

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

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.

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. Refer to the adverse experiences section for details.
- *Restylane* must not be implanted into blood vessels. Localized superficial necrosis may occur after injection in or near dermal vessels, such as the 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.

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. 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.
- As with all transcutaneous procedures, *Restylane* implantation carries a risk of infection. Standard precautions associated with injectable materials should be followed.
- ~~The safety and efficacy of *Restylane* for lip augmentation has not been established.~~
- 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 430-610 patients (including 151-153 African-Americans and 37-78 other patients of Fitzpatrick ~~Skin-skin~~ Types-types IV, V and VI). For additional information please refer to Studies MA-1300-15, MA-04-003, 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.
- *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 ~~four~~five U.S. studies that reported adverse experiences.

In three U.S. studies (i.e., Study MA-1400-01, Study MA-1400-02, and 31GE0003) involving 430 patients at 33 centers, the adverse outcomes reported in patient diaries during 14 days after treatment 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 97. 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. Table 108 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 119. 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.

In the fifth U.S. study (MA-1300-15) involving 180 subjects at 12 centers, the adverse outcomes reported in subject diaries are presented in Tables 7 and 8. Physician reported treatment emergent adverse events reported 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 retreatment in the lips with *Restylane*.

Table 1. Maximum Intensity of Symptoms after Initial Treatment, 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%)

¹Events 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, 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 (%)
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, Patient Diary (Study MA-1400-02) ¹										
	<i>Restylane</i>	<i>Perlane</i>	<i>Restylane</i> Patients				<i>Perlane</i> Patients			
	Total patients reporting symptoms	Total patients reporting symptoms	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 (%)	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

¹Missing values are not reported.

²Prospective definitions for: tolerable, affected daily activity and disabling were not provided in the diary or protocol.

³Two 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, Patient Diary (Study MA-1400-02) ¹										
	<i>Restylane</i> Patients	<i>Perlane</i> Patients	<i>Restylane</i> Patients				<i>Perlane</i> Patients			
	Total Patients reporting symptoms n (%)	Total Patients reporting symptoms n (%)	Number of days ²				Number of days ²			
			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%)

¹Missing values are not reported.

²Data are cumulated from up to four injection sites per patient with earliest and latest time point for any reaction provided.

³Two 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, Patient Diary (Study MA-1400-01)^{1,2}

	<i>Restylane</i>	<i>Perlane</i>	<i>Restylane Patients</i>				<i>Perlane Patients</i>			
	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%)	0 (0%)	NA	3 (100%)	0 (0%)	0 (0%)

¹Missing values are not reported.

²Events are reported as local events; because of the design (split-face) of the study, causality of the systemic adverse events cannot be assigned.

³Prospective definitions for: tolerable, affected daily activity and disabling were not provided in the diary or protocol.

⁴Two 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, Patient Diary (Study MA-1400-01)^{1,2}

	<i>Restylane Patients</i>	<i>Perlane Patients</i>	<i>Restylane Patients</i>				<i>Perlane Patients</i>			
	Total patients reporting symptoms n (%)	Total patients reporting symptoms n (%)	Number of days ³				Number of days ³			
			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%)

¹Missing values are not reported.

²Events are reported as local events; because of the design (split-face) of the study, causality of the systemic adverse events cannot be assigned.

³Data are cumulated from up to two injection sites per patient with earliest and latest time point for any reaction provided.

⁴Two patients reported mild transient headache and one patient reported mild "twitching"; neither could be associated with a particular product.

