

# 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 BDE, 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.

**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 subcutaneous 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 glabella 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 Pre-market Approval Studies (that included 42 patients under the age of 35 and 520 patients over the age of 35), the incidence of swelling was higher in younger patients (82%) 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.

**Precutions**  
Restylane is packaged for single patient use. Do not reutilize. 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- and 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 severe 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 Medics 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 subcutaneous 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 subcutaneous 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 (67/795, 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 (mucocoele) during the study. The mucocoele 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 anconerom 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 frequent 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 hypoesthesia 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 lumps 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, atypogen streptococci, gram positive cocci infection, polymorphonuclear neutrophils (PMN) with no bacteria and positive propionibacterium malissosia. 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 Medics 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)

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 (%)	
Brusing	72 (52.2%)	67 (48.6%)	63 (45.6%)	32 (22.2%)	35 (25.4%)	5 (3.6%)	68 (49.3%)	43 (31.2%)	23 (16.7%)	10 (7.0%)
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%)	10 (7.2%)	2 (1.4%)	0
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%)

\* 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							
Total patients reporting symptoms n (%)	Total patients reporting symptoms n (%)	Number of days	Number of days							
		1 n (%)	2-7 n (%)	8-13 n (%)	14 n (%)	1 n (%)	2-7 n (%)	8-13 n (%)	14 n (%)	
Brusing	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%)	18 (13.0%)	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)

Restylane	Perlane	Restylane Patients	Perlane Patients							
Total patients reporting symptoms n (%)	Total patients reporting symptoms n (%)	None n (%)	Tolerable <sup>1</sup> n (%)	Affected Daily Activity <sup>2</sup> n (%)	Disabling <sup>3</sup> n (%)	None n (%)	Tolerable <sup>1</sup> n (%)	Affected Daily Activity <sup>2</sup> n (%)	Disabling <sup>3</sup> n (%)	
Brusing	111 (78.2%)	122 (86.5%)	28 (24.1%)	82 (59%)	20 (17.4%)	1 (0.7%)	17 (12.2%)	97 (69.8%)	24 (17.2%)	1 (0.7%)
Redness	114 (80.3%)	118 (83.7%)	25 (18.1%)	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 (77.9%)	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 (2.1%)	1 (0.7%)	NA	NA	NA	NA	NA	NA	NA	NA

<sup>1</sup> Missing values are not reported.  
<sup>2</sup> Data are cumulated from up to four injection sites per patient with earliest and latest time point for any reaction provided.  
<sup>3</sup> Two patients reported mild (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)

Restylane Patients	Perlane Patients	Restylane Patients	Perlane Patients							
Total patients reporting symptoms n (%)	Total patients reporting symptoms n (%)	Number of days <sup>1</sup>	Number of days <sup>2</sup>							
		1 n (%)	2-7 n (%)	8-13 n (%)	14 n (%)	1 n (%)	2-7 n (%)	8-13 n (%)	14 n (%)	
Brusing	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 (8.6%)	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 (34.2%)	69 (63.5%)	7 (6.1%)	0 (0%)	46 (40.4%)	69 (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 (66.7%)	6 (9.0%)	1 (1.5%)	19 (42.2%)	23 (51.1%)	3 (6.7%)	0 (0%)
Other*	3 (2.1%)	1 (0.7%)	3 (100%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)

<sup>1</sup> Missing values are not reported.  
<sup>2</sup> Data are cumulated from up to four injection sites per patient with earliest and latest time point for any reaction provided.  
<sup>3</sup> Two patients reported mild (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)

Restylane	Perlane	Restylane Patients	Perlane Patients							
Total patients reporting symptoms n (%)	Total patients reporting symptoms n (%)	None n (%)	Tolerable <sup>1</sup> n (%)	Affected Daily Activity <sup>2</sup> n (%)	Disabling <sup>3</sup> n (%)	None n (%)	Tolerable <sup>1</sup> n (%)	Affected Daily Activity <sup>2</sup> n (%)	Disabling <sup>3</sup> n (%)	
Brusing	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	67 (58%)	62 (51.3%)	33 (27.9%)	51 (42.3%)	6 (4.9%)	0 (0%)	57 (38.3%)	52 (33%)	7 (4.7%)	

**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 Zylplast in a "within-patient" control model of augmentation or 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.

