October 2011

Restylane®

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

Description

Restylane is a gel of hyaluronic acid generated by Streptococcus species of bacteria, chemically crosslinked with BDDE, stabilized and suspended in phosphate buffered saline at pH=7 and concentration of 20 mg/mL.

Indication

Restylane is indicated for mid-to-deep dermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds.

Restylane is indicated for submucosal implantation for lip augmentation in patients over the age of 21.

Contraindications

- *Restylane* is contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.
- *Restylane* contains trace amounts of gram positive bacterial proteins, and is contraindicated for patients with a history of allergies to such material.
- *Restylane* is contraindicated for patients with bleeding disorders.
- *Restylane* is contraindicated for implantation in anatomical spaces other than the dermis or submucosal implantation for lip augmentation.

Warnings

- Defer use of *Restylane* at specific sites in which an active inflammatory process (skin eruptions such as cysts, pimples, rashes, or hives) or infection is present until the process has been controlled.
- Injection site reactions (e.g., swelling, redness, tenderness, or pain) to *Restylane* have been observed as consisting mainly of short-term minor or moderate inflammatory symptoms starting early after treatment and with less than 7 days duration in the nasolabial folds and less than 14 days duration in the lips. Rare post-market reports of immediate post-injection reactions included extreme swelling of lips, the whole face and symptoms of hypersensitivity such as anaphylactic shock.
- *Restylane* must not be implanted into blood vessels. Localized superficial necrosis and scarring may occur after injection in or near vessels, such as in the lips, nose, or glabellar area. It is thought to result from the injury, obstruction, or compromise of blood vessels.
- Delayed onset inflammatory papules have been reported following the use of dermal fillers. Inflammatory papules that may occur rarely should be considered and treated as a soft tissue infection.
- Injections of greater than 1.5 mL per lip (upper or lower) per treatment session significantly increases the occurrence of the total of moderate and severe injection site reactions. If a volume of more than 3 mL is needed to achieve optimal correction, a follow-up treatment session is recommended.
- In a meta-analysis of all *Restylane* Premarket Approval Studies (that included 42 patients under the age of 36 and 820 patients over the age of 35), the incidence of swelling was higher in younger patients (28%) compared to older patients (18%) and incidence of contusion was higher in older patients (28%) compared to younger patients (14%). The majority of these events were mild in severity.

Precautions

- *Restylane* is packaged for single patient use. Do not resterilize. Do not use if package is opened or damaged.
- Based on U.S. clinical studies, patients should be limited to 6.0 mL per patient per treatment in wrinkles and folds such as the nasolabial folds and to 1.5 mL per lip per treatment. The safety of injecting greater amounts has not been established.
- The safety or effectiveness of *Restylane* for the treatment of anatomic regions other than nasolabial folds or lips has not been established in controlled clinical studies.
- The safety and efficacy of *Restylane* for lip augmentation has not been established in patients under the age of 21 years.
- As with all transcutaneous procedures, *Restylane* implantation carries a risk of infection. Standard precautions associated with injectable materials should be followed.
- The safety of *Restylane* for use during pregnancy, in breastfeeding females or in patients under 18 years has not been established.
- Formation of keloids may occur after dermal filler injections including *Restylane*. Keloid formation was not observed in studies involving 430 patients (including 151 African-Americans and 37 other patients of Fitzpatrick Skin Types IV, V and VI). For additional information please refer to Studies MA-1400-02, MA-1400-01, and 31GE0003 in the Clinical Trials Section.
- *Restylane* injection may cause hyperpigmentation at the injection site. In a clinical study of 150 subjects with pigmented skin (of African-American heritage and Fitzpatrick Skin Types IV, V, and VI), the incidence of post-inflammatory hyperpigmentation was 9% (14/150). 50% of these events lasted up to six weeks after initial implantation.
- The safety profile for *Restylane* lip augmentation in persons of color is based upon information from 38 and 3 subjects with Fitzpatrick Skin Types IV and V, respectively. Within this population, the incidence of adverse events was similar to the overall study population, with the exception that swelling occurred more frequently in persons of color.
- *Restylane* should be used with caution in patients on immunosuppressive therapy.
- Bruising or bleeding may occur at *Restylane* injection sites. *Restylane* should be used with caution in patients who have undergone therapy with thrombolytics, anticoagulants, or inhibitors of platelet aggregation in the preceding 3 weeks.
- After use, syringes and needles should be handled as potential biohazards. Disposal should be in accordance with accepted medical practice and applicable local, state and federal requirements.
- The safety of *Restylane* with concomitant dermal therapies such as epilation, UV irradiation, or laser, mechanical or chemical peeling procedures has not been evaluated in controlled clinical trials.
- Patients should minimize exposure of the treated area to excessive sun, UV lamp exposure and extreme cold weather at least until any initial swelling and redness has resolved.
- If laser treatment, chemical peeling or any other procedure based on active dermal response is considered after treatment with *Restylane*, there is a possible risk of eliciting an inflammatory reaction at the implant site. This also applies if *Restylane* is administered before the skin has healed completely after such a procedure.
- Injection of *Restylane* into patients with a history of previous herpetic eruption may be associated with reactivation of the herpes.
- *Restylane* is a clear, colorless gel without particulates. In the event that the content of a syringe shows signs of separation and/or appears cloudy, do not use the syringe and notify Medicis Aesthetics Inc. at 1-800-555-5115. Glass is subject to breakage under a variety of unavoidable conditions. Care should be taken with the handling of the glass syringe and with disposing of broken glass to avoid laceration or other injury.
- *Restylane* should not be mixed with other products before implantation of the device.

Adverse Experiences

There were six U.S. studies that reported adverse experiences. Four of the six studies were conducted in support of the indication of mid-to-deep dermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds, and two of the six studies were conducted in support of the indication of submucosal implantation for lip augmentation.

Studies conducted in moderate to severe facial wrinkles and folds, such as nasolabial folds

Three U.S. studies (i.e., Study 31GE0003, MA-1400-01, and Study MA-1400-02) involved 430 patients at 33 centers. In study 31GE0003, 138 patients at 6 centers received *Restylane* injections in 1 side of the face and a bovine collagen dermal filler (Zyplast®) in the other side of the face. In Study MA-1400-01, 150 patients were injected with *Restylane* on one side of the face and *Perlane*® on the other side of the face. In study MA-1400-02, 283 patients were randomized to receive either *Restylane* or *Perlane* injection on both sides of the face. The adverse outcomes reported in patient diaries during 14 days after treatment in these studies are presented in Tables 1–6. The physician diagnosed adverse events identified in studies MA-1400-01 and MA-1400-02 at 72 hours after injection are presented in Table 7. Table 8 presents all investigator-identified adverse experiences recorded at study visits 2 weeks or more after injection in studies MA-1400-01, MA-1400-02, and 31GE0003.

In the fourth U.S. study (MA-004-03) involving 75 patients at 3 centers, adverse events reported by *Restylane* patients are presented in Table 9. Patients in the study received *Restylane* injections in both nasolabial folds at baseline, a second treatment in one nasolabial fold at 4.5 months and in the contralateral nasolabial fold at 9 months.

Table 7 shows the number of adverse experiences identified by investigators at 72 hours after injection for Studies MA-1400-01 and MA-1400-02. Some patients had multiple adverse experiences or had the same adverse experience at multiple injection sites. No adverse experiences were of severe intensity.

Table 8 presents the number of patients and per patient incidence of all adverse experiences identified by investigators at visits occurring two or more weeks after injection.

In a clinical study (31GE0003) in which safety was followed for 12 months with repeat administration of *Restylane* at six to nine months following the initial correction, the incidence and severity of adverse experiences were similar in nature and duration to those recorded during the initial treatment sessions.

In all three studies, investigators reported the following local and systemic events that were judged unrelated to treatment and occurred at an overall incidence of less than 2%, i.e., acne; arthralgia; tooth disorders (e.g., pain, infection, abscess, fracture); dermatitis (e.g., rosacea, unspecified, contact, impetigo, herpetic); unrelated injection site reactions (e.g., desquamation, rash, anesthesia); facial palsy with co-administration of botulinum toxin; headache/migraine; nausea (with or without vomiting); syncope; gastroenteritis; upper respiratory or influenza-like illness; bronchitis; sinusitis; pharyngitis; otitis; viral infection; cystitis; diverticulitis; injuries; lacerations; back pain; rheumatoid arthritis; and various medical conditions such as chest pain, depression, pneumonia, renal stones, urinary incontinence, and uterine fibroids.

Table 9 presents the number of patients and per patient incidence and severity of injection site adverse events identified by the investigator.

Two subjects had adverse events that were severe, one subject with bilateral facial bruising and one subject with infection at the injection site. These events were considered probably or possibly related and both subjects had their events resolve in approximately 3 weeks.

Studies conducted for submucosal implantation for lip augmentation

In the U.S. pivotal study (MA-1300-15) involving 180 subjects at 12 centers, the adverse outcomes reported in subject diaries are presented in Tables 10 and 11. Physician reported treatment emergent adverse events are presented in Table 12. At baseline, subjects were randomized to receive *Restylane* injections in the lips or no treatment (control group). At 6 months, all subjects were eligible to receive treatment or re-treatment in the lips with *Restylane*.