Table 7. MA-1300-15 Intensity of Adverse Event, Subject Diary

	No Treatment (N = 45) Subjects Reporting Symptoms	1 st Treatment (N=172) Subjects Reporting Symptoms	2 nd treatment (N = 93) Subjects Reporting Symptoms	No Treatment (N = 45)				1 st Treatment with Restylane (N=172)				2 nd Treatment with Restylane (N = 93)			
				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 Lip	1	167	86	38 (97%)	1 (3%)	0	0	2 (1%)	90 (53%)	62 (37%)	15 (9%)	3 (3%)	59 (66%)	23 (26%)	4 (4%)
Lower Lip	2	161	79	37 (95%)	2 (5%)	0	0	7 (4%)	98 (58%)	51 (30%)	12 (7%)	9 (10%)	54 (61%)	22 (25%)	3 (3%)
Bruising															
Upper Lip	1	130	54	38 (97%)	1 (3%)	0	0	39 (23%)	97 (57%)	28 (17%)	5 (3%)	35 (39%)	44 (49%)	9 (10%)	1 (1%)
Lower Lip	2	132	48	37 (95%)	2 (5%)	0	0	36 (21%)	107 (64%)	22 (13%)	3 (2%)	40 (45%)	40 (45%)	7 (8%)	1 (1%)
Redness															
Upper Lip	0	126	55	39 (100%)	0	0	0	43 (25%)	115 (68%)	11 (7%)	0	34 (38%)	50 (56%)	2 (2%)	3 (3%)
Lower Lip	1	120	54	38 (97%)	1 (3%)	0	0	48 (29%)	112 (67%)	8 (5%)	0	34 (39%)	49 (56%)	3 (3%)	2 (2%)
Swelling															
Upper Lip	0	166	85	39 (100%)	0	0	0	3 (2%)	92 (54%)	64 (38%)	10 (6%)	4 (4%)	62 (70%)	20 (22%)	3 (3%)
Lower Lip	0	158	77	39 (100%)	0	0	0	10 (6%)	102 (61%)	48 (29%)	8 (5%)	11 (13%)	54 (61%)	21 (24%)	2 (2%)

Table 7. MA-1300-15 Intensity of Adverse Event, Subject Diary

	No Treatment (N = 45) Subjects Reporting Symptoms	1 st Treatment (N=172) Subjects Reporting Symptoms	2 nd treatment (N = 93) Subjects Reporting Symptoms	No Treatment (N = 45)				1 st Treatment with Restylane (N=172)				2 nd Treatment with Restylane (N = 93)			
				None	Tolerable	Affects Daily Activity	Disabling	None	Tolerable	Affects Daily Activity	Disabling	None	Tolerable	Affects Daily Activity	Disabling
Pain (includes burning)															
Upper Lip	0	143	67	39 (100%)	0	0	0	26 (15%)	111 (66%)	25 (15%)	7 (4%)	22 (25%)	51 (57%)	13 (15%)	3 (3%)
Lower Lip	0	134	62	39 (100%)	0	0	0	34 (20%)	107 (64%)	20 (12%)	7 (4%)	26 (30%)	47 (53%)	13 (15%)	2 (2%)
Tenderness															
Upper Lip	0	162	78	39 (100%)	0	0	0	7 (4%)	120 (71%)	38 (22%)	4 (2%)	11 (12%)	61 (69%)	14 (16%)	3 (3%)
Lower Lip	1	152	72	38 (97%)	1 (3%)	0	0	16 (10%)	116 (69%)	32 (19%)	4 (2%)	16 (18%)	55 (63%)	15 (17%)	2 (2%)
Itching															
Upper Lip	0	49	19	39 (100%)	0	0	0	120 (71%)	46 (27%)	3 (2%)	0	70 (79%)	18 (20%)	1 (1%)	0
Lower Lip	0	48	19	39 (100%)	0	0	0	120 (71%)	45 (27%)	3 (2%)	0	69 (78%)	19 (22%)	0	0

Note: "Other" symptoms were reported by 72 subjects receiving their first treatment with Restylane, and the most frequently reported symptoms were lump(s)/bump(s), difficulty drinking, eating or talking, dryness, chapped lips, blisters, peeling, tingling, numbness, sore/soreness, cold sore(s)/sore(s), trouble whistling, stiffness, and unevenness. "Other" symptoms were reported by 17 subjects receiving a second treatment with Restylane, and the most frequently reported symptoms were lump(s)/bump(s), chapped lips, dryness, peeling, cold sores, hurt lips, unevenness, soreness, blister, and tingling. Severity of "other" symptoms could not be assessed.

