adverse Events (AEs) resolved or TI determined that follow-up was no longer necessary. Retreatment was provided using RHA® 4 (the Control device was not used).

2. Study Endpoints

The primary effectiveness endpoint was the analysis of non-inferiority of RHA® 4 versus Control in terms of change from Baseline (pre-injection) 8 weeks after injection, as measured by a Blinded Live Evaluator (BLE) using the proprietary and validated 5-grade Teoxane Midface Volume Deficit Scale (TMVDS).
Secondary effectiveness endpoints included TMVDS change from Baseline and rates of responders, as assessed by the BLE at each study visits (see data in Table 12 and Figure 2), Global Aesthetic Improvement (GAI), as assessed by the subject, TI and BLE, impact and effectiveness of study treatment procedures from the subjects' perspective as assessed by the satisfaction with cheeks module (at rest and when smiling) of the FACE-Q©, and subject satisfaction.
Safety endpoints were evaluated throughout the study, with a 30-day subject diary capturing post-injection signs/symptoms following every study injection, and AE assessments at each visit, and included self-assessment of injection site pain by the subject using a 100mm Visual Analog Scale.

3. Demographics

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

Table 12. Demographics

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

[a] Number of subjects in the ITT/Safety populations
[b] a subject can be counted in several categories

4. Treatment Characteristics

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

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

5. Effectiveness Results

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

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

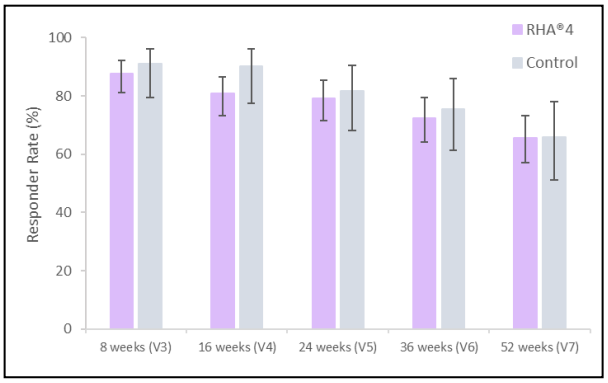
	RHA® 4	**Control**
Week 8[a]	-1.3 (0.78)	-1.3 (0.63)
Week 16	-1.2 (0.83)	-1.3 (0.75)
Week 24	-1.1 (0.79)	-1.0 (0.76)

	RHA® 4	Control
Week 36	-0.9 (0.81)	-0.9 (0.66)
Week 52	-0.9 (0.79)	-0.8 (0.69)

[a] Primary effectiveness endpoint
ITT population

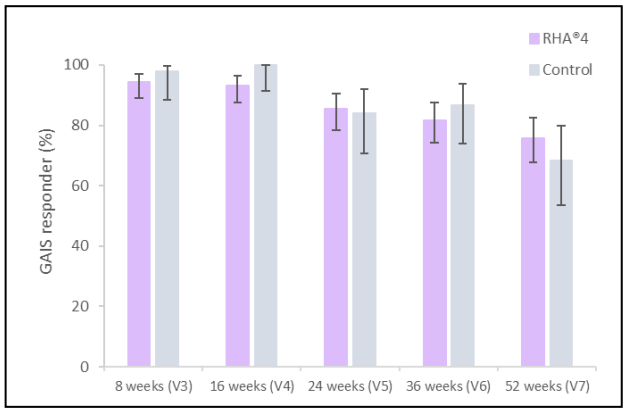
The results demonstrated that non-inferiority to the Control treatment was achieved for RHA®4 at 8 weeks for the treatment of midface volume deficiencies. Results also showed that RHA® 4 was not inferior to the Control treatment at all study visits.
Throughout the follow-up period, the aesthetic improvement of midface volume treated with RHA® 4 continued to be clinically significant (≥ 1-grade difference from pre-treatment on the TMVDS) for more than 65% of the subjects at 52 weeks after last treatment (Figure 2).

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



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

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

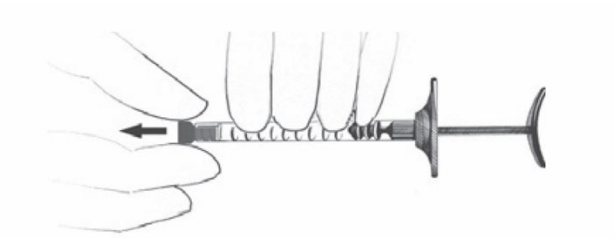


The subjects treated with RHA® 4 consistently reported improvement up to 52 weeks based on the *Satisfaction with cheeks* module, at rest and when smiling, of the FACE-Q© questionnaire with the mean score improving from Baseline by 53 and 56 points at Week 8, respectively, to more than 38 points throughout the follow-up period. RHA® 4 demonstrated durability throughout the study with a slow decline over time.
More than 89% of the subjects reported to be satisfied or very satisfied 8 weeks after treatment and the rate of satisfaction remained at more than 82% at 52 weeks (the scale grades were: very satisfied, satisfied, neither satisfied nor dissatisfied, dissatisfied, or very dissatisfied).

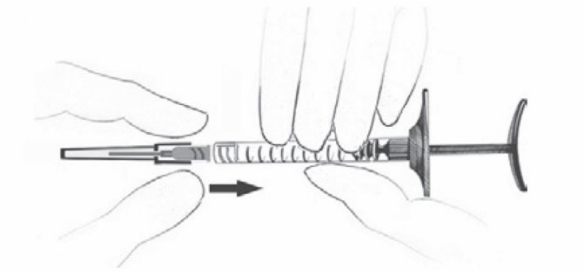
Repeat treatment with RHA®4 only, irrespective of their initial group assignment, was provided to 50.7% and 59.2% of subjects initially assigned to the RHA®4 and Control treatment groups, respectively, at the end of the study. The effectiveness and safety profiles after repeat treatment were similar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

DIRECTIONS FOR ASSEMBLY OF THE NEEDLE TO THE SYRINGE

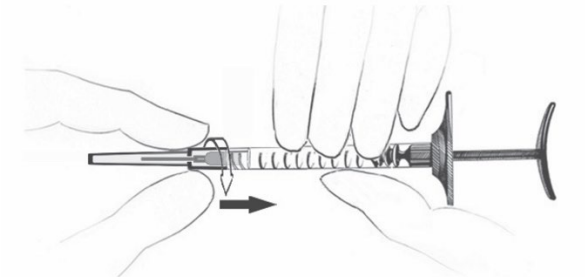
1. Remove the stopper from the syringe by pulling it off.