Of the 180 subjects enrolled in the study, 172 subjects received their first treatment with *Restylane* at either baseline/Day 0 or at 6 months, and 93 subjects received a second treatment at 6 months. There were 8 subjects enrolled in the study that were never treated. The number of events and subjects reporting TEAEs decreased between the first and second treatments. 87% of subjects receiving their first treatment reported a total of 795 TEAEs while 65% of subjects that received a second treatment reported a total of 267 TEAEs. Furthermore, an overwhelming majority of these TEAEs were mild in intensity (672/795, 85%; and 264/267, 99%; first and second treatment respectively), and were transient in nature, resolving in approximately 15 days or less.

The study results showed injection of greater than 1.5 mL per lip (upper or lower), per treatment session increased the occurrence of the total of moderate and severe injection site reactions. The incidence was 43% (33/76) for subjects receiving more than 3.0 mL of *Restylane* and 21% (20/96) for subjects receiving less than 3.0 mL of *Restylane* in a single treatment session. When optimal correction requires greater than 1.5 mL per upper or lower lip, subsequent treatment using additional product is recommended.

97% of the subjects reported at least one event of swelling, redness, tenderness, or pain in their diaries. These were mainly short-term events, which occurred immediately after treatment and resolved within 14 days. 15% of the subjects reported adverse events (typically swelling and tenderness) that lasted longer than 15 days in their diary. 46% of subjects reported at least one event as "affecting their daily activity" or "disabling."

Additional safety assessments in the study included lip texture, firmness, symmetry, movement, function, sensation, mass formation, and product palpability, which were evaluated as appropriate at the screening visits and at follow-up visits.

The majority of texture and firmness assessments showed mild abnormalities and lasted for less than 4 weeks. Sixteen subjects reported severe asymmetry (difference > 2mm) post-treatment, which all resolved within 4 weeks. GAIS assessments by these 16 subjects were rated as at least improved during those visits.

Assessments made by the trained health care provider showed 92% of subjects had product palpability at week 8, and 61% at week 24. The majority of palpations were rated as "expected feel." 3% of the subjects reported "unexpected feel" during the study, all of which were resolved with massaging.

One subject reported one mass formation (mucocele) during the study. The mucocele was drained and resolved by the next visit.

All other lip safety assessments showed no remarkable findings.

In the pilot study MA-1300-13K, 20 subjects were enrolled at 1 center and received *Restylane* for lip augmentation. Subjects were followed up through 24 weeks. Seven adverse events were reported. Two of the seven events, which were mild bruising, were related to injection procedure. The adverse outcomes reported in subject diaries are presented in Table 13.

Table 12 presents commonly reported (≥ 5%) treatment emergent adverse events (TEAEs) by treatment group.

For study MA-1300-13K, seven treatment emergent adverse events were experienced by four subjects. Two of these events, mild bruising, were considered related to treatment.

Post-Marketing Surveillance

The following adverse events were received from post-marketing surveillance for *Restylane* and *Perlane* in the U.S. and other countries: presumptive bacterial infections, inflammatory adverse events, necrosis, injection site numbness/tingling, and vasovagal reactions. Reported treatments have included systemic steroids, systemic antibiotics, and intravenous administrations of medications. Additionally, delayed inflammatory reaction to *Restylane* has been observed with swelling, redness, tenderness, induration and rarely acneform papules at the injection site with onset as long as several weeks after the initial treatment. Average duration of these effects is two weeks.

Implant and injection site reactions, mostly non-serious events, have also been reported. These include: discoloration, bruising, swelling, mass formation, erythema, pain, scarring and ischemia. Most instances of discoloration including hyperpigmentation, sometimes described as a blue or brown color and ranging from mild to severe, have occurred within the same day as treatment but have also occurred up to 6 months post-treatment. These events typically resolve within a few days but with some infrequent instances lasting up to 18 months. Implant and/or injection site bruising, swelling, erythema and pain generally occurred on the same day as treatment usually resolving within 1 to 4 weeks. Some occurrences have persisted for up to 6 months. Severity for these events is generally mild to moderate although some cases have been severe. Mild to moderate mass formations (typically described as lumps or bumps) have also been seen ranging in onset from 1 day to 6 months post-implantation. Rarely, events of this type have been observed for up to 13 months. These events usually resolved within 1 to 5 months. Mild to moderate scarring was rarely observed. Onset of symptoms ranged from immediate post-treatment to up to 1 year following implantation. Symptom resolution was approximately 3 weeks with 1 instance lasting up to 3 years. Most ischemic events have occurred immediately following implantation and ranged in severity from moderate to severe. Events were resolving as early as 2 days and up to 9 weeks post-treatment.

Symptoms associated with herpetic eruptions which included swelling, pain, whiteheads, vesicles and erythema have been reported and commonly occurred within 2 days to 1 month following implantation. Severity ranged from mild to moderate and resolution of symptoms ranged from 1 to 15 weeks.

Telangiectasias and capillary disorders, commonly characterized as broken capillaries, have been reported and occurred with an onset of 1 day to 7 weeks. Most events ranged in severity from mild to moderate with a few severe instances. Duration of events ranged from 2 weeks up to 13 months.

Very rarely, instances of moderate to severe biopsy confirmed granuloma were observed. Onset ranged from 3 weeks to 4 months with resolution between 6 weeks to 11 months.

Events of mild to moderate hypoaesthesia have occurred ranging in onset from 1 day to 1 week. Duration and resolution occurred between 1 day and 10 weeks.

Serious adverse events have been rarely reported. The most commonly reported serious adverse events (by MedDRA Preferred Term) were hypersensitivity, and implant and/or injection site swelling, ischemia and discoloration. Of these infrequently reported serious events, only the following occurred in a frequency of 5 or greater:

- Hypersensitivity reactions ranging from moderate to severe mostly occurred within 1 to 2 days of implantation and up to 3 weeks. Reported symptoms included swelling; itching on chest and back; puffy, burning, watery, and itchy eyes; and shortness of breath. Treatments included steroids, diphenhydramine, unspecified intravenous medication, oxygen and various creams. An evaluation of patients who reported potential hypersensitivity reactions did not demonstrate any evidence of IgE or cell mediated immunologic reactions specifically directed at hyaluronic acid. Most hypersensitivity events resolved within 1 to 14 days with or without treatment.
- *Allergic reaction and anaphylactic shock*: Eight patients experienced immediate post-injection reactions which included extreme swelling of lips and the whole face. Two of these patients had symptoms of hypersensitivity and one patient experienced anaphylactic shock and presented with shortness of breath, headache, nausea and vomiting. These patients had to be admitted to the emergency room or were hospitalized for immediate medical interventions. *Delayed hypersensitivity*: Two patients developed symptoms of hypersensitivity 7–10 days after injection. One patient experienced severe erythema and swelling in the lips and all over her face to the point that her eyes were shut and the other had swelling of the lips accompanied by dyspnea, lymphadenopathy, peripheral and laryngeal edema.
- *Vascular accidents and necrosis*: In 5 patients, skin discoloration, bruising, and blanching was seen immediately post-injection due to vascular accidents. The lesions later turned into necrosis and in some cases remained as scarring or dark spots. One example was a patient who had a "mustache-like" mark above her lips, even after receiving treatments. Later, one patient in this group developed hard bumps in her upper lips that looked like "granulomas."
- *Infection/Abscess*: Serious abscess formations ranging from moderate to severe occurred in eleven patients. Onset ranged from 3 days to one week with an average duration of approximately one month to resolution. Symptoms included swelling, redness, pain and hard nodules. Five patients required hospitalization for incision and drainage (I&D) and intravenous (IV) antibiotic therapy. Cultures for all patients ranged from gram positive staphylococcal, gram negative cellulitis, apathogen streptococci, gram positive cocci infection, polymorphonuclear neutrophils (PMN) with no bacteria and positive proprionibacterium malassezia. The remaining cultures were either negative or not reported. Treatment included various antibiotics and steroids in some cases.

The following non-serious events, extrusion of device, ischemia/necrosis, and device dislocation, were also reported in a frequency of 5 or more. These events were considered non-serious as they did not meet seriousness criteria.

Adverse reactions should be reported to Medicis Aesthetics Inc. at 1-866-222-1480.

Clinical Trials

The safety and effectiveness of *Restylane* in the treatment of facial folds and wrinkles (nasolabial folds and oral commissures) were evaluated in three prospective randomized controlled clinical studies involving 430 *Restylane*-treated subjects.

Restylane was shown to be effective when compared to crosslinked collagen and crosslinked hyaluronic acid dermal fillers with respect to the correction of moderate to severe facial folds and wrinkles, such as nasolabial folds.