Table 8. MA-1300-15 Duration of Adverse Event, Subject Diary
No Treatment at Baseline
(N = 45)

Location/ Adverse Event	Number of Days				
	Any n (%)	1 n (%)	2-7 n (%)	8-13 n (%)	14 n (%)
Upper Lip					
Bruising	1 (2%)	1 (100%)	0	0	0
Redness	0	0	0	0	0
Swelling	0	0	0	0	0
Pain (includes Burning)	0	0	0	0	0
Tenderness	0	0	0	0	0
Itching	0	0	0	0	0
Lower Lip					
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)					
Location/ Adverse Event	Number of Days				
	Any ¹ n (%)	1 n (%)	2-7 n (%)	8-13 n (%)	14 n (%)
Upper Lip					
Bruising	130 (76%)	8 (6%)	88 (68%)	31 (24%)	3 (2%)
Redness	126 (73%)	20 (16%)	86 (68%)	19 (15%)	1 (<1%)
Swelling	166 (97%)	7 (4%)	95 (57%)	43 (26%)	21 (13%)
Pain (includes Burning)	143 (83%)	37 (26%)	94 (66%)	10 (7%)	2 (1%)
Tenderness	162 (94%)	15 (9%)	84 (52%)	45 (28%)	18 (11%)
Itching	49 (28%)	17 (35%)	27 (55%)	5 (10%)	0
Lower Lip					
Bruising	132 (77%)	11 (8%)	99 (75%)	19 (14%)	3 (2%)
Redness	120 (70%)	21 (18%)	84 (70%)	14 (12%)	1 (<1%)
Swelling	158 (92%)	7 (4%)	93 (59%)	34 (22%)	24 (15%)
Pain (includes Burning)	134 (78%)	35 (26%)	86 (64%)	12 (9%)	1 (<1%)
Tenderness	152 (88%)	10 (7%)	84 (55%)	39 (26%)	19 (13%)
Itching	48 (28%)	15 (31%)	29 (60%)	4 (8%)	0
Second Treatment with Restylane (N = 93)					
Location/ Adverse Event	Number of Days				
	Any ¹ n (%)	1 n (%)	2-7 n (%)	8-13 n (%)	14 n (%)
Upper Lip					
Bruising	54 (58%)	6 (11%)	36 (67%)	12 (22%)	0
Redness	55 (59%)	13 (24%)	37 (67%)	5 (9%)	0
Swelling	85 (91%)	9 (11%)	53 (62%)	20 (24%)	3 (4%)
Pain (includes Burning)	67 (72%)	19 (28%)	42 (63%)	4 (6%)	2 (3%)
Tenderness	78 (84%)	5 (6%)	52 (67%)	14 (18%)	7 (9%)
Itching	19 (20%)	9 (47%)	10 (53%)	0	0
Lower Lip					
Bruising	48 (52%)	4 (8%)	36 (75%)	8 (17%)	0
Redness	54 (58%)	15 (28%)	34 (63%)	4 (7%)	1 (2%)
Swelling	77 (83%)	11 (14%)	50 (65%)	12 (16%)	4 (5%)
Pain (includes Burning)	62 (67%)	17 (27%)	40 (65%)	2 (3%)	3 (5%)
Tenderness	72 (77%)	4 (6%)	48 (67%)	14 (19%)	6 (8%)
Itching	19 (20%)	8 (42%)	11 (58%)	0	0

Duration of "other" diary symptoms could not be calculated.

Table 97 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 97. All Investigator-Identified Adverse Experiences (72 Hours)
Number of Events per Patient per Study

Study Term	MA-1400-01		MA-1400-02	
	Number of Events <i>Restylane</i> (N=150)	Number of Events <i>Perlane</i> (N=150)	Number of Events <i>Restylane</i> (N=142)	Number of Events <i>Perlane</i> (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 108 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.

Table 108. Investigator-Identified Adverse Experiences (2 Weeks or More After Implantation) (Number of Patients) (<i>Restylane</i> v. Specified Active Controls – All Studies)						
Study Term	MA-1400-01 <i>Restylane</i> (n=150) (%)	MA-1400-01 <i>Perlane</i> (n=150) (%)	MA-1400-02 <i>Restylane</i> (n=142) (%)	MA-1400-02 <i>Perlane</i> (n=141) (%)	31GE0003 <i>Restylane</i> (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%)

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

Adverse Event	Number of Subjects with Events (%) N=75	Total Number of Events [†]	Severity		
			Mild	Moderate	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.

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.