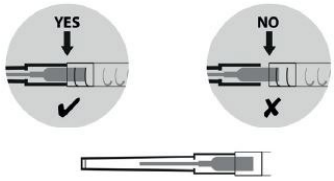
2. Insert the screw thread of the needle firmly into the syringe end-piece.



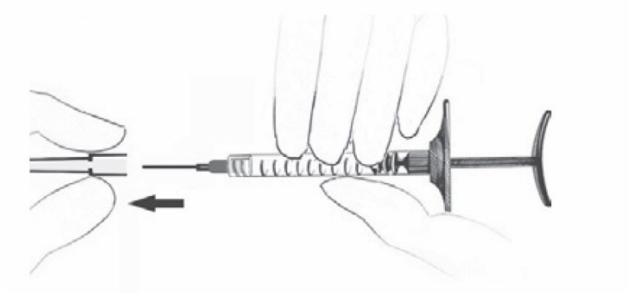
3. Screw the needle clockwise, while maintaining slight pressure between the needle and the syringe.



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.



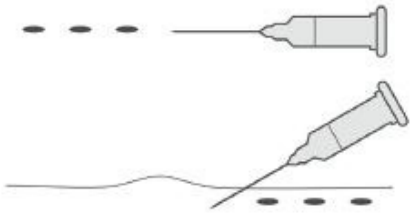
PRE-TREATMENT GUIDELINES

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

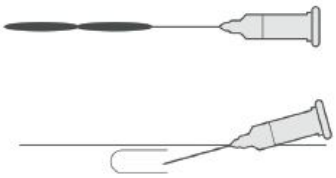
INJECTION TECHNIQUES

- RHA® Dynamic Volume is administered for injection into dynamic facial wrinkles and folds by using a thin gauge needle (27 G x ½") or a blunt tip cannula (25 G x 2"). RHA®4 is supplied with 27 G x ½" needles. The TSK STERiGLIDE™ cannulas were used in the clinical trials and are recommended for use with RHA® Dynamic Volume.
- RHA® Dynamic Volume is administered for injection for midface volume deficiency using a thin gauge needle (27 G x ½") or a blunt tip cannula (25 G x 2"). The TSK STERiGLIDE™ cannula was used in the clinical trials and is recommended for use with RHA®Dynamic Volume.
- When using a needle, the needle is inserted into the deep dermis to superficial subcutaneous at an approximate angle of 15° to 30° parallel to the length of the wrinkle or fold.
- When injecting into supraperiosteal layer with a needle the needle is inserted bevel down with an angle of 90° to the skin surface until touching the bone.
- When using a cannula, an entry point is made in the skin with the provided pre-hole needle.
- RHA® Dynamic Volume can be injected by a number of different techniques that depend on the injector's experience and preference, treated area, and patient characteristics.

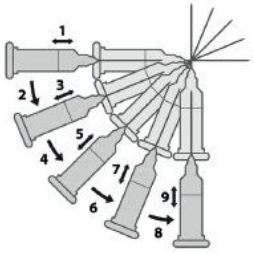
A. Serial puncture: (only recommended for needle): consists of multiple injections, evenly and closely spaced all along wrinkles or folds. This technique is considered to be more precise, but may result in more discomfort for the patient due to the number of punctures.



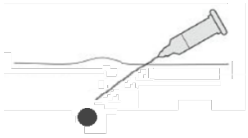
B. Linear threading: the needle/cannula is fully introduced in the wrinkle or the fold, and the product is injected along the line, as a "thread", while withdrawing (retrograde) or pushing (antegrade) the needle/cannula.



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



D. Multiple bolus technique: the needle/cannula is fully introduced as deep as possible into the cheeks hitting the periosteum and boluses of the product are injected slowly and using a low pressure. Identical or different injection volumes may be used for each bolus.



- RHA® Dynamic Volume is injected slowly into the deep dermis to superficial subcutaneous in the wrinkle or the fold.
- RHA® Dynamic Volume is injected slowly onto the supraperiosteum or from subcutaneous to supraperiosteal, if multilayering, when treating midface volume deficiency.
- 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, volume should be limited to 6.0ml per treatment session and should not exceed 3mL per side for the NLF. Based on the US clinical study, volume should be limited to 6.0mL per treatment session and should not exceed 3mL per side for the midface. The safety of injecting greater amounts has not been established.
- If blanching is observed (e.g., the overlying skin turns a whitish color), the injection should be stopped immediately and the area massaged until it returns to a normal color. Blanching may represent a vessel occlusion. If normal skin coloring does not return, do not continue with the injection. Treat in accordance with American Society for Dermatologic Surgery guidelines, which include hyaluronidase injection.
- If the wrinkles or midface need further treatment with RHA® Dynamic Volume, the same procedure should be repeated until a satisfactory result is obtained.

POST-TREATMENT GUIDELINES

- When the injection is completed for the correction of moderate to severe dynamic facial wrinkles and folds such as NLF, 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.
- When the injection is completed for the treatment of midface volume deficiencies, massaging the treated site should be avoided to prevent displacement of filler from the desired location. If an overcorrection has occurred, massage the area gently with your fingers 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 pack 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 an injury occurs.

STERILE NEEDLES OR CANNULAS

- After use, needles and cannulas 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/cannulas. Recapping by hand is a hazardous practice and should be avoided.
- RHA® Dynamic Volume is provided with 2 needles that do not contain engineered injury protection. Administration of RHA® Dynamic Volume 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/cannulas occurs.