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

**Effectiveness**  
Primary:  
The difference in effect of *Restylane* and Zylplast 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 by term 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.

**Demographics:**  
The study enrolled a population of predominantly 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	Tobacco use		
Male: 9 (6.6%)	Non-smokers: 118 (86.1%)		
Female: 128 (93.4%)	Smokers: 19 (13.9%)		

Ethnicity	Sun Exposure		
Caucasian: 122 (89.0%)	None: 83 (60.6%)		
Black: 2 (1.5%)	Natural Sun: 52 (38.0%)		
Asian: 2 (1.5%)	Artificial: 2 (1.5%)		
Hispanic: 11 (8.0%)			

**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.

Time point	<i>Restylane</i>	Control	Absolute Difference
Pre-treatment	1.38	3.29	0.02
Baseline	1.38	1.80	0.01
6 months	1.34	2.36	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.

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

**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 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.

**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.

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

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., 5.3/142 (3.7%)). 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 biopsies 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 was studied with 6 months follow-up. Safety was studied with 6 months follow-up.

**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.

**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.

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

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 biopsies 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.

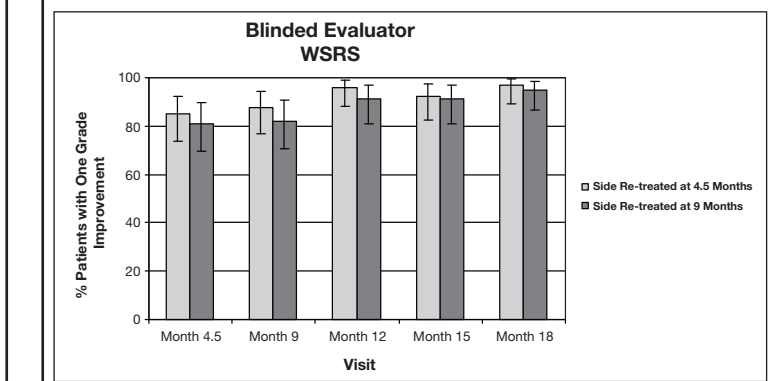
**Demographics:**  
The study enrolled an adult population of predominantly Caucasian, healthy, non-smoking females.

Number of Subjects	Age	Gender	Race	Prior Augmentation to NLF		History of Tobacco Use		History of Sun Exposure	
				Yes	No	Yes	No	Yes	No
75	Mean ± SD 53.8 ± 8.4	Male 5 (6.7%)	White 50 (66.7%)	Yes 6 (8.0%)	No 65 (73.3%)	Yes 20 (26.7%)	No 20 (26.7%)	Yes 12 (16.0%)	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%)	No 12 (16.0%)		
Minimum	26		Hispanic 22 (29.3%)						
Maximum	73								

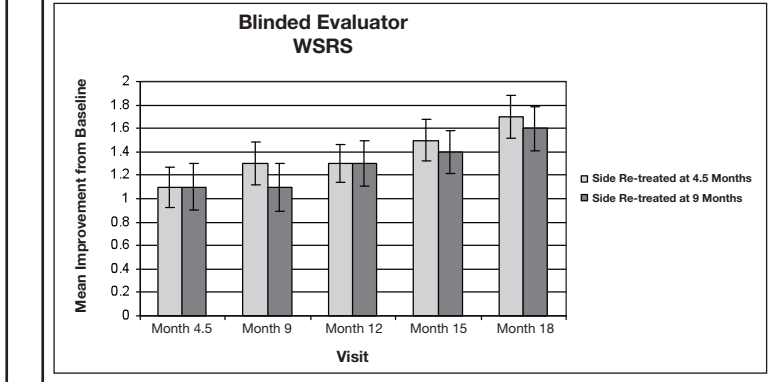
**Volume (mL) of *Restylane* Treatment Used by Visit**

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 PR 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.