Table 1. Maximum Intensity of Symptoms after Initial Treatment for the Nasolabial Fold Indication, Patient Diary (Study 31GE0003)[1]

	Restylane side	Zyplast side	*Restylane* side				Zyplast side			
	Total patients reporting symptoms n (%)	Total patients reporting symptoms n (%)	None n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	None n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Bruising	72 (52.2%)	67 (48.6%)	63 (45.6%)	32 (23.2%)	35 (25.4%)	5 (3.6%)	68 (49.3%)	43 (31.2%)	23 (16.7%)	1 (0.7%)
Redness	117 (84.8%)	117 (84.8%)	17 (12.3%)	56 (40.6%)	54 (39.1%)	7 (5.1%)	17 (12.3%)	72 (52.2%)	37 (26.8%)	8 (5.8%)
Swelling	120 (87.0%)	102 (73.9%)	14 (10.1%)	54 (39.1%)	61 (44.2%)	5 (3.6%)	32 (23.2%)	65 (47.1%)	35 (25.4%)	2 (1.4%)
Pain	79 (57.2%)	58 (42.0%)	55 (39.9%)	40 (29.0%)	34 (24.6%)	5 (3.6%)	76 (55.1%)	46 (33.3%)	10 (7.2%)	2 (1.4%)
Tenderness	107 (77.5%)	89 (64.5%)	27 (19.6%)	60 (43.5%)	43 (31.2%)	4 (2.9%)	45 (32.6%)	70 (50.7%)	17 (12.3%)	2 (1.4%)
Itching	42 (30.4%)	33 (23.9%)	91 (65.9%)	31 (22.5%)	11 (8.0%)	0 (0.0%)	101 (73.2%)	27 (19.6%)	6 (4.4%)	0 (0.0%)
Other	34 (24.6%)	33 (23.9%)	93 (67.4%)	14 (10.1%)	15 (10.9%)	5 (3.6%)	94 (68.1%)	20 (14.5%)	10 (7.2%)	3 (2.2%)

[1] Events are reported as local events; because of the design (split-face) of the study, causality of the systemic adverse events cannot be assigned.

Table 2. Duration of Adverse Events after Initial Treatment for the Nasolabial Fold Indication, Patient Diary (Study 31GE0003)

	Restylane side	Zyplast side	*Restylane* side				Zyplast side			
			Number of days				Number of days			
	Total patients reporting symptoms n (%)	Total patients reporting symptoms n (%)	1 n (%)	2–7 n (%)	8–13 n (%)	14 n (%)	1 n (%)	2–7 n (%)	8–13 n (%)	14 n (%)
Bruising	72 (52.2%)	67 (48.6%)	7 (5.1%)	56 (40.6%)	6 (4.4%)	3 (2.2%)	7 (5.1%)	53 (38.4%)	5 (3.6%)	2 (1.4%)
Redness	117 (84.8%)	117 (84.8%)	19 (13.8%)	68 (49.3%)	18 (13.0%)	12 (8.7%)	19 (13.8%)	71 (51.4%)	15 (10.9%)	12 (8.7%)
Swelling	120 (87.0%)	102 (73.9%)	16 (11.6%)	84 (60.9%)	16 (11.6%)	4 (2.9%)	14 (10.1%)	70 (50.7%)	16 (11.6%)	2 (1.4%)
Pain	79 (57.2%)	58 (42.0%)	29 (21.0%)	48 (34.8%)	2 (1.4%)	0 (0.0%)	31 (22.5%)	25 (18.1%)	1 (0.7%)	1 (0.7%)
Tenderness	107 (77.5%)	89 (64.5%)	21 (15.2%)	78 (56.5%)	6 (4.4%)	2 (1.4%)	27 (19.6%)	54 (39.1%)	6 (4.4%)	2 (1.4%)
Itching	42 (30.4%)	33 (23.9%)	11 (8.0%)	25 (18.1%)	6 (4.4%)	0 (0.0%)	8 (5.8%)	22 (15.9%)	3 (2.2%)	0 (0.0%)
Other	34 (24.6%)	33 (23.9%)	7 (5.1%)	23 (16.7%)	3 (2.2%)	1 (0.7%)	10 (7.2%)	15 (10.9%)	6 (4.4%)	2 (1.4%)

Table 3. Maximum Intensity of Symptoms after Initial Treatment for the Nasolabial Fold Indication, Patient Diary (Study MA-1400-02)[1]

	Restylane	*Perlane*	*Restylane* Patients				*Perlane* Patients			
	Total patients reporting symptoms n (%)	Total patients reporting symptoms n (%)	None	Tolerable[2]	Affected Daily Activity[2]	Disabling[2]	None	Tolerable[2]	Affected Daily Activity[2]	Disabling[2]
			n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Bruising	111 (78.2%)	122 (86.5%)	28 (20.1%)	82 (59%)	28 (20.1%)	1 (0.7%)	17 (12.2%)	97 (69.8%)	24 (17.3%)	1 (0.7%)
Redness	114 (80.3%)	118 (83.7%)	25 (18%)	96 (69.1%)	17 (12.2%)	1 (0.7%)	21 (15.1%)	105 (75.5%)	12 (8.6%)	1 (0.7%)
Swelling	127 (89.4%)	128 (90.8%)	12 (8.6%)	102 (73.4%)	23 (16.5%)	2 (1.4%)	11 (7.9%)	107 (77%)	19 (13.7%)	2 (1.4%)
Pain	108 (76.1%)	114 (80.9%)	31 (22.3%)	93 (66.9%)	14 (10.1%)	1 (0.7%)	25 (18%)	96 (69.1%)	18 (12.9%)	0 (0%)
Tenderness	123 (86.6%)	130 (92.2%)	16 (11.5%)	109 (78.4%)	12 (8.6%)	2 (1.4%)	9 (6.5%)	112 (80.6%)	18 (12.9%)	0 (0%)
Itching	67 (47.2%)	45 (31.9%)	72 (51.8%)	66 (47.5%)	1 (0.7%)	0 (0%)	94 (67.6%)	40 (28.8%)	3 (2.2%)	2 (1.4%)
Other[3]	3 (2.1%)	1 (0.7%)	NA	NA	NA	NA	NA	NA	NA	NA

[1] Missing values are not reported.
[2] Prospective definitions for: tolerable, affected daily activity and disabling were not provided in the diary or protocol.
[3] Two patients reported pimples (one *Perlane*/one *Restylane*); one *Restylane* patient reported a sore throat; one *Restylane* patient reported a runny nose; degree of disability was not reported for any of the four events.

Table 4. Duration of Adverse Events after Initial Treatment for the Nasolabial Fold Indication, Patient Diary (Study MA-1400-02)[1]

	Restylane Patients	*Perlane* Patients	*Restylane* Patients				*Perlane* Patients			
			Number of days[2]				Number of days[2]			
	Total patients reporting symptoms n (%)	Total patients reporting symptoms n (%)	1 n (%)	2–7 n (%)	8–13 n (%)	14 n (%)	1 n (%)	2–7 n (%)	8–13 n (%)	14 n (%)
Bruising	111 (78.2%)	122 (86.5%)	9 (8.1%)	69 (62.2%)	30 (27%)	3 (2.7%)	6 (4.9%)	81 (66.4%)	28 (23%)	7 (5.7%)
Redness	114 (80.3%)	118 (83.7%)	31 (27.2%)	71 (62.3%)	9 (7.9%)	3 (2.6%)	19 (16.1%)	87 (73.7%)	8 (6.8%)	4 (3.4%)
Swelling	127 (89.4%)	128 (90.8%)	12 (9.4%)	93 (73.2%)	19 (15.0%)	3 (2.4%)	6 (4.7%)	100 (78.1%)	17 (13.3%)	5 (3.9%)
Pain	108 (76.1%)	114 (80.9%)	37 (34.3%)	69 (63.9%)	2 (1.9%)	0 (0%)	46 (40.4%)	66 (57.9%)	2 (1.8%)	0 (0%)
Tenderness	123 (86.6%)	130 (92.2%)	21 (17.1%)	92 (74.8%)	9 (7.3%)	1 (0.8%)	24 (18.5%)	89 (68.5%)	16 (12.3%)	1 (0.8%)
Itching	67 (47.2%)	45 (31.9%)	22 (32.8%)	38 (56.7%)	6 (9.0%)	1 (1.5%)	19 (42.2%)	23 (51.1%)	3 (6.7%)	0 (0%)
Other[3]	3 (2.1%)	1 (0.7%)	3 (100%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)

[1] Missing values are not reported.
[2] Data are cumulated from up to four injection sites per patient with earliest and latest time point for any reaction provided.
[3] Two patients reported pimples (one *Perlane*/one *Restylane*); one *Restylane* patient reported a sore throat; one *Restylane* patient reported a runny nose; degree of disability was not reported for any of the four events.