PATIENT INSTRUCTIONS

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

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

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

- Any side effect other than those described above or that occur weeks or months after injection
- Adverse reactions should be reported to Revance Therapeutics, Inc at 877-3REV-NOW (877-373-8669) and to Medical@teoxane.com.

HOW SUPPLIED

RHA® Dynamic Volume is supplied in individual blisters containing a 1.2mL 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 Dynamic Volume must be used prior to the expiration date printed on the package.
Store at room temperature (up to 25°C/77°F). Do not expose to direct sunlight. DO NOT FREEZE.

RxOnly

Manufactured by:

TEOXANE SA.
Rue de Lyon, 105
CH 1203 Geneva
Switzerland

Distributed by:

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

RHA® is a registered trademark of TEOXANE SA.

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

REF Catalog number

LOT Lot / batch number

Expiration date (YYYY-MM-DD)

Consult Instructions for use

Single use only

STERILE Sterilized using steam

Do not use if the package is damaged

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

TEOXANE

RHA®4

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

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

DEVICE DESCRIPTION

RHA®4 is a viscoelastic, sterile, non-pyrogenic, clear, colorless, homogeneous and biodegradable gel implant. It is produced with sodium Hyaluronate (NaHA) with a concentration of 23 mg/g obtained from bacterial fermentation using the *Streptococcus equi* bacterial strain, crosslinked with 1,4-butanediol diglycidyl ether (BDDE) and reconstituted in a physiological buffer (pH 7.3). RHA®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.

RHA®4 is indicated for injection into the subcutaneous to supraperiosteal layers for cheek augmentation and/or correction of age-related midface contour deficiencies, in adults aged 22 years or older.

CONTRAINDICATIONS

- RHA®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

- 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, 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. 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 and the Post-marketing Surveillance section for more details.
- Inflammatory reaction, anaphylactic reaction, edema, implant migration papule, acne, blisters, scarring, papules, unsatisfactory, results, scarring and delayed onset of granulomas have been reported following the use of dermal fillers.

PRECAUTIONS

- In order to minimize the risks of potential complications, this product should only be used by experienced health care practitioners who have appropriate training in filler injection techniques, and who are knowledgeable about the anatomy at and around the site of injection.
- Health care practitioners are encouraged to discuss all potential risks of soft tissue injection with their patients prior to treatment and ensure that patients are aware of signs and symptoms of potential complications.
- The safety and effectiveness for the treatment of 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 for dynamic facial wrinkles and folds 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.
- The safety and effectiveness of cannula injection for cheek augmentation have only been clinically evaluated with TSK STERiGLIDE™ cannulas that were 25G and 2 inches in length.
- As with all transcutaneous procedures, dermal filler implantation carries a risk of infection. Standard precautions associated with injectable materials should be followed.
- The safety in patients with known susceptibility to keloid formation, hypertrophic scarring, and pigmentation disorders has not been studied.
- The safety for use in sites in the presence of other implants (including permanent implants) has not been studied.
- The safety for use during pregnancy, in breastfeeding females, and in patients under 22 years of age has not been established.
- RHA®4 should be used with caution in patients on immunosuppressive therapy.

- Bruising or bleeding may occur at RHA®4 injection sites. RHA®4 should be used with caution in patients who are using substances that can prolong bleeding (such as thrombolytics, anticoagulants, or inhibitors of platelet aggregation).
- Injection of RHA®4 into patients with a history of previous herpetic eruption may be associated with reactivation of the herpes.
- If laser treatment, chemical peeling or any other procedure based on active dermal response is considered after treatment with RHA®4, there is a possible risk of eliciting an inflammatory reaction at the implant site. This also applies if RHA®4 is administered before the skin has healed completely after such a procedure.
- RHA®4 is to be used as supplied. Modification or use of the product outside the Instructions for Use may adversely impact the sterility, safety, homogeneity, or performance of the product.
- RHA®4 is packaged for single-patient use. Do not reuse a syringe between two treatments and/or between two patients. Do not resterilize.
- Do not use if package is opened or damaged. The sterility of the product is not guaranteed in the case of failure to comply with this precaution.
- 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).
- Failure to comply with the needle/blunt cannula attachment instructions could result in needle/blunt cannula disengagement and/or product leakage at the Luer-lock and needle/blunt cannula hub connection.

ADVERSE EXPERIENCES

There were three U.S. studies from which safety is summarized. One study was conducted in support of the indication for correction moderate to severe dynamic wrinkles and folds, such as NLF, one study was conducted in support of using a small bore, blunt-tip cannula for the same indication, and one was conducted in support of the indication for cheek augmentation and/or correction of age-related midface contour deficiencies.

1. Clinical Evaluation of RHA®4 Into the NLFs

Clinical study TEO-RHA-1402 was a multicenter, controlled, randomized, double-blinded, within-subject (split-face), prospective US study designed to compare the safety of RHA®4 versus a Control treatment for the treatment of moderate to severe nasolabial folds, and demonstrated similar safety profiles. The expected signs and symptoms that occur following the injection of a hyaluronic acid-based dermal filler (i.e., Common Treatment Responses; CTR) were individually assessed by subjects in a preprinted 14-day diary after each injection.
Subjects were asked to rate each CTR as None, Mild, Moderate or Severe:

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

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

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

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

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

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

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

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

[a] Number of subject NLF treated with the respective device

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

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

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

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

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

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

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

• Mild: Little discomfort, no effect on daily activities, no medication or make-up required

• Moderate: some discomfort, some effect on daily activities, possibly medication or make-up required

• Severe: Great discomfort, daily activities compromised, very likely medication or make-up required

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

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

• Proportions of subjects experiencing at least one CTR of each category was similar between RHA®4 injected with a cannula and between RHA®4 injected with a needle.

• When analyzed for each individual sign or symptom, the number of subjects who experienced at least 1 CTR was consistently and markedly lower in the RHA®4-cannula group, with a significant difference between treatment groups for bruising, lumps/bumps, redness, itching, and pain.

• The majority (73%) of CTRs had resolved by Day 14.