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

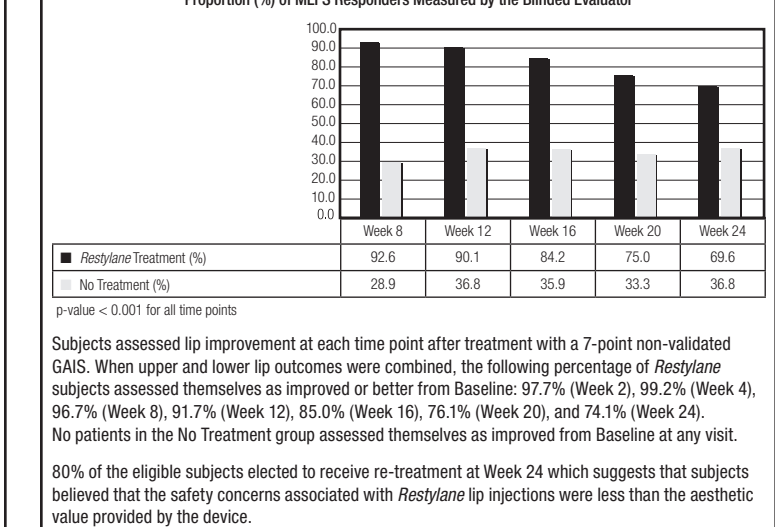
Characteristics		Total (N=180)	Characteristics		Total (N=180)
<b>Age (years)</b>			<b>Race</b>		
n	180		American Indian/Alaskan Native	2 (1%)	
Mean (S.D.)	47.6 (10.6)		Black/African American	2 (1%)	
Median	50.0		Native Hawaiian/Pacific Islander	1 (<1%)	
Minimum	18		Asian	0	
Maximum	65		White	169 (94%)	
<b>Gender</b>			Other	6 (3%)	
Male	1 (<1%)		<b>Ethnicity</b>		
Female	179 (99%)		Not Hispanic or Latino	161 (89%)	
<b>Fitzpatrick Skin</b>			Hispanic or Latino	19 (11%)	
I, II, and III	139 (77%)		<b>Fitzpatrick Skin</b>		
IV and V	41 (23%)		I, II, and III	139 (77%)	
			IV and V	41 (23%)	

**Volume (mL) of *Restylane* used:**

Assessment (upper and lower lips)	Initial Treatment		6 Month Treatment	
	No Treatment (N=45)	<i>Restylane</i> (1st Treatment) (N=150)	No Treatment (1st Treatment) (N=45)	<i>Restylane</i> (2nd Treatment) (N=150)
<b>Volume of injection (mL) (includes treatment and touch up)</b>				
n	45	150	45	150
Mean (S.D.)	0.0	2.853 (0.984)	0.0	2.387 (1.380)
Median	0.0	2.000	0.0	1.700
Minimum	0.0	0.60	0.0	0.03
Maximum	0.0	5.60	0.0	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.



**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

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*
Lip Improvement Using the Blinded Evaluator's Assessment <sup>1</sup>	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

\* Due to the protocol deviation, the live blinded evaluator's assessment was a photo assessment.

**Outcomes**

Lip	Mean Volume Used	
	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.

- Unscrew the tip cap (B) of the syringe carefully.
- 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.
- Grasp the wider part of the needle shield firmly (D).
- Press and turn the needle shield 90° (a quarter turn).
- The quarter turn is necessary to lock the needle onto the syringe.
- Remove the patient record label marked with three small arrows (E) and attach to patient chart.
- Pull off the needle shield.

**F. Serial Puncture**  
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.

**G. Linear Threading (includes retrograde and antegrade)**  
Linear threading (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 vermilion of the lip, the retrograde linear threading technique is the most advisable.

**H. Cross-hatching**  
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.

**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 1/2" or 29 G x 1/2"). 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 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