Table 5. Maximum Intensity of Symptoms after Initial Treatment for the Nasolabial Fold Indication, Patient Diary (Study MA-1400-01)[1,2]

	Restylane	*Perlane*	*Restylane* Patients				*Perlane* Patients			
	Total patients reporting symptoms n (%)	Total patients reporting symptoms n (%)	None	Tolerable[3]	Affected Daily Activity[3]	Disabling[3]	None	Tolerable[3]	Affected Daily Activity[3]	Disabling[3]
			n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Bruising	70 (46.7%)	74 (49.3%)	79 (53%)	66 (44.3%)	4 (2.7%)	0 (0%)	75 (50.3%)	67 (45%)	7 (4.7%)	0 (0%)
Redness	87 (58%)	92 (61.3%)	62 (41.6%)	81 (54.4%)	6 (4%)	0 (0%)	57 (38.3%)	85 (57%)	7 (4.7%)	0 (0%)
Swelling	125 (83.3%)	121 (80.7%)	24 (16.1%)	109 (73.2%)	14 (9.4%)	2 (1.3%)	28 (18.8%)	108 (72.5%)	11 (7.4%)	2 (1.3%)
Pain	96 (64%)	103 (68.7%)	53 (35.6%)	84 (56.4%)	11 (7.4%)	1 (0.7%)	46 (30.9%)	90 (60.4%)	12 (8.1%)	1 (0.7%)
Tenderness	122 (81.3%)	130 (86.7%)	27 (18.1%)	110 (73.8%)	11 (7.4%)	1 (0.7%)	19 (12.8%)	116 (77.9%)	13 (8.7%)	1 (0.7%)
Itching	53 (35.3%)	58 (38.7%)	96 (64.4%)	49 (32.9%)	4 (2.7%)	0 (0%)	91 (61.1%)	54 (36.2%)	4 (2.7%)	0 (0%)
Other[4]	3 (2%)	3 (2%)	NA	3 (100%)	0 (%)	0 (%)	NA	3 (100%)	0 (%)	0 (%)

[1] Missing values are not reported.
[2] Events are reported as local events; because of the design (split-face) of the study, causality of the systemic adverse events cannot be assigned.
[3] Prospective definitions for: tolerable, affected daily activity and disabling were not provided in the diary or protocol.
[4] Two patients reported mild transient headache and one patient reported mild "twitching"; neither could be associated with a particular product.

Table 6. Duration of Adverse Events after Initial Treatment for the Nasolabial Fold Indication, Patient Diary (Study MA-1400-01)[1,2]

	Restylane Patients	*Perlane* Patients	*Restylane* Patients				*Perlane* Patients			
			Number of days[3]				Number of days[3]			
	Total patients reporting symptoms n (%)	Total patients reporting symptoms n (%)	1 n (%)	2–7 n (%)	8–13 n (%)	14 n (%)	1 n (%)	2–7 n (%)	8–13 n (%)	14 n (%)
Bruising	70 (46.7%)	74 (49.3%)	13 (18.6%)	51 (72.9%)	6 (8.6%)	0 (0%)	23 (31.1%)	44 (59.5%)	6 (8.1%)	1 (1.4%)
Redness	87 (58%)	92 (61.3%)	33 (37.9%)	52 (59.8%)	2 (2.3%)	0 (0%)	38 (41.3%)	52 (56.5%)	2 (2.2%)	0 (0%)
Swelling	125 (83.3%)	121 (80.7%)	23 (18.4%)	89 (71.2%)	12 (9.6%)	1 (0.8%)	22 (18.2%)	85 (70.2%)	11 (9.1%)	3 (2.5%)
Pain	96 (64%)	103 (68.7%)	27 (28.1%)	67 (69.8%)	2 (2.1%)	0 (0%)	32 (31.1%)	67 (65%)	2 (1.9%)	2 (1.9%)
Tenderness	122 (81.3%)	130 (86.7%)	28 (23%)	87 (71.3%)	7 (5.7%)	0 (0%)	26 (20%)	94 (72.3%)	6 (4.6%)	4 (3.1%)
Itching	53 (35.3%)	58 (38.7%)	22 (41.5%)	27 (50.9%)	4 (7.5%)	0 (0%)	29 (50%)	26 (44.8%)	2 (3.4%)	1 (1.7%)
Other[4]	3 (2%)	3 (2%)	3 (100%)	0 (0%)	0 (0%)	0 (0%)	3 (100%)	0 (0%)	0 (0%)	0 (0%)

[1] Missing values are not reported.
[2] Events are reported as local events; because of the design (split-face) of the study, causality of the systemic adverse events cannot be assigned.
[3] Data are cumulated from up to two injection sites per patient with earliest and latest time point for any reaction provided.
[4] Two patients reported mild transient headache and one patient reported mild "twitching"; neither could be associated with a particular product.

Table 7. All Investigator-Identified Adverse Experiences (72 Hours) Number of Events per Patient per Study for the Nasolabial Fold Indication

Study Term	MA-1400-01		MA-1400-02	
	Number of Events *Restylane* (N=150)	Number of Events *Perlane* (N=150)	Number of Events *Restylane* (N=142)	Number of Events *Perlane* (N=141)
Ecchymosis	9	10	48	44
Edema	4	4	6	10
Erythema	13	13	3	5
Tenderness	4	4	7	5
Pain	2	2	2	2
Hyperpigmentation	2	3	0	1
Pruritus	2	1	1	0
Papule	1	0	2	2
Burning	1	0	0	0
Hypopigmentation	1	0	0	0
Injection site scab	3	0	0	0

Table 8. Investigator-Identified Adverse Experiences (2 Weeks or More After Implantation) (Number of Patients) (*Restylane* v. Specified Active Controls—All Studies for the Nasolabial Fold Indication)

Study Term	MA-1400-01 *Restylane* (n=150) (%)	MA-1400-01 *Perlane* (n=150) (%)	MA-1400-02 *Restylane* (n=142) (%)	MA-1400-02 *Perlane* (n=141) (%)	31GE0003 *Restylane* (n=138) (%)	31GE0003 Zyplast (n=138) (%)
Ecchymosis	4 (2.7%)	7 (4.6%)	14 (9.9%)	15 (10.6%)	8 (5.8%)	6 (4.3%)
Edema	0 (0%)	0 (0%)	2 (1.4%)	3 (2.1%)	11 (8.0%)	14 (10.1%)
Erythema	2 (1.3%)	2 (1.3%)	1 (0.7%)	2 (1.4%)	30 (21.7%)	37 (26.8 %)
Tenderness	0 (0%)	1 (0.7%)	0 (0%)	1 (0.7%)	8 (5.8%)	10 (7.2%)
Pain	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	4 (2.9%)	3 (2.2%)
Papule	1 (0.7%)	0 (0%)	2 (1.4%)	1 (0.7%)	5 (3.6%)	13 (9.4%)
Pruritus	1 (0.7%)	0 (0%)	1 (0.7%)	0 (0%)	4 (2.9%)	8 (5.8%)
Rash	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)	1 (0.7%)
Hyperpigmentation	8 (5.3%)	7 (4.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Injection site scab	1 (0.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Skin exfoliation	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 9. MA-004-03 Adverse Events Reported by *Restylane* Patients Treated in the Nasolabial Folds

Adverse Event	Number of Subjects with Events(%) N=75	Total Number of Events†	Severity Mild	Severity Moderate	Severity Severe
Swelling	18 (24%)	46	37	9	0
Bruising	14 (19%)	33	19	12	2
Pain/Soreness	4 (5%)	14	12	2	0
Discoloration	3 (4%)	5	5	0	0
Infection	1 (1%)	1	0	0	1
Hardness/Nodule	2 (3%)	3	2	1	0

†Most subjects had bilateral events at either the initial injection or touch-up. Bilateral events are counted as two events.

Table 10. MA-1300-15 Intensity of Adverse Event, Subject Diary for the Lip Augmentation Indication Study

	No Treatment (N=45)	1st Treatment (N=172)	2nd treatment (N=93)	No Treatment (N=45)				1st Treatment with *Restylane* (N=172)				2nd Treatment with *Restylane* (N=93)			
	Subjects Reporting Symptoms	Subjects Reporting Symptoms	Subjects Reporting Symptoms	None	Tolerable	Affects Daily Activity	Disabling	None	Tolerable	Affects Daily Activity	Disabling	None	Tolerable	Affects Daily Activity	Disabling
Maximum Severity Reported for any Diary AE															
Upper and Lower Lips Combined	2	167	89	37 (95%)	2 (5%)	0	0	2 (1%)	88 (52%)	62 (37%)	17 (10%)	1 (1%)	60 (67%)	25 (28%)	4 (4%)
Bruising															
Upper and Lower Lips Combined	2	147	58	37 (95%)	2 (5%)	0	0	22 (13%)	109 (65%)	33 (20%)	5 (3%)	31 (35%)	48 (53%)	10 (11%)	1 (1%)
Redness															
Upper and Lower Lips Combined	1	130	60	38 (97%)	1 (3%)	0	0	39 (23%)	118 (70%)	12 (7%)	0	30 (33%)	55 (62%)	2 (2%)	3 (3%)
Swelling															
Upper and Lower Lips Combined	0	166	89	39 (100%)	0	0	0	3 (2%)	90 (53%)	65 (38%)	11 (7%)	1 (1%)	64 (71%)	22 (25%)	3 (3%)
Pain (includes burning)															
Upper and Lower Lips Combined	1	146	72	38 (97%)	1 (3%)	0	0	23 (14%)	111 (66%)	27 (16%)	8 (5%)	18 (20%)	55 (61%)	14 (16%)	3 (3%)
Tenderness															
Upper and Lower Lips Combined	1	164	81	38 (97%)	1 (3%)	0	0	5 (3%)	120 (71%)	40 (24%)	4 (2%)	9 (10%)	63 (70%)	15 (17%)	3 (3%)
Itching															
Upper and Lower Lips Combined	0	56	23	39 (100%)	0	0	0	114 (67%)	51 (30%)	5 (3%)	0	67 (74%)	22 (25%)	1 (1%)	0

Table 11. MA-1300-15 Duration of Adverse Event, Subject Diary for the Lip Augmentation Indication Study