• For nearly all CTRs (more than 80%) experienced by any treatment group (initial treatment or touch-up treatment), the maximal severity reported was "Mild" or "Moderate".

• There were approximately the same number of subjects who reported severe CTR with RHA®4 injected with a cannula (10%) as RHA®4 injected with a needle (14%)

Table 3. Common Treatment Responses by maximum severity after initial treatment with RHA®4 injected using a cannula and RHA®4 injected using a needle reported in subject 28-day-diary – Safety Population

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

Common Treatment Responses	TOTALS		RHA®4-cannula (N[a]=50 NLF)			RHA®4-needle (N[a]=50 NLF)		
	RHA®4-C n[b] %	RHA®4-N n[b] %	Mild n[b] %	Mod[d] n[b] %	Sev[e] n[b] %	Mild n[b] %	Mod[d] n[b] %	Sev[e] n[b] %
Swelling	36 72%	41 82%	25 50%	10 20%	1 2%	23 46%	16 32%	2 4%
Tenderness	38 76%	44 88%	27 54%	9 18%	2 4%	32 64%	10 20%	2 4%

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

Table 4. Duration of Common Treatment Responses after RHA®4 injection using a cannula and using a needle reported in subject 28-day-diary – Safety Population

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

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

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

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

3. Clinical Evaluation of RHA®4 for midface volume deficiency

Clinical study TEO-RHA-2004 was a multicenter, controlled, randomized, double-blinded, between-subject, prospective US study designed to compare the safety of RHA®4 versus a Control treatment for the treatment of midface volume deficiency, and demonstrated similar safety profiles. The expected signs and symptoms that occur following the injection of a hyaluronic acid-based dermal filler (i.e., CTRs) were individually assessed by subjects in a preprinted 30-day diary after each injection.

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

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

CTR by severity and duration are presented respectively, in Table 5 and Table 6.

- The most frequent CTRs were tenderness, firmness, swelling and lumps/bumps.
- Proportion of subjects experiencing at least one CTR of each category was similar between RHA®4 and Control treatment.

- The majority (68%, 87 of the 128 RHA4 subjects experiencing at least 1 CTR) of subjects had their CTRs resolved by Day 14. Similar results were observed in Control treatment group.
- The proportion of subjects reporting severe CTRs was similar in RHA®4 and Control treatment groups.
- 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 5. Common Treatment Responses by maximum severity after initial treatment with RHA®4 and the Control Device reported in subject 30-day-diary – Safety Population

Common Treatment Responses	TOTALS		RHA®4 (N[a]=152)			Control Device (N[a]=49)		
	RHA®4 n[b] %	CTRL[c] n[b] %	Mild N[c] %	Mod[e] N[c] %	Sev[f] N[c] %	Mild N[c] %	Mod[e] N[c] %	Sev[f] N[c] %
Subject with at least 1 CTR	128 90.8%	44 95.7%	69 53.9%	52 40.6%	7 5.5%	26 59.1%	15 34.1%	3 6.8%
Bruising	74 52.5%	16 34.8%	55 74.3%	17 23.0%	2 2.7%	15 93.8%	1 6.3%	0 0.0%
Discoloration	32 22.7%	6 13.0%	24 75.0%	8 25.0%	0 0.0%	6 100%	0 0.0%	0 0.0%
Firmness	108 76.6%	34 73.9%	72 66.7%	32 29.6%	4 3.7%	21 61.8%	11 32.4%	2 5.9%
Itching	17 12.1%	2 4.3%	15 88.2%	2 11.8%	0 0.0%	2 100%	0 0.0%	0 0.0%
Lumps/Bumps	77 54.6%	23 50.0%	43 55.8%	30 39.0%	4 5.2%	14 60.9%	8 34.8%	1 4.3%
Pain	70 49.6%	20 43.5%	55 78.6%	15 21.4%	0 0.0%	18 90.0%	2 10.0%	0 0.0%
Redness	61 43.3%	17 37.0%	51 83.6%	10 16.4%	0 0.0%	13 76.5%	3 17.6%	1 5.9%
Swelling	98 69.5%	28 60.9%	68 69.4%	29 29.6%	1 1.0%	24 85.7%	4 14.3%	0 0.0%
Tenderness	113 80.1%	39 84.8%	86 76.1%	26 23.0%	1 0.9%	33 84.6%	5 12.8%	1 2.6%

[a] Number of subjects' midface treated with the respective device

[b] Number of subjects' midface with any specific Common Treatment Response. All percentages are based on the number of CTR diaries retrieved by injection by subgroup in the population. In the RHA®4 group, 152 subjects were treated with initial injection and 141 CTR diaries were retrieved. In the Control treatment groups, 49 subjects were treated with initial injection and 46 CTR diaries were retrieved.

[c] Number of subjects with each specific CTR by maximum severity. All percentages are based on the number of subjects with the specific CTR by injection by subgroup in the population. In the RHA®4 group, 152 subjects were treated with initial injection and 128 subjects experienced at least 1 CTR. In Control treatment group, 49 subjects were treated with initial injection and 44 subjects experienced at least 1 CTR.

[d] CTRL = Control treatment

[e] Mod = Moderate

[f] Sev = Severe

Table 6. Duration of Common Treatment Responses after initial treatment with RHA®4 and the Control Device reported in subject 30-day-diary – Safety Population