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

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	222	99 (58%)	101	51 (55%)
Tenderness	0	0	69	38 (22%)	29	16 (17%)
Nasopharyngitis	3	2 (4%)	9	9 (5%)	2	2 (2%)
Contusion (bruising/ ecchymosis)	0	0	130	75 (44%)	40	25 (27%)
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.

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 acneiform 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 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 one adverse event has 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.

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 cross-linked collagen and cross-linked hyaluronic acid dermal fillers with respect to the correction of moderate to severe facial folds and wrinkles, such as nasolabial folds.

U.S. Clinical Studies

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

Design	<p>1:1 randomized, prospective study at 6 U.S. centers, which compared the safety and effectiveness of <i>Restylane</i> and <i>Zyplast</i> in a “within-patient” control model of augmentation correction of bilateral nasal folds, using <i>Restylane</i> 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.</p> <p>Effectiveness was studied with 6-month follow-up. Safety was studied with 12-month follow-up.</p>
Endpoints	<p>Effectiveness</p> <p>Primary: The difference in effect of <i>Restylane</i> and <i>Zyplast</i> on the visual severity of the nasolabial folds, as assessed by an Evaluating Investigator at 6 months after baseline.</p> <p>Secondary: Wrinkle Severity Rating Scale (WSRS) score assessed at other follow-up points by the evaluating investigator and by the subject.</p> <p>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.</p> <p>Number of treatment sessions to achieve optimal cosmesis.</p> <p>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.</p> <p>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.</p>

Randomized study, continued

Outcomes	<p>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.</p> <ul style="list-style-type: none"> • Gender <table style="margin-left: 20px; border: none;"> <tr> <td>Male:</td> <td>9</td> <td>(6.6%)</td> </tr> <tr> <td>Female:</td> <td>128</td> <td>(93.4%)</td> </tr> </table> • Ethnicity <table style="margin-left: 20px; border: none;"> <tr> <td>Caucasian:</td> <td>122</td> <td>(89.0%)</td> </tr> <tr> <td>Black:</td> <td>2</td> <td>(1.5%)</td> </tr> <tr> <td>Asian:</td> <td>2</td> <td>(1.5%)</td> </tr> <tr> <td>Hispanic:</td> <td>11</td> <td>(8.0%)</td> </tr> </table> • Tobacco use <table style="margin-left: 20px; border: none;"> <tr> <td>Non-smokers:</td> <td>118</td> <td>(86.1%)</td> </tr> <tr> <td>Smokers:</td> <td>19</td> <td>(13.9%)</td> </tr> </table> • Sun Exposure <table style="margin-left: 20px; border: none;"> <tr> <td>None:</td> <td>83</td> <td>(60.6%)</td> </tr> <tr> <td>Natural Sun:</td> <td>52</td> <td>(38.0%)</td> </tr> <tr> <td>Artificial:</td> <td>2</td> <td>(1.5%)</td> </tr> </table> <p>Effectiveness Primary: Based on the per patient evaluation, the WSRS scores at 6 months by the evaluating investigator demonstrated that WSRS for</p> <table style="margin-left: 40px; border: none;"> <tr> <td><i>Restylane</i> was lower (better) than Control:</td> <td style="text-align: right;">in 78 patients</td> </tr> <tr> <td><i>Restylane</i> was equal to Control:</td> <td style="text-align: right;">in 46 patients</td> </tr> <tr> <td><i>Restylane</i> was higher (worse) than Control:</td> <td style="text-align: right;">in 13 patients</td> </tr> </table> <p>For the entire cohort, however, the Mean of the WSRS Score by evaluating investigator demonstrated that while there was essentially no difference between <i>Restylane</i> 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.</p> <table border="1" style="margin-left: 40px; border-collapse: collapse; width: 100%;"> <thead> <tr style="background-color: black; color: white;"> <th colspan="5">Table 1349. Blinded Evaluator Mean Wrinkle Severity Scores</th> </tr> <tr> <th></th> <th>N</th> <th><i>Restylane</i></th> <th>Control</th> <th>Absolute Difference</th> </tr> </thead> <tbody> <tr> <td>Pre-treatment</td> <td>138</td> <td>3.29</td> <td>3.31</td> <td>0.02</td> </tr> <tr> <td>Baseline</td> <td>138</td> <td>1.80</td> <td>1.79</td> <td>0.01</td> </tr> <tr> <td>6 months</td> <td>134</td> <td>2.36</td> <td>2.94</td> <td>0.58</td> </tr> </tbody> </table>	Male:	9	(6.6%)	Female:	128	(93.4%)	Caucasian:	122	(89.0%)	Black:	2	(1.5%)	Asian:	2	(1.5%)	Hispanic:	11	(8.0%)	Non-smokers:	118	(86.1%)	Smokers:	19	(13.9%)	None:	83	(60.6%)	Natural Sun:	52	(38.0%)	Artificial:	2	(1.5%)	<i>Restylane</i> was lower (better) than Control:	in 78 patients	<i>Restylane</i> was equal to Control:	in 46 patients	<i>Restylane</i> was higher (worse) than Control:	in 13 patients	Table 1349. Blinded Evaluator Mean Wrinkle Severity Scores						N	<i>Restylane</i>	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
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MA-1400-02: Prospective, Randomized, Blinded, Controlled Clinical Study