	No Treatment at Baseline (N=45)				
	Number of Days				
Location/Adverse Event	Any n (%)	1 n (%)	2–7 n (%)	8–13 n (%)	14 n (%)
Upper and Lower Lip Combined					
Bruising	2 (4%)	2 (100%)	0	0	0
Redness	1 (2%)	1 (100%)	0	0	0
Swelling	0	0	0	0	0
Pain (includes Burning)	1 (2%)	1 (100%)	0	0	0
Tenderness	1 (2%)	1 (100%)	0	0	0
Itching	0	0	0	0	0
	First Treatment with *Restylane* (N=172)				
	Number of Days				
Location/Adverse Event	Any[1] n (%)	1 n (%)	2–7 n (%)	8–13 n (%)	14 n (%)
Upper and Lower Lip Combined					
Bruising	147 (85%)	7 (5%)	93 (63%)	43 (29%)	4 (3%)
Redness	130 (76%)	20 (15%)	86 (66%)	23 (18%)	1 (<1%)
Swelling	166 (97%)	3 (2%)	88 (53%)	50 (30%)	25 (15%)
Pain (includes Burning)	146 (85%)	35 (24%)	95 (65%)	14 (10%)	2 (1%)
Tenderness	164 (95%)	11 (7%)	81 (49%)	49 (30%)	23 (14%)
Itching	55 (32%)	16 (29%)	32 (58%)	7 (13%)	0
	Second Treatment with *Restylane* (N=93)				
	Number of Days				
Location/Adverse Event	Any[1] n (%)	1 n (%)	2–7 n (%)	8–13 n (%)	14 n (%)
Upper and Lower Lip Combined					
Bruising	59 (63%)	3 (5%)	40 (68%)	16 (28%)	0
Redness	60 (65%)	16 (27%)	38 (63%)	5 (8%)	1 (2%)
Swelling	89 (96%)	10 (11%)	54 (61%)	21 (24%)	4 (5%)
Pain (includes Burning)	72 (77%)	21 (30%)	43 (60%)	5 (7%)	3 (4%)
Tenderness	81 (87%)	5 (6%)	52 (65%)	16 (20%)	8 (10%)
Itching	23 (25%)	10 (43%)	13 (57%)	0	0

[1] Duration of "other" diary symptoms could not be calculated.

Table 12. MA-1300-15 Summary of Treatment Emergent Adverse Events for the Lip Augmentation Indication Study

Adverse Event	No Treatment at Baseline (N=45)		First Treatment with *Restylane* (N=172)		Second Treatment with *Restylane* (N=93)	
	Events	Subjects	Events	Subjects	Events	Subjects
Pain	1	1 (2%)	97	36 (21%)	51	19 (20%)
Swelling	0	0	224	100 (58%)	103	52 (56%)
Tenderness	0	0	69	38 (22%)	29	16 (17%)
Nasopharyngitis	3	2 (4%)	9	9 (5%)	2	2 (2%)
Contusion (bruising/ ecchymosis)	0	0	131	76 (44%)	41	26 (28%)
Headache	3	2 (4%)	17	12 (7%)	3	3 (3%)
Erythema	0	0	57	29 (17%)	19	10 (11%)
Skin Exfoliation**	0	0	21	14 (8%)	2	2 (2%)

**Includes sloughing of the skin, peeling, desquamation, and superficial desquamation.

Table 13. MA-1300-13K Maximum Intensity of Symptoms after Initial Treatment, Subject Diary for the Lip Augmentation Indication Pilot Study

Reaction (N=20)	Total subjects reporting symptoms n (%)	None n (%)	Tolerable n (%)	Affected Daily Activity n (%)	Disabling n (%)
Bruising	17 (85%)	3 (15%)	13 (65%)	4 (20%)	0 (0%)
Redness	14 (70%)	6 (30%)	12 (60%)	2 (10%)	0 (0%)
Swelling	19 (95%)	1 (5%)	12 (60%)	7 (35%)	0 (0%)
Pain	17 (85%)	3 (15%)	17 (85%)	0 (0%)	0 (0%)
Tenderness	19 (95%)	1 (5%)	18 (90%)	1 (5%)	0 (0%)
Itching	2 (10%)	18 (90%)	2 (10%)	0 (0%)	0 (0%)
Mass Formation[1]	18 (90%)	2 (10%)	17 (85%)	1 (5%)	0 (0%)

[1] Documentation of mass formation was the result of a miscommunication with the subjects. Subjects were specifically instructed to record any product palpability as mass formation in their diary, whether or not the palpability was the intended feel of the product.

U.S. Clinical Studies

31GE0003: Prospective, Randomized, Blinded, Controlled, Clinical Study

Design

1:1 randomized, prospective study at 6 U.S. centers, which compared the safety and effectiveness of *Restylane* and Zyplast in a "within-patient" control model of augmentation correction of bilateral nasal folds, using *Restylane* on the randomized nasal labial fold and the control treatment on the opposite nasal labial fold. Patients were partially masked; evaluating physicians were independent and masked; treating physicians were unmasked.

Effectiveness was studied with 6-month follow-up. Safety was studied with 12-month follow-up.

Endpoints

Effectiveness
Primary:
The difference in effect of *Restylane* and Zyplast on the visual severity of the nasolabial folds, as assessed by an Evaluating Investigator at 6 months after baseline.

Secondary:
Wrinkle Severity Rating Scale (WSRS) score assessed at other follow-up points by the evaluating investigator and by the subject.

Global Aesthetic Improvement (GAI): Very much improved / much improved / improved / no change / worse, assessed at 2, 4, and 6 months by the evaluating investigator and by the subject.

Number of treatment sessions to achieve optimal cosmesis.

The primary evaluation parameter was the 5-point WSRS Score. A change in WSRS=1 was considered to be clinically significant during follow-up. Baseline was defined to begin at the follow-up demonstrating that optimal correction had been sustained for 2 weeks.

Optimal correction was defined to be the best cosmetic result obtainable, as determined by the evaluating physician. A specific, objective score or goal for correction was not defined; 2 injectable implant sessions were expected.

Outcomes

Demographics:
The study enrolled a population of predominately healthy, female, Caucasian non-smokers with history of prior facial aesthetic procedures and minimal sun exposure. There were few men or other racial/ethnic groups; few smokers or patients with extensive sun exposure.

- Gender
  - Male: 9 (6.6%)
  - Female: 128 (93.4%)
- Ethnicity
  - Caucasian: 122 (89.0%)
  - Black: 2 (1.5%)
  - Asian: 2 (1.5%)
  - Hispanic: 11 (8.0%)
- Tobacco use
  - Non-smokers 118 (86.1%)
  - Smokers: 19 (13.9%)
- Sun Exposure
  - None: 83 (60.6%)
  - Natural Sun: 52 (38.0%)
  - Artificial: 2 (1.5%)

Effectiveness
Primary:

Based on the per patient evaluation, the WSRS scores at 6 months by the evaluating investigator demonstrated that WSRS for

Restylane was lower (better) than Control:	in 78 patients
Restylane was equal to Control:	in 46 patients
Restylane was higher (worse) than Control:	in 13 patients

For the entire cohort, however, the Mean of the WSRS Score by evaluating investigator demonstrated that while there was essentially no difference between *Restylane* and Control-treated cohort sides at pre-treatment (0.02 units WSRS) and baseline (0.01 units WSRS), for the cohort of 134 patients, there was a difference of 0.58 units of WSRS at 6 months.

Table 14. Blinded Evaluator Mean Wrinkle Severity Scores

	N	*Restylane*	Control	Absolute Difference
Pre-treatment	138	3.29	3.31	0.02
Baseline	138	1.80	1.79	0.01
6 months	134	2.36	2.94	0.58

MA-1400-02: Prospective, Randomized, Blinded, Controlled Clinical Study

Design

1:1 randomized, prospective study at 17 U.S. centers, which compared the safety and effectiveness of *Restylane* and *Perlane* following treatment to baseline condition. Patients were randomized to either *Restylane* or *Perlane* treatment. A touch-up was allowed 2 weeks after initial treatment. Patients were partially masked; evaluating physicians were independent and masked; treating physicians were unmasked.

Effectiveness was studied with 6 months follow-up. Safety was studied with 6 months follow-up.

Endpoints

Effectiveness
Primary:
The difference in effect of *Restylane* at week 12 versus baseline condition on the visual severity of the nasolabial folds, as assessed by the Blinded Evaluator.

The primary study endpoint was wrinkle severity 12 weeks after optimal correction was achieved. Wrinkle severity was evaluated on a five-step validated Wrinkle Severity Rating Scale (WSRS) (i.e., none, mild, moderate, severe, extreme) by a live evaluator blinded to treatment. Patient success was defined as maintaining at least a one point improvement on the WSRS at 12 weeks after optimal correction was achieved. The percent of patient successes were calculated for each treatment group. Each group was compared to its own baseline, with no comparison of *Restylane* to *Perlane*.

Secondary:
Wrinkle Severity Rating Scale (WSRS) assessed at other follow-up points (2, 6, and 24 weeks after optimal correction) by the Blinded Evaluator, the investigator and the patient and compared to baseline score by the same evaluator. Duration of effect was defined as 6 months or time point, if earlier, at which less than 50% of patients had at least a 1-grade response remaining in both nasolabial folds (NLFs).