Common Treatment Responses	RHA®4 (N[a]=152) N[b] %					Control Device (N[a]=49) N[b] %				
Duration[c]	1-3d	4-7d	8-14d	15-30d	Last Day	1-3d	4-7d	8-14d	15-30d	Last Day
Bruising	19 13.5%	28 19.9%	17 12.1%	10 7.1%	3 2.1%	5 10.9%	6 13.0%	5 10.9%	0 0%	0 0%
Discoloration	17 12.1%	5 3.5%	6 4.3%	4 2.8%	4 2.8%	3 6.5%	3 6.5%	0 0%	0 0%	0 0%
Firmness	34 24.1%	35 24.8%	19 13.5 %	20 14.2%	6 4.3%	10 21.7%	9 19.6%	5 10.9%	10 21.7%	2 4.3%
Itching	7 5.0%	3 2.1%	5 3.5%	2 1.4%	1 0.7%	2 4.3%	0 0%	0 0%	0 0%	0 0%
Lumps/ Bumps	30 21.3%	13 9.2%	12 8.5%	22 15.6%	15 10.6%	7 15.2%	5 10.9%	4 8.7%	7 15.2%	1 2.2%
Pain	39 27.7%	17 12.1%	8 5.7%	6 4.3%	1 0.7%	9 19.6%	5 10.9%	5 10.9%	1 2.2%	0 0%
Redness	41 29.1%	11 7.8%	4 2.8%	5 3.5%	2 1.4%	11 23.9%	5 10.9%	0 0%	1 2.2%	0 0%
Swelling	47 33.3%	32 22.7%	13 9.2%	6 4.3%	1 0.7%	16 34.8%	8 17.4%	1 2.2%	3 6.5%	0 0%
Tenderness	34 24.1%	39 27.7%	24 17.0 %	16 11.3%	2 1.4%	10 21.7%	15 32.6%	9 19.6%	5 10.9%	1 2.2%

[a] Number of subjects treated with the respective device

[b] Number of subjects with each specific CTR by maximum duration. All percentages are based on the number of CTR diaries retrieved by injection by subgroup in the population. In RHA®4 group 152 subjects were treated with initial injection and 141 CTR diaries were retrieved. in Control treatment group, 49 subjects were treated with initial injection and 46 CTR diaries were retrieved.

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

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

- Both RHA®4 and Control treatment groups presented with similar adverse event (AE) profiles with 36 (23.7%) subjects in the RHA®4 group experiencing a total of 67 treatment-related AEs after initial treatment and touch-up injections.
- All treatment-related AEs were mostly mild, with some that were moderate, no severe treatment-related AEs were reported after all treatments (i.e., initial, touch up and retreatment).
- Most of treatment-related AEs experienced in both treatment groups were typical of the expected signs and symptoms observed following an injection of a hyaluronic acid-based dermal filler, such as: injection site mass, injection site induration and injection site pain. Other reported treatment-related AEs such as headache, periorbital pain 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): 91% (61/67) were either a CTR, or listed as Others, or from the list of pre-identified AEs on the diary and 9% (6/67) were identified by the TI, in the in the RHA®4 group. Similar results were found in the Control treatment group.
- The proportion of subjects with reported treatment related AE was similar across the 2 treatment groups. Most treatment-related AEs (82%, 55/67) in the RHA®4 group

resolved within 14 days and was similar in Control treatment group. The duration of treatment-related AEs varied from 1 to 90 days, except for 1 treatment-related AE in the RHA®4 group. One event was an injection site mass that lasted 227 days, this event was mild in severity and resolved without sequelae. No treatment was administered for this event. These treatment-related AEs were typical and expected signs and symptoms observed following the injection of a dermal filler.

- There were no treatment-related serious AEs.
- Eleven AE of Special Interest (AESI) were reported. AESI is defined as any new vision disturbance. 10 AESIs in 5 subjects randomly assigned to RHA4 group between Visit 1 and Visit 7 and 1 AESI in 1 subject in the RHA4 group after retreatment. None of the AESIs were related to device and 2 subjects had 4 AESIs considered related to the procedure. All events were mild and none of the events fulfilled seriousness criteria. All AESI events either resolved without sequelae or were ongoing at the end of the study and Treating Investigator considered that no additional follow-up is needed.
- 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, ethnicity, age, sex, administration method and volume injected were not different between both treatment groups.

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

4. 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: skin edema/skin swelling, injection site masses (inflammatory or non-inflammatory nodules), skin induration, injection site inflammation, pain, erythema, granuloma, vascular complication, ecchymosis, skin infection and tenderness Additionally, other less frequent adverse reactions have also been reported, and includes implant migration, allergic reaction, skin discoloration/Tyndall effect, abscess, overcorrection, pruritus, anaphylactic reaction, skin necrosis, urticaria, blister, scab, angioedema, chapped lips, dermatitis, dry skin, fibrosis, herpes breakout, numbness, pustules, telangiectasia and visual impairment.
Delayed-onset inflammation near the site of dermal filler injections is one of the known adverse events associated with dermal fillers. Cases of delayed-onset inflammation have been reported to occur at the dermal filler treatment site following viral or bacterial illnesses or infections, vaccinations, or dental procedures. Typically, the reported inflammation was responsive to treatment or resolved on its own.

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

CLINICAL STUDIES

A. Pivotal STUDY for RHA®4 into the NLFs

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

1. Pivotal Study Design

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

2. Study Endpoints

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

3. Demographics

A total of 120 subjects (27 to 86 years old) were allocated to RHA®4 and Control treatment, and 20 were allocated to

untreated controls. 118 subjects were included in the ITT population.
Subject's demographics are presented in Table 7.

Table 7. Demographics

Number / % of subjects	RHA®4 versus Control Device N[a]=118	
Age		
Mean (SD)	57.4	(10.0)
min max	27	86
Gender		
Female	106	89.8%
Male	12	10.2%
Race		
Caucasian	97	82.2%
Black	19	16.1%
Am. Indian/N. Alask.	1	0.9%
N. Hawaiian/P. Isl.	0	0.0%
Asian	1	0.9%
Other	0	0.0%
Ethnicity		
Hispanic/Latino	30	25.4%
Not Hispanic/Latino	88	74.6%
Fitzpatrick Skin Phototype		
I	4	3.4%
II	21	17.8%
III	40	33.9%
IV	31	26.3%
V	14	11.9%
VI	8	6.8%

[a] Number of subjects in the ITT populations

4. Treatment Characteristics

The study protocol allowed a maximum of 3.0 mL in a single NLF per treatment session. The overall total median volume of RHA®4 injected to achieve optimal correction results was 1.7 mL. The proportion of subjects who received touch-up treatment with RHA®4 at Week 2 was 27.1%.

In general, a linear threading or multiple 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 8.