Design	<p>1:1 randomized, prospective study at 17 U.S. centers, which compared the safety and effectiveness of <i>Restylane</i> and <i>Perlane</i> following treatment to baseline condition. Patients were randomized to either <i>Restylane</i> or <i>Perlane</i> 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.</p> <p>Effectiveness was studied with 6 months follow-up. Safety was studied with 6 months follow-up.</p>
Endpoints	<p>Effectiveness</p> <p>Primary: The difference in effect of <i>Restylane</i> at week 12 versus baseline condition on the visual severity of the nasolabial folds, as assessed by the Blinded Evaluator.</p> <p>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 <i>Restylane</i> to <i>Perlane</i>.</p> <p>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).</p> <p>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.</p>
Outcomes	<p>Demographics: The study enrolled 283 (i.e., 142 <i>Restylane</i> and 141 <i>Perlane</i>) 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 <i>Restylane</i>. The greatest amount used in any patient was 8.8 mL.</p> <p>Gender – Female: 266 (94%); Male: 17 (6%)</p>

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 144. 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 144: Blinded Evaluator Wrinkle Severity Response Scores

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%) 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

¹All *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	<p>1:1 randomized, prospective study at 10 U.S. centers, which compared the safety and effectiveness of <i>Restylane</i> and <i>Perlane</i> following treatment to baseline condition in 150 patients with pigmented skin and predominantly African-American ethnicity. Patients were randomized to <i>Restylane</i> or <i>Perlane</i> 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.</p> <p>Effectiveness was studied with 6 months follow-up. Safety was studied with 6 months follow-up.</p>
Endpoints	<p>Effectiveness</p> <p>Primary: The difference in effect of <i>Restylane</i> at week 12 versus baseline condition on the visual severity of the NLFs.</p> <p>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 <i>Restylane</i> to <i>Perlane</i>.</p> <p>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.</p> <p>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.</p>