Safety assessments included: collection of patient symptoms in a 14-day diary; investigator evaluation of adverse experiences at 72 hours, and at 2, 6, 12, and 24 weeks; development of humoral or cell-mediated immunity; and the relationship of adverse experiences to injection technique.

Outcomes

Demographics:
The study enrolled 283 (i.e., 142 *Restylane* and 141 *Perlane*) patients with moderate to severe NLF wrinkles. The patients were predominantly healthy ethnically diverse females. Bilateral NLFs and oral commissures were corrected with 2.1 mL to 5.2 mL of *Restylane.* The greatest amount used in any patient was 8.8 mL.

Gender – Female: 266 (94%); Male: 17 (6%)

Ethnicity – White: 226 (80%); Hispanic or Latino: 31 (11%); African American: 23 (8%); Asian: 3 (1%)

Efficacy:
The results of the blinded evaluator assessment of NLF wrinkle severity for *Restylane* and control (*Perlane*) are presented in Table 15. In the primary effectiveness assessment at 12 weeks, 77% of the *Restylane* and 87% of the control patients had maintained at least a 1-point improvement over baseline.

Table 15. Blinded Evaluator Wrinkle Severity Response Scores

Time point	No. of *Restylane* Patients	No. of *Restylane* Pts. maintaining ≥ 1 Unit Improvement of NLF on WSRS	No. of *Perlane* Patients	No. of *Perlane* Pts. maintaining ≥1 Unit Improvement of NLF on WSRS
6 weeks	136	113 (83%)[1]	136	121 (89%)[1]
12 weeks	140	108 (77%)[1]	141	122 (87%)[1]
24 weeks	140	103 (74%)[1]	138	87 (63%)[1]

[1] All p-values <0.0001 based on t-test compared to baseline condition

Antibody Testing:
15/142 (10.6%) subjects displayed a pre-treatment antibody response against *Restylane* (which was believed to be related to co-purifying *Streptococcus* capsule antigens). One subject also developed measurable increase in antibody titer after *Restylane* injection. 7/21 (33.3%) patients with antibodies against *Restylane* had adverse experiences at the injection site, which was similar to the local adverse event rate observed in the entire *Restylane* population (i.e., 53/142 (37%)). No severe events were noted and the subject who developed an antibody response after *Restylane* injection did not experience any adverse event at the injection site. Immediate type skin testing demonstrated that no patient developed IgE to *Restylane*. Post-exposure histopathology of skin biopsies of an implant site on each patient demonstrated that no patient developed cell-mediated immunity to *Restylane*.

MA-1400-01: Prospective, Randomized, Blinded, Controlled Clinical Study

Design

1:1 randomized, prospective study at 10 U.S. centers, which compared the safety and effectiveness of *Restylane* and *Perlane* following treatment to baseline condition in 150 patients with pigmented skin and predominantly African-American ethnicity. Patients were randomized to *Restylane* or *Perlane* treatment in a "within-patient" model of augmentation correction of bilateral nasolabial folds (NLFs) and oral commissures with one treatment assigned to one side and the other treatment to the other side. A touch-up was allowed 2 weeks after initial treatment. Patients and treating physicians were partially masked. Evaluations were performed by live investigator assessment for the primary analysis.

Effectiveness was studied with 6 months follow-up. Safety was studied with 6 months follow-up.

Endpoints

Effectiveness

Primary:
The difference in effect of *Restylane* at week 12 versus baseline condition on the visual severity of the NLFs.

The primary study endpoint was wrinkle severity 12 weeks after optimal correction was achieved. Wrinkle severity was evaluated with a five-step validated Wrinkle Severity Rating Scale (WSRS) (i.e., none, mild, moderate, severe, extreme) by an on-site blinded evaluator. Patient success was defined as maintaining at least a one point improvement on the WSRS at 12 weeks after optimal correction was achieved. The percent of patient successes was calculated for each group. Each treatment group was compared to its own baseline, with no comparison of *Restylane* to *Perlane*.

Secondary:
Wrinkle Severity Rating Scale (WSRS) was assessed at other follow-up points (2, 6, and 24 weeks after optimal correction) by the investigator and the patient and compared to baseline score by the same evaluator. A photographic assessment of patient outcomes was also performed. Duration of effect was defined as 6 months or time point, if earlier, at which less than 50% of patients had at least a 1-grade response at both nasolabial folds.

Safety assessments included: collection of patient symptoms in a 14-day diary; investigator evaluation of adverse experiences at 72 hours, and at 2, 6, 12, and 24 weeks; development of humoral or cell-mediated immunity; and the relationship of adverse experiences to injection technique.

Outcomes

Demographics:

The study enrolled 150 patients with moderate to severe NLF wrinkles. The patients were predominantly healthy African-American females.

Gender – Female: 140/150 (93%); Male 10/150 (7%)

Ethnicity – White: 2 (1.3%); Hispanic or Latino: 9 (6%); African-American: 137 (91%); American Indian: 2 (1.3%)

Fitzpatrick Skin Type – I to III: 0 (0%); IV: 44 (29%); V: 68 (45%); VI: 38 (25%)

Efficacy:
The results of the live blinded evaluator assessment of wrinkle severity for *Restylane* and control (*Perlane*) are presented in Table 16 and are based on the Intent-to-Treat analysis. In the primary effectiveness assessment at 12 weeks, 93% of the *Restylane*-treated and 92% of the *Perlane*-treated NLF maintained at least a 1-point improvement over baseline.

Table 16. Live Evaluator Wrinkle Severity Response Scores

Time point	No. of patients	No. of *Restylane* Pts. maintaining 1 Unit Improvement on WSRS	95% *Restylane* Confidence Interval	No. of *Perlane* Pts. maintaining [1] 1 Unit Improvement on WSRS	95% *Perlane* Confidence Interval
6 weeks	148	142 (96%)[1]	92–99%	140 (95%)[1]	90–99%
12 weeks	149	139 (93%)[1]	89–98%	137 (92%)[1]	87–97%
24 weeks	147	108 (73%)[1]	66–81%	104 (71%)[1]	63–77%

[1] All p-values <0.0001 based on t-test compared to baseline condition

Antibody Testing:
9/150 (6%) subjects displayed a pre-treatment antibody response against *Restylane* (which was believed to be related to co-purifying *Streptococcus* capsule antigens). No subjects developed a measurable increase in antibody titer after *Restylane* injection. 1/6 (17%) patients with antibodies against *Restylane* had adverse experiences at the injection site as compared to the local adverse event rate observed in the entire *Restylane* population (i.e., 28/150 (18.7%)). All the adverse experiences in the patients with a humoral response against *Restylane* were mild in severity. Immediate type skin testing demonstrated that no patient developed IgE to *Restylane*. Post-exposure histopathology of skin biopsies of an implant site on each patient demonstrated that no patient developed cell-mediated immunity to *Restylane*.

MA-04-003

The duration of effectiveness of *Restylane* for correction of nasolabial folds (NLF) was evaluated in a randomized, evaluator-blinded, multi-center study. *Restylane* was shown to have an overall duration of effectiveness of 18 months from baseline following re-treatment at 4.5 or 9 months.

MA-04-003: Randomized Clinical Study

Design

Randomized, evaluator-blinded study at 3 U.S. centers, which compared the safety and effectiveness of *Restylane* using two re-treatment schedules. Initially *Restylane* was injected in both nasolabial folds (NLF). Subsequently, one NLF was re-treated at 4.5 months after the initial treatment. The contralateral NLF was treated with *Restylane* and re-treated at 9 months (± 1 week). The Blinded Evaluators were blinded to the re-treatment schedule while patients and treating physicians were not.

Effectiveness was studied at 18 months after the initial injection (i.e., either 9 or 13.5 months after the second treatment).

Endpoints

Effectiveness
Primary:
The difference in effect of *Restylane* injected 4.5 or 9 months after the initial treatment on the visual severity of the nasolabial folds was assessed by an Evaluating Investigator at 18 months after the baseline treatment. The primary study endpoint was the proportion of subjects with at least one grade improvement in the Wrinkle Severity Rating Scale (WSRS) from baseline as assessed by the Blinded Evaluator at the 18 month visit.

Secondary:
The Wrinkle Severity Rating Scale (WSRS) score was assessed by the evaluating investigator at all follow-up visits prior to the 18 month visit and at all visits by subjects and independent photographic reviewers.

Global Aesthetic Improvement Scale (GAIS) comparing the pre-treatment appearance at all follow-up visits up to 18 months, was determined by the treating investigator and patient. The GAIS is a 5-point scale for assessing global aesthetic improvement: "very much improved / much improved / improved / no change / worse."

Safety
Severity and duration of injection site reactions and adverse events were recorded.

Outcomes

Demographics:
The study enrolled an adult population of predominately Caucasian, healthy, non-smoking females.