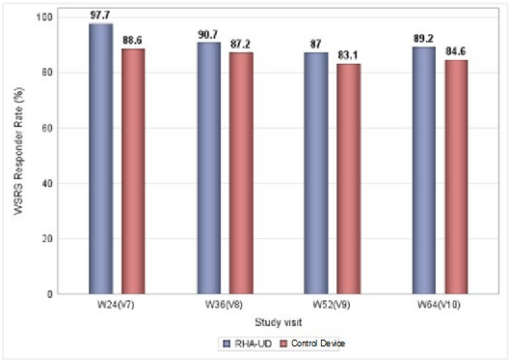
Table 8. NLF-Wrinkle Severity Rating Scale scores assessed by a Blinded Live Evaluator throughout the study

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

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

The results demonstrated that non-inferiority to the control was achieved for RHA®4, at 24 weeks for the treatment of NLFs. Results also showed that RHA®4 was not inferior to the Control treatment at all study visits.
Throughout the follow-up period, the aesthetic improvement of the RHA®4 treated NLF continued to be clinically significant (≥ 1 grade difference from pre-treatment on the NLF-WSRS) for more than 89% of the subjects at 64 weeks after initial treatment (Figure 1).

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



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

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

On the Global Aesthetic Improvement (GAI) scale (the scale included the following grades: 1-Much improved – 2- Improved – 3-No change – 4-Worse – 5-Much worse), more than 87% of the subjects reported that the NLF treated with RHA®4 was improved or very much improved from week 24 to week 64. The subjects consistently reported improvement up to 64 weeks based on the NLF module of the FACE-Q© questionnaire with the mean score improving from 24 to more than 70 throughout the follow-up period. More than 93% of the subjects reported to be satisfied or very satisfied from week 24 to week 64 (the scale grades were: very satisfied, satisfied, neither satisfied nor dissatisfied, dissatisfied or very dissatisfied).

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

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

1. Clinical Study Design

A multicenter, controlled, single-blinded, within-subject (split-face), prospective study was conducted to evaluate the clinical safety and effectiveness using RHA®4 injected with a blunt cannula (25G x 2" long) or with a sharp needle (27G x ½") for the treatment of moderate to severe nasolabial folds.
Subjects were randomized to undergo RHA®4 treatment into their NLFs with the cannula on one side of the face, and with a sharp needle on the other side.
If deemed necessary by the Treating Investigator, additional NLF correction was performed after 4 weeks (touch-up), with the same study device used for initial treatment.

All 50 subjects received a safety follow-up call within 3-days of initial treatment, and if applicable, within 3 days of touch-up treatment. Thereafter, subjects were to return periodically for safety and effectiveness evaluations at 4, 8 and 12 weeks after the last treatment. The primary endpoint was at 12 weeks after initial or touch-up treatment, assessed by the BLE.
If a subject presented with an unresolved clinically significant device-related adverse event (AE), an optional visit or phone-call follow-up was scheduled within 4 weeks of the last study visit, and until the AE was resolved or the TI determined that additional follow-up was no longer necessary.

2. Study Endpoints

The primary effectiveness endpoint was the analysis of non-inferiority of RHA®4 injected with a cannula versus with a needle, in terms of change from pre-injection to 12 weeks after injection, as measured by the BLE using a proprietary and validated 5-grade scale for scoring the severity of nasolabial folds, the NLF-WSRS.
Secondary effectiveness endpoints included rates of responders (≥ 1 grade difference from pre-treatment on the NLF-WSRS), as measured by the BLE, Global Aesthetic Improvement (GAI), as assessed by the subject and by the BLE, impact and effectiveness of study treatment procedures from the subjects' perspective as assessed by the nasolabial fold domain of the FACE-Q©, and subject satisfaction.
Safety endpoints were evaluated throughout the study, with a 28-day subject diary capturing post-injection signs/symptoms following every study injection, and AE assessments at each visit, and included self-assessment of injection site pain by the subject using a Visual Analog Scale.

3. Demographics

A total of 50 subjects (42 to 77 years old) were injected with RHA®4 into their NLFs with a cannula on one side of the face, and with a sharp needle on the other side.
Subject's demographics are presented in Table 9.

Table 9. Demographics

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

[a] Number of subjects in the ITT populations

4. Treatment Characteristics

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

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

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

5. Effectiveness Results

The primary effectiveness endpoint was met. The study demonstrated the non-inferiority of RHA®4 administered with a cannula versus a needle, as assessed (using the WSRS) by the BLE at 12 weeks after baseline, and results are presented in Table 10.

Table 10. NLF-Wrinkle Severity Rating Scale scores assessed by a Blinded Live Evaluator throughout the study

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

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

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

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

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

C. Pivotal STUDY for RHA®4 for midface volume deficiency

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

1. Pivotal Study Design

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

A total of 201 subjects were randomized and underwent treatment with either RHA® 4 (N = 152) or Control treatment (N = 49) in the midface area for cheek augmentation and/or correction of age-related midface contour deficiencies. Injection was performed with a needle and/or cannula. If deemed necessary to achieve optimal correction, additional midface correction was performed after 4 weeks (touch-up), with the same study device used for initial treatment.
The follow-up period consisted of safety and effectiveness follow-up visits at 2, 4, 8, 16, 24, 36, and 52 weeks after the last treatment.
Subjects were eligible for optional retreatment if necessary, at Weeks 52, and were then followed for 3 months after retreatment or until all Adverse Events (AEs) resolved or TI determined that follow-up was no longer necessary. Retreatment was provided using RHA® 4 (the Control device was not used).

2. Study Endpoints

The primary effectiveness endpoint was the analysis of non-inferiority of RHA® 4 versus Control in terms of change from Baseline (pre-injection) 8 weeks after injection, as measured by a Blinded Live Evaluator (BLE) using the proprietary and validated 5-grade Teoxane Midface Volume Deficit Scale (TMVDS).
Secondary effectiveness endpoints included TMVDS change from Baseline and rates of responders, as assessed by the BLE at each study visits (see data in Table 12 and Figure 2), Global Aesthetic Improvement (GAI), as assessed by the subject, TI and BLE, impact and effectiveness of study treatment procedures from the subjects' perspective as assessed by the satisfaction with cheeks module (at rest and when smiling) of the FACE-Q©, and subject satisfaction.
Safety endpoints were evaluated throughout the study, with a 30-day subject diary capturing post-injection signs/symptoms following every study injection, and AE assessments at each visit, and included self-assessment of injection site pain by the subject using a 100mm Visual Analog Scale.