Outcomes	<p>Demographics: The study enrolled 150 patients with moderate to severe NLF wrinkles. The patients were predominantly healthy African-American females.</p> <p>Gender – Female: 140/150 (93%); Male 10/150 (7%)</p> <p>Ethnicity – White: 2 (1.3%); Hispanic or Latino: 9 (6%); African-American: 137 (91%); American Indian: 2 (1.3%)</p> <p>Fitzpatrick Skin Type – I to III: 0 (0%); IV: 44 (29%); V: 68 (45%); VI: 38 (25%)</p> <p>Efficacy: The results of the live blinded evaluator assessment of wrinkle severity for <i>Restylane</i> and control (<i>Perlane</i>) are presented in Table 152 and are based on the Intent-to-Treat analysis. In the primary effectiveness assessment at 12 weeks, 93% of the <i>Restylane</i>[®] treated and 92% of the <i>Perlane</i>-treated NLF maintained at least a 1 point improvement over baseline.</p> <p style="text-align: center;">Table 152: Live Evaluator Wrinkle Severity Response Scores</p> <table border="1"> <thead> <tr> <th>Time point</th> <th>No. of patients</th> <th>No. of <i>Restylane</i> Pts. maintaining 1 Unit Improvement on WSRS</th> <th>95% <i>Restylane</i> Confidence Interval</th> <th>No. of <i>Perlane</i> Pts. maintaining ¹ 1 Unit Improvement on WSRS</th> <th>95% <i>Perlane</i> Confidence Interval</th> </tr> </thead> <tbody> <tr> <td>6 weeks</td> <td>148</td> <td>142 (96%)¹</td> <td>92-99%</td> <td>140 (95%)¹</td> <td>90-99%</td> </tr> <tr> <td>12 weeks</td> <td>149</td> <td>139 (93%)¹</td> <td>89-98%</td> <td>137 (92%)¹</td> <td>87-97%</td> </tr> <tr> <td>24 weeks</td> <td>147</td> <td>108 (73%)¹</td> <td>66-81%</td> <td>104 (71%)¹</td> <td>63-77%</td> </tr> </tbody> </table> <p style="text-align: center;">¹All <i>p</i> values <0.0001 based on t-test compared to baseline condition</p> <p>Antibody Testing: 9/150 (6%) subjects displayed a pre-treatment antibody response against <i>Restylane</i> (which was believed to be related to co-purifying <i>Streptococcus</i> capsule antigens). No subjects developed a measurable increase in antibody titer after <i>Restylane</i> injection. 1/6 (17%) patients with antibodies against <i>Restylane</i> had adverse experiences at the injection site as compared to the local adverse event rate observed in the entire <i>Restylane</i> population (i.e., 28/150 (18.7%)). All the adverse experiences in the patients with a humoral response against <i>Restylane</i> were mild in severity. Immediate type skin testing demonstrated that no patient developed IgE to <i>Restylane</i>. Post-exposure histopathology of skin biopsies of an implant site on each patient demonstrated that no patient developed cell-mediated immunity to <i>Restylane</i>.</p>	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 1 Unit Improvement on WSRS	95% <i>Perlane</i> 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%
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 1 Unit Improvement on WSRS	95% <i>Perlane</i> Confidence Interval																				
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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	<p>Randomized, evaluator-blinded study at 3 U.S. centers, which compared the safety and effectiveness of <i>Restylane</i> using two re-treatment schedules. Initially <i>Restylane</i> was injected in both nasolabial folds (NLF). Subsequently, one NLF was retreated at 4.5 months after the initial treatment. The contralateral NLF was treated with <i>Restylane</i> and re-treated at 9 months (\pm 1 week). The Blinded Evaluators were blinded to the re-treatment schedule while patients and treating physicians were not.</p> <p>Effectiveness was studied at 18 months after the initial injection (i.e., either 9 or 13.5 months after the second treatment).</p>
Endpoints	<p>Effectiveness</p> <p>Primary:</p> <p>The difference in effect of <i>Restylane</i> 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.</p> <p>Secondary:</p> <p>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.</p> <p>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 subject. The GAIS is a 5-point scale for assessing global aesthetic improvement: “very much improved / much improved / improved / no change / worse.”</p> <p>Safety</p> <p>Severity and duration of injection site reactions and adverse events were recorded.</p>

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
	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

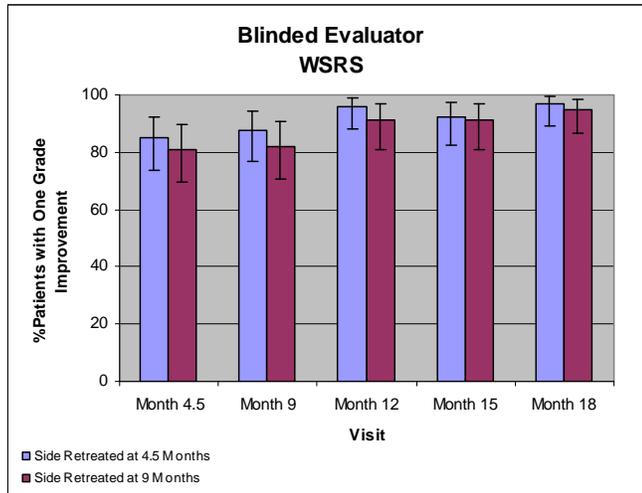
	SCR/TRT	Touch-up	Wk2	M 4.5	M9	M12	M15	M18
Enrolled	75	-	75	75	75	75	75	75
Withdrew Consent (total)	0	-	1	5	6	6	6	7
Lost to Follow-up	0	-	0	2	4	4	4	4
Missed Visit	0	-	2	1	0	1	1	1
Actual	75	44	72	67	65	64	64	64