Number of Subjects	Age		Gender		Race		Prior Augmentation to NLF		History of Tobacco Use		History of Sun Exposure	
75	Mean ± SD	53.8 ± 8.4	Male	5 (6.7%)	White	50 (66.7%)	Yes	6 (8.0%)	No	55 (73.3%)	No	63 (84.0%)
	Median	54	Female	70 (93.3%)	Black	3 (4.0%)	No	69 (92.0%)	Yes	20 (26.7%)	Yes	12 (16.0%)
	Minimum	26			Hispanic	22 (29.3%)						
	Maximum	73										

Number of Subjects enrolled and observed at 4.5, 9, 12, 15 and 18 months

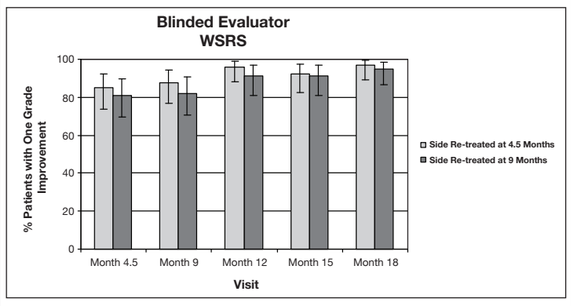
	SCR/TRT	Touch-up	Wk2	M 4.5	M9	M12	M15	M18
Enrolled	75	-	75	75	75	75	75	75
Withdrew Consent (total)	0	-	1	5	6	6	6	7
Lost to Follow-up	0	-	0	2	4	4	4	4
Missed Visit	0	-	2	1	0	1	1	1
Actual	75	44	72	67	65	64	64	64

Volume (mL) of *Restylane* Treatment Used by Visit

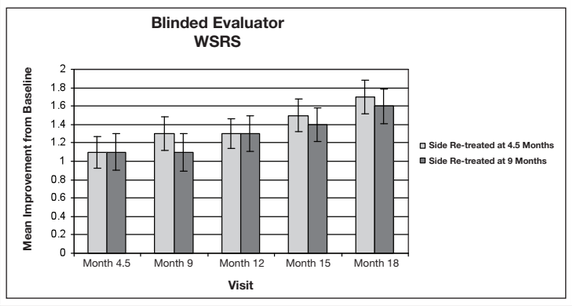
Visit	Side Assigned to Re-treatment at 4.5 Months	Side Assigned to Re-treatment at 9 Months
Baseline		
N	75	75
Mean ± SD	1.1 ± 0.61	1.1 ± 0.56
Median	1.0	1.0
Minimum	0.1	0.2
Maximum	2.5	2.5
Touch-up Visit		
N	44	44
Mean ± SD	0.5 ± 0.22	0.5 ± 0.21
Median	0.5	0.5
Minimum	0.2	0.2
Maximum	1.0	1.0
Re-treatment Visit (4.5 Months/9 months)		
N	67	63
Mean ± SD	0.7 ± 0.33	0.7 ± 0.36
Median	0.8	0.6
Minimum	0.2	0.1
Maximum	1.8	2.0

Effectiveness

The results of the blinded evaluator assessment of NLF wrinkle severity for subjects treated at baseline, 4.5 or 9 months is presented in the Figure below for subject outcomes at 4.5, 9, 12, 15 and 18 months after initial treatment.



At 18 months after the initial treatment, the blinded evaluator determined that 97% of the NLFs re-treated at 4.5 months displayed at least 1 WSRS grade improvement over baseline, with a mean change in wrinkle severity score of 1.7 units. At 18 months after the initial treatment, the blinded evaluator determined that 95% of the NLFs re-treated at 9 months displayed at least 1 WSRS grade improvement over baseline, with a mean change in wrinkle severity score of 1.6 units.



MA-1300-15

The safety and effectiveness of *Restylane* for lip fullness augmentation was evaluated in a randomized, evaluator blinded, no treatment controlled study.

MA-1300-15: Randomized Clinical Study

Design

This was a randomized, evaluator blinded, no treatment as a control study of 180 subjects who were seeking lip fullness augmentation at 12 investigational centers. At entry of the study, subjects were randomized in a 3:1 ratio to (1) Restylane treatment or (2) no treatment. The study recruited a minimum of 30 subjects with darker skin types based on classification of Fitzpatrick skin types IV, V, or VI. Each lip qualified by MLFS score was analyzed for effectiveness and all lips were analyzed for safety. Subjects randomized to treatment at baseline were re-treated at 6 months and subjects randomized to no treatment at baseline received their first treatment at 6 months. The safety of all subjects was then monitored for one month after the 6 month treatment.

Endpoints

Effectiveness
Primary:
The primary effectiveness objective was to identify whether *Restylane* was more effective in lip augmentation than no treatment. This was determined by the blinded evaluator assessment of lip fullness at 8 weeks after the first treatment as compared to the baseline assessment by the treating investigator, separately in the upper and lower lips (co-primary endpoints), using separate 5-grade Medicis Lip Fullness Scales (MLFS) with photoguides for each (one scale for upper lip and one scale for lower lip). Treatment success was defined as at least a one grade improvement in the MLFS for the blinded evaluator assessments at Week 8 (as compared to the treating investigator's baseline assessment of the MLFS) for both the upper and lower lips.

The primary safety objective was to define the incidence of all adverse events; including subject complaints reported during the first fourteen days after treatment as recorded in the subject diary; safety assessments at the 72 hour visits; treating investigator assessments at 2, 4, 8, 12, 16, 20, 24 weeks as well as 2 and 4 weeks after the 6 month treatment; and any reported or observed adverse events.

Secondary:
Secondary effectiveness objectives included:

- Assessment of lip fullness augmentation after treatment with *Restylane* as compared to no treatment, as measured by the blinded evaluator, treating investigator, and IPR at post-baseline time points as compared to the baseline assessment. Response was determined by at least one grade improvement from baseline in the upper and lower lips using the MLFS.
- Identification of lip improvement at each time point after treatment with *Restylane* as compared to no treatment using the GAIS by the treating investigator and the subject. Response is defined as a GAIS rating of "improved" or better in the upper or lower lips.

The secondary safety objectives included assessment of lip texture, firmness, symmetry, product palpability, mass formation, lip movement, function, and sensation.

Outcomes

Demographics:
The study enrolled an adult population of predominately Caucasian healthy females.

Characteristics	Total (N=180)
Age (years)	
n	180
Mean (S.D.)	47.6 (10.6)
Median	50.0
Minimum	18
Maximum	65
Gender	
Male	1 (<1%)
Female	179 (99%)

Characteristics	Total (N=180)
Race	
American Indian/Alaskan Native	2 (1%)
Black/African American	2 (1%)
Native Hawaiian/Pacific Islander	1 (<1%)
Asian	0
White	169 (94%)
Other	6 (3%)
Ethnicity	
Not Hispanic or Latino	161 (89%)
Hispanic or Latino	19 (11%)
Fitzpatrick Skin	
I, II, and III	139 (77%)
IV and V	41 (23%)

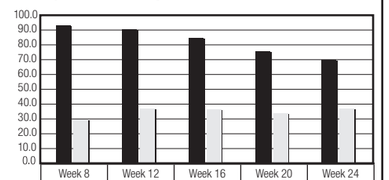
Volume (mL) of *Restylane* used:

Assessment (upper and lower lips)	Initial Treatment: No Treatment (N=45)	Initial Treatment: *Restylane (1st Treatment)* (N=135)	6 Month Treatment: No Treatment *(1st Treatment)* (N=45)	6 Month Treatment: *Restylane (2nd Treatment)* (N=135)
Volume of Injection (mL) (includes treatment and touch up)				
n	–	135	37	93
Mean (S.D.)	–	2.853 (0.984)	2.387 (1.380)	1.783 (0.921)
Median	–	3.000	2.250	1.700
Minimum	–	0.60	0.60	0.03
Maximum	–	5.60	8.00	5.00

Effectiveness
The purpose of this study was to evaluate the safety and effectiveness of *Restylane* for soft tissue augmentation of the lips. The results confirm that *Restylane* is highly effective for adding fullness to both the upper and lower lips for at least 6 months.

The results of the blinded evaluator MLFS assessments of lip fullness are presented in the figure below for subject outcomes 8, 12, 16, 20, and 24 weeks.

Proportion (%) of MLFS Responders Measured by the Blinded Evaluator



	Week 8	Week 12	Week 16	Week 20	Week 24
Restylane Treatment (%)	92.6	90.1	84.2	75.0	69.6
No Treatment (%)	28.9	36.8	35.9	33.3	36.8

p-value < 0.001 for all time points

Subjects assessed lip improvement at each time point after treatment with a 7-point non-validated GAIS. When upper and lower lip outcomes were combined, the following percentage of *Restylane* subjects assessed themselves as improved or better from Baseline: 97.7% (Week 2), 99.2% (Week 4), 96.7% (Week 8), 91.7% (Week 12), 85.0% (Week 16), 76.1% (Week 20), and 74.1% (Week 24). No patients in the No Treatment group assessed themselves as improved from Baseline at any visit.

80% of the eligible subjects elected to receive re-treatment at Week 24 which suggests that subjects believed that the safety concerns associated with *Restylane* lip injections were less than the aesthetic value provided by the device.

MA-1300-13K

Design

A prospective, open label, single center, blinded evaluator study in 20 subjects

Endpoints

The effectiveness evaluation parameter was the Global Aesthetic Improvement Scale (GAIS)

To assess the incidence and severity of adverse experiences from *Restylane* when used in the lips

Outcomes

A total of 20 subjects (2 male, 18 female) were enrolled and 19 subjects completed the study. One 80 year old subject died during the study due to cardio-respiratory arrest. Mean age was 52.8 years old. Seventeen subjects were white.