3. Demographics

A total of 201 subjects (24 to 79 years old) were enrolled and included in the ITT and the Safety population, with 152 subjects allocated to RHA® 4 treatment, and 49 allocated to the Control treatment. Subjects' demographics are presented in Table 11.

Table 11. Demographics

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

[a] Number of subjects in the ITT/Safety populations
[b] a subject can be counted in several categories

4. Treatment Characteristics

The study protocol allowed a maximum of 6 mL at each treatment session, with a maximum of 3 mL per cheek per treatment session. The overall total median volume of RHA® 4 injected to achieve optimal correction (initial + touch-up) was 3.50 mL. Injection volumes into the cheeks tended to be lower after retreatment, with total median injection volume being 1.30 mL after retreatment. Similar injection volumes were used in subjects treated with the Control device to achieve OCR.

However, after retreatment, the median injection volume for the group initially treated with RHA4 was 1.30 mL while subjects who were initially treated with the Control treatment received 2.30 mL.
The proportion of subjects who received touch-up treatment at Week 4 was lower with RHA® 4 (63.2%) than with Control treatment (83.7%).

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

5. Effectiveness Results

The primary effectiveness endpoint was met for RHA® 4. The primary effectiveness endpoint was the volume improvement of the cheeks treated with RHA® 4 from pre-injection compared to the improvement from pre-injection of the cheeks treated with the Control treatment, using the TMVDS, as assessed by the BLE at 8 weeks; results are presented in Table 12.

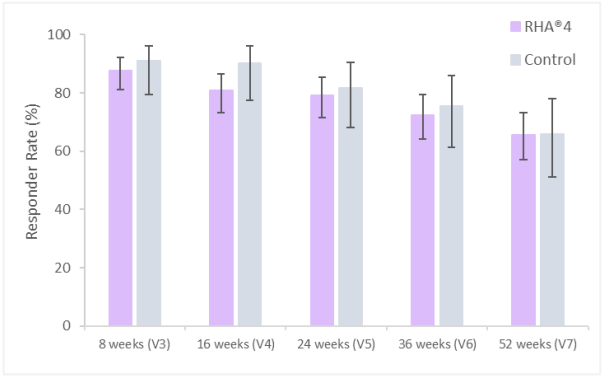
Table 12. Effectiveness results through 1 year as assessed by the BLE/Mean TVMDS change from Baseline (SD)

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

[a] Primary effectiveness endpoint
ITT population

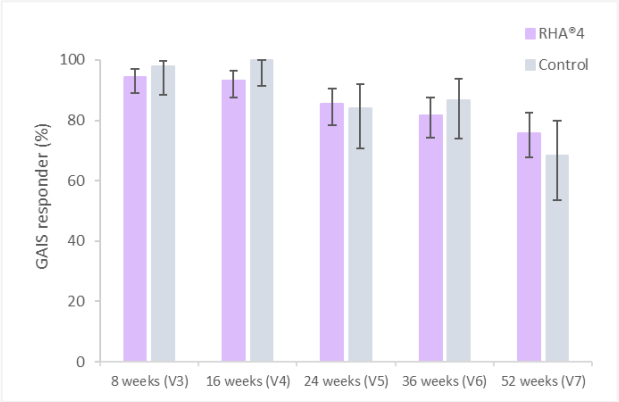
The results demonstrated that non-inferiority to the Control treatment was achieved for RHA®4 at 8 weeks for the treatment of midface volume deficiencies. Results also showed that RHA® 4 was not inferior to the Control treatment at all study visits.
Throughout the follow-up period, the aesthetic improvement of midface volume treated with RHA® 4 continued to be clinically significant (≥ 1-grade difference from pre-treatment on the TMVDS) for more than 65% of the subjects at 52 weeks after last treatment (Figure 2).

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



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

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

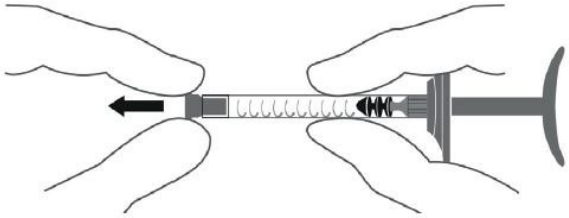


The subjects treated with RHA® 4 consistently reported improvement up to 52 weeks based on the *Satisfaction with cheeks* module, at rest and when smiling, of the FACE-Q© questionnaire with the mean score improving from Baseline by 53 and 56 points at Week 8, respectively, to more than 38 points throughout the follow-up period. RHA® 4 demonstrated durability throughout the study with a slow decline over time.
More than 89% of the subjects reported to be satisfied or very satisfied 8 weeks after treatment and the rate of satisfaction remained at more than 82% at 52 weeks (the scale grades were: very satisfied, satisfied, neither satisfied nor dissatisfied, dissatisfied, or very dissatisfied).

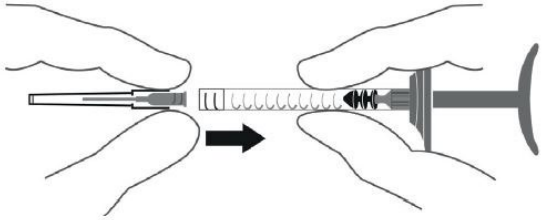
Repeat treatment with RHA®4 only irrespective of their initial group assignment was provided to 50.7% and 59.2% of subjects initially assigned to the RHA®4 and Control treatment groups, respectively, at the end of the study. The effectiveness and safety profiles after repeat treatment were similar to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

DIRECTIONS FOR ASSEMBLY OF THE NEEDLE TO THE SYRINGE

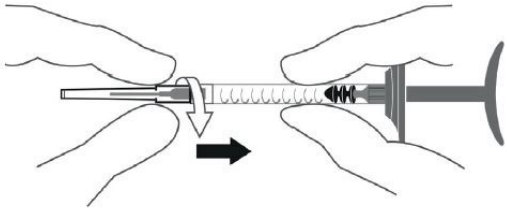
1. Remove the stopper from the syringe by pulling it off.