Volume (mL) of Restylane Treatment Used by Visit

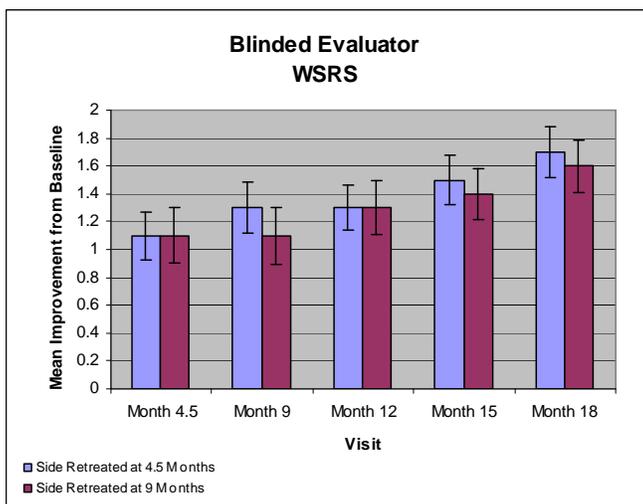
Visit	Side Assigned to Re-treatment at 4.5 Months	Side Assigned to Re-treatment at 9 Months
Baseline		
N	75	75
Mean ± SD	1.1 ± 0.61	1.1 ± 0.56
Median	1.0	1.0
Minimum	0.1	0.2
Maximum	2.5	2.5
Touch-up Visit		
N	44	44
Mean ± SD	0.5 ± 0.22	0.5 ± 0.21
Median	0.5	0.5
Minimum	0.2	0.2
Maximum	1.0	1.0
Re-treatment 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 retreated 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 retreated 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.

<p>Design</p>	<p><u>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 retreated 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.</u></p>
<p>Endpoints</p>	<p>Effectiveness Primary:</p> <p><u>The primary effectiveness objective was to identify whether Restylane was more effective in lip augmentation than no treatment. This was as 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.</u></p> <p><u>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.</u></p> <p>Secondary:</p> <p><u>Secondary effectiveness objectives included:</u></p> <ul style="list-style-type: none">• <u>Assessment of lip fullness augmentation after treatment with <i>Restylane</i> as compared to no treatment, as measured by the blinded evaluator, treating investigator, and IRP 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</u>

	<p><u>lower lips using the MLFS.</u></p> <ul style="list-style-type: none">• <u>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.</u> <p><u>The secondary safety objectives included assessment of lip texture, firmness, symmetry, product palpability, mass formation, lip movement, function, and sensation.</u></p>
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Outcomes

Demographics:

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

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

Volume (mL) of Restylane used:

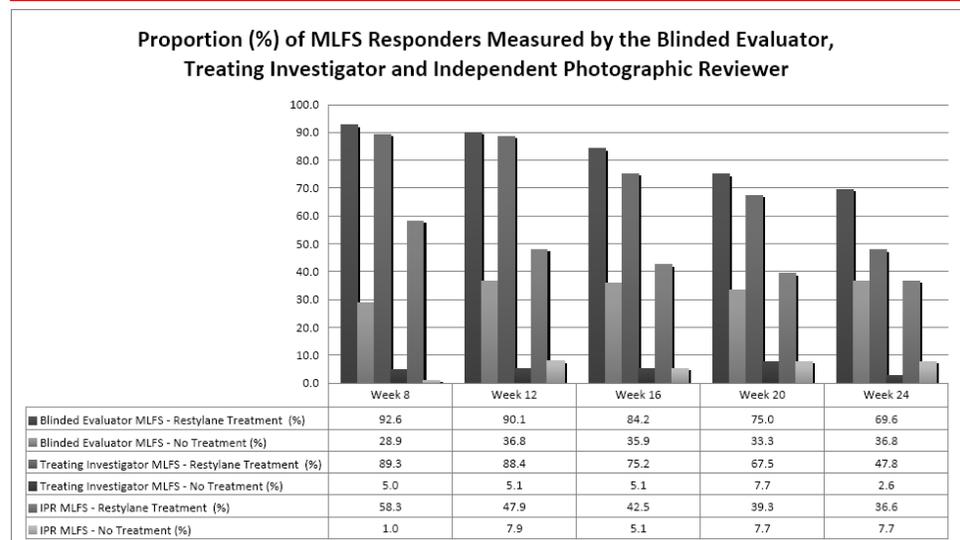
<u>Assessment (upper and lower lips)</u>	<u>Initial Treatment</u>		<u>6 Month Treatment</u>	
	<u>No Treatment (N=45)</u>	<u>Restylane (1st Treatment) (N=135)</u>	<u>No Treatment (1st Treatment) (N=45)</u>	<u>Restylane (2nd Treatment) (N=135)</u>
<u>Volume of Injection (mL) (includes treatment and touch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