At 12 weeks, 7/19 (37%) subjects were rated as improved on their GAIS assessment by the Blinded Evaluator. At 12 weeks, all (100%) subjects rated themselves as improved on their GAIS assessment.

Parameter	N	n	Subjects with Lip Improvement	Percent	90% CI	p-Value[1]
Lip Improvement Using the Blinded Evaluator's Assessment[1]	20	19	7	37%	(0.19, 0.58)	0.820
Lip Improvement Using the Treating Investigator's Assessment	20	19	19	100%	(0.85, 1.00)	<0.001
Lip Improvement Using the Subject's Assessment	20	17	17	100%	(0.84, 1.00)	<0.001

[1] Due to the protocol deviation, the live blinded evaluator's assessment was a photo assessment.

Mean Volume Used		
Lip	**Statistic**	**Volume of Injection (mL)**
Upper	N	20
	Mean (S.D.)	0.82 (0.30)
	Median	0.73
	Min, Max	0.08, 1.40
Lower	N	20
	Mean (S.D.)	0.88 (0.37)
	Median	0.80
	Min, Max	0.05, 1.80
Total	N	20
	Mean (S.D.)	1.69 (0.62)
	Median	1.60
	Min, Max	0.13, 3.20

DIRECTIONS FOR ASSEMBLY

ASSEMBLY OF 30 G NEEDLE TO SYRINGE

For safe use of *Restylane*, it is important that the needle is properly assembled. Improper assembly may result in separation of the needle and syringe during implantation.

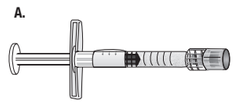
See pictures A through E.

1. Unscrew the tip cap (B) of the syringe carefully.
2. Grasp the narrow part of the needle shield loosely; mount the needle on the Luer-Lok (C) by turning it clockwise until you feel counterpressure.
3. Grasp the wider part of the needle shield firmly (D).
4. Press and turn the needle shield 90° (a quarter turn).

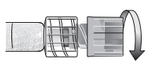
4a. The quarter turn is necessary to lock the needle onto the syringe.

5. Remove the patient record label marked with three small arrows (E) and attach to patient chart.
6. Pull off the needle shield.

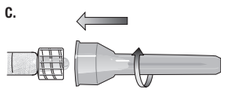
A.



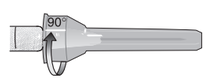
B.



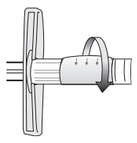
C.



D.

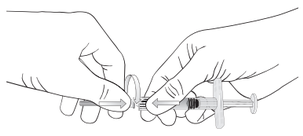


E.



ASSEMBLY OF 29 G NEEDLE TO SYRINGE

Use the thumb and forefinger to hold firmly around both the glass syringe barrel and the Luer-Lok adapter. Grasp the needle shield with the other hand. To facilitate proper assembly, both push and rotate firmly.



PRE-TREATMENT GUIDELINES

Prior to treatment, the patient should avoid taking aspirin, nonsteroidal anti-inflammatory medications, St. John's Wort, or high doses of Vitamin E supplements. These agents may increase bruising and bleeding at the injection site.

TREATMENT PROCEDURE

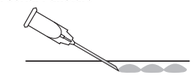
1. It is necessary to counsel the patient and discuss the appropriate indication, risks, benefits and expected responses to the *Restylane* treatment.

   Advise the patient of the necessary precautions before commencing the procedure.
2. Assess the patient's need for appropriate anesthetic treatment for managing comfort, i.e., topical anesthetic, local or nerve block.
3. 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.
4. Sterile gloves are recommended while injecting *Restylane*.
5. Before injecting, press rod carefully until a small droplet is visible at the tip of the needle.
6. *Restylane* is administered using a thin gauge needle (30 G x ½" or 29 G x ½"). The needle is inserted at an approximate angle of 30° parallel to the length of the wrinkle, fold, or lip. For the nasolabial folds, *Restylane* should be injected into the mid-to-deep dermis. For lip augmentation, *Restylane* should be injected into the submucosal layer; care should be taken to avoid intramuscular injection. If *Restylane* is injected too superficially this may result in visible lumps and/or bluish discoloration.
7. Inject *Restylane* applying even pressure on the plunger rod. It is important that the injection is stopped just before the needle is pulled out of the skin to prevent material from leaking out or ending up too superficially in the skin.
8. Only correct to 100% of the desired volume effect. Do not overcorrect. With cutaneous deformities the best results are obtained if the defect can be manually stretched to the point where it is eliminated. The degree and duration of the correction depend on the character of the defect treated, the tissue stress at the implant site, the depth of the implant in the tissue and the injection technique.
9. Typical usage for each treatment session is specific to the site as well as wrinkle severity. In a prospective study of midface wrinkle correction, the median total dose was 3.0 mL. Based on U.S. clinical studies, the maximum recommended dose per treatment is 6.0 mL for the nasolabial folds and 1.5 mL per lip per treatment.

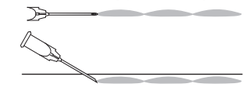
INJECTION TECHNIQUES

1. *Restylane* can be injected by a number of different techniques that depend on the treating physician's experience and preference, and patient characteristics.
2. **Serial puncture** (F) involves multiple, closely spaced injections along wrinkles or folds. Although serial puncture allows precise placement of the filler, it produces multiple puncture wounds that may be undesirable to some patients.
3. **Linear threading** (includes retrograde and antegrade) (G) is accomplished by fully inserting the needle into the middle of the wrinkle or fold and injecting the filler along the track as a "thread." Although threading is most commonly practiced after the needle has been fully inserted and is being withdrawn, it can also be performed while advancing the needle ("push-ahead" technique). To enhance the vermillion of the lip, the retrograde linear threading technique is the most advisable.
4. Serial threading is a technique that utilizes elements of both approaches.
5. **Cross-hatching** (H) consists of a series of parallel linear threads injected at intervals of five to ten mm followed by a new series of threads injected at right angles to the first set to form a grid. This technique is particularly useful in facial contouring when coverage of the treatment region needs to be maximized.

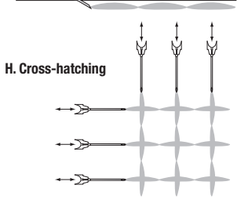
F. Serial Puncture



G. Linear Threading (includes retrograde and antegrade)



H. Cross-hatching



6. **Note! The correct injection technique is crucial for the final result of the treatment.** Dissection of the sub-epidermal plane with lateral movement of the needle, rapid flows (>0.3 mL/min), rapid injection or high volumes may result in an increase in short-term episodes of bruising, swelling, redness, pain, or tenderness at the injection site.
7. When the injection is completed, the treated site should be gently massaged so that it conforms to the contour of the surrounding tissues. If an overcorrection has occurred, massage the area firmly between your fingers, or against the underlying area to obtain optimal results.
8. If so called "blanching" is observed, i.e., the overlying skin turns a whitish color, the injection should be stopped immediately and the area massaged until it returns to a normal color.
9. If the wrinkle or lips need further treatment, the same procedure should be repeated until a satisfactory result is obtained. Additional treatment with *Restylane* may be necessary to achieve the desired correction.
10. If the treated area is swollen directly after the injection, an ice pack can be applied on the site for a short period. Ice should be used with caution if the area is still numb from anesthetic to avoid thermal injury.
11. Patients may have mild to moderate injection site reactions, which typically resolve in less than 7 days in the nasolabial folds and less than 14 days in the lip.

STERILE NEEDLE(S)

- Follow national, local or institutional guidelines for use and disposal of medical sharp devices. Obtain prompt medical attention if injury 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 reshield used needles. Recapping by hand is a hazardous practice and should be avoided.
- Discard unshielded needles in approved sharps collectors.
- *Restylane* is provided with a needle that does not contain engineered injury protection. Administration of *Restylane* requires direct visualization and complete and gradual insertion of the needle making engineered protections infeasible. Care should be taken to avoid sharps exposure by proper environmental controls.

Ordering Information
Medicis Aesthetics Inc. and its distributor, McKesson Specialty, are your only sources for FDA-approved *Restylane*. Purchasing from any other agent is illegal.

To order call 877-520-0500.

HOW SUPPLIED
Restylane is supplied in a disposable glass syringe with a Luer-Lok® fitting. *Restylane* is co-packed with sterilized needle(s) as indicated on the carton, either 30 G x ½" or 29 G x ½".

A patient record label is a part of the syringe label. Remove it by pulling the flap marked with three small arrows. This label is to be attached to patient records to ensure traceability of the product.

The contents of the syringe are sterile.

The volume in each syringe and needle gauge is as stated on the syringe label and on the carton.

SHELF LIFE AND STORAGE
Restylane must be used prior to the expiration date printed on the package.

Store at a temperature of up to 25° C (77° F). Do not freeze. Protect from sunlight. Refrigeration is not required.

Do not resterilize *Restylane* as this may damage or alter the product.

Do not use if the package is damaged. Immediately return the damaged product to Medicis Aesthetics Inc.

℞ only

U.S. PATENT 5,827,937

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