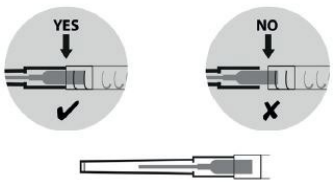
2. Insert the screw thread of the needle firmly into the syringe end-piece.



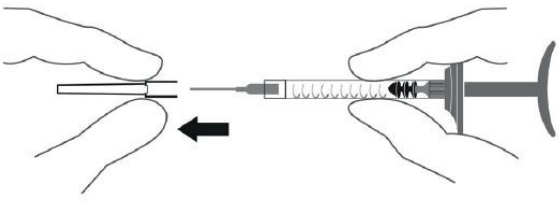
3. Screw the needle clockwise, while maintaining slight pressure between the needle and the syringe.



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.

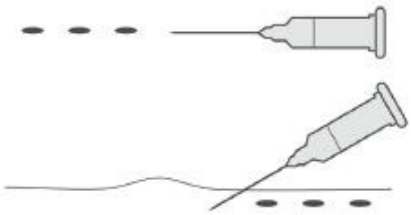


PRE-TREATMENT GUIDELINES

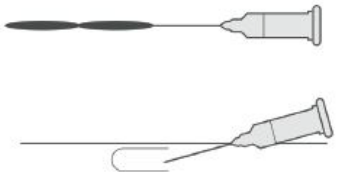
- Prior to treatment, the patient should avoid taking medications or supplements which thin the blood (e.g., aspirin, nonsteroidal anti-inflammatory medications, St. John's Wort, or high doses of Vitamin E supplements) as these agents may increase bruising and bleeding at the injection site.
- Before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

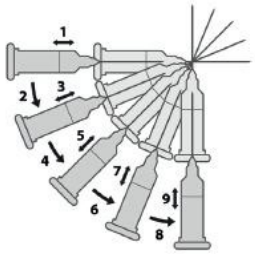
- RHA®4 is administered for injection into dynamic facial wrinkles and folds by using a thin gauge needle (27 G x ½") or a blunt tip cannula (25 G x 2"). RHA®4 is supplied with 27 G x ½" needles. The SoftFil® Precision and TSK STERiGLIDE™ cannulas were used in the clinical trials and are recommended for use with RHA®4.
- RHA®4 is administered for injection for midface volume deficiency using a thin gauge needle (27 G x ½") or a blunt tip cannula (25 G x 2"). The TSK STERiGLIDE™ cannula was used in the clinical trials and is 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 injecting into supraperiosteal layer with a needle the needle is inserted bevel down with an angle of 90° to the skin surface until touching the bone.
- When using a cannula, an entry point is made in the skin with the provided pre-hole needle.
- RHA®4 can be injected by a number of different techniques that depend on the injector's experience and preference, treated area, and patient characteristics.
  - **A. Serial puncture:** (only recommended for needle): consists of multiple injections evenly and closely spaced all along wrinkles or folds. This technique is considered to be more precise, but may result in more discomfort for the patient due to the number of punctures.



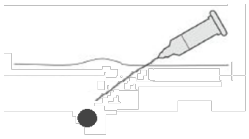
B. Linear threading: the needle/cannula is fully introduced in the wrinkle or the fold, and the product is injected along the line, as a "thread", while withdrawing (retrograde) or pushing (antegrade) the needle/cannula.



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



D. Multiple bolus technique: the needle/cannula is fully introduced as deep as possible into the cheeks hitting the periosteum and boluses of the product are injected slowly and using a low pressure. Identical or different injection volumes may be used for each bolus.



- RHA®4 is injected slowly into the deep dermis to superficial subcutaneous in the wrinkle or the fold.
- RHA®4 is injected slowly onto the supraperiosteum or from subcutaneous to supraperiosteal, if multilayering, when treating midface volume deficiency.
- 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, volume should be limited to 6.0mL per treatment session and should not exceed 3mL per side for the NLF. Based on the US clinical study, volume should be limited to 6.0mL per treatment session and should not exceed 3mL per side for the midface. The safety of injecting greater amounts has not been established.
- If blanching is observed (e.g., the overlying skin turns a whitish color), the injection should be stopped immediately and the area massaged until it returns to a normal color. Blanching may represent a vessel occlusion. If normal skin coloring does not return, do not continue with the injection. Treat in accordance with American Society for Dermatologic Surgery guidelines, which include hyaluronidase injection.
- If the wrinkles or midface 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 for the correction of moderate to severe dynamic facial wrinkles and folds such as NLF, 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.
- When the injection is completed for the treatment of midface volume deficiencies, massaging the treated site should be avoided to prevent displacement of filler from the desired location. If an overcorrection has occurred, massage the area gently with your fingers 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 pack 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 an injury occurs.

STERILE NEEDLES OR CANNULAS

- After use, needles and cannulas 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. To avoid needle stick injury and sharp exposure, take care to inject in appropriate conditions.

PATIENT INSTRUCTIONS

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

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

HOW SUPPLIED

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

The content of the syringe is sterile and non-pyrogenic. Do not resterilize. Do not use if package is opened or damaged.
Each syringe is packaged into a blister with two unique device identifier traceability labels.

SHELF-LIFE AND STORAGE

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

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

RxOnly

Manufactured by:
TEOXANE SA.
Rue de Lyon, 105
CH 1203 Geneva
Switzerland

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

SYMBOLS

 Manufacturer's name and address

 Catalog number

 Lot / batch number

 Expiration date (YYYY-MM-DD)

 Consult Instructions for use

 Single use only

 Sterilized using steam

 Do not use if the package is damaged

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

TEOXANE