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.

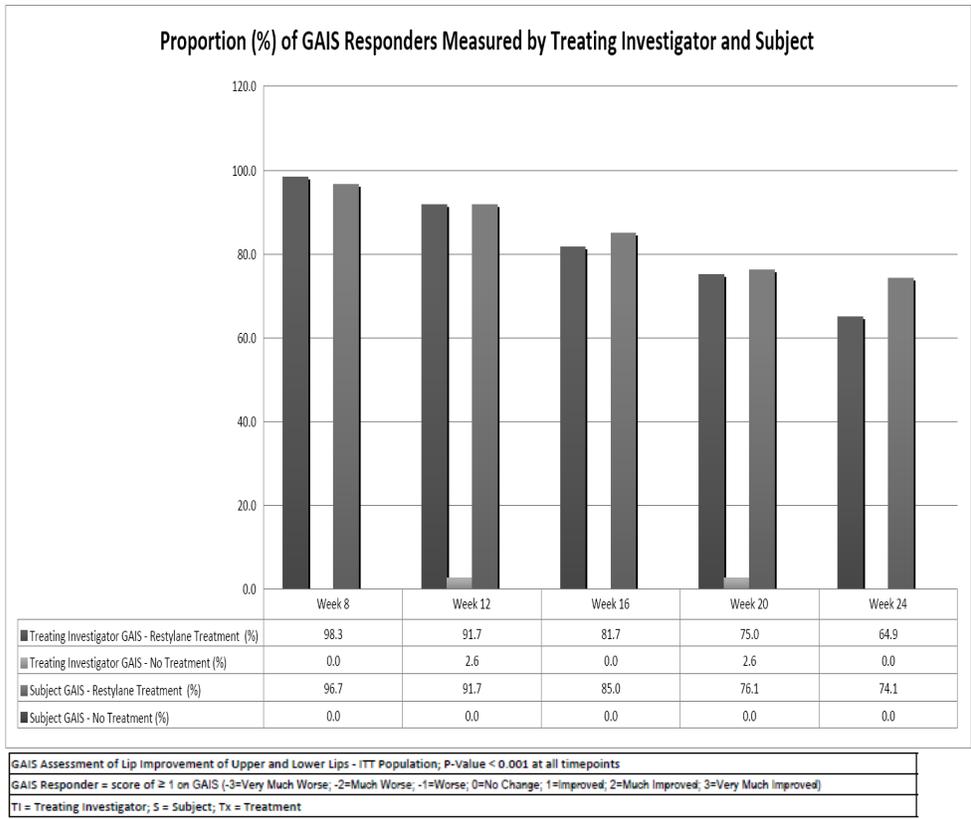
Additionally, subjects and the treating investigators completed an assessment of the appearance of the subject’s lip fullness compared to baseline using the GAIS at post baseline time points, A vast majority of subjects treated with Restylane at baseline were rated as “improved” or better through Week 24 by both the subject and the investigator, whereas subjects in the no treatment group demonstrated virtually no improvement.

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



MLFS Assessment of Lip Fullness of Upper and Lower Lips - ITT Population; P-Value < 0.001 at all timepoints
 MLFS Responder = 1 grade increase from baseline on the MLFS (1=Very Thin; 2=Thin; 3=Medium; 4=Full; 5=Very Full)
 BE = Blinded Evaluator; IPR = Independent Photographic Reviewer; MLFS = Medicis Lip Fullness Scale; TI = Treating Investigator; Tx = Treatment

The results of the treating investigator and subject GAIS assessments are presented in the figure below for subject outcomes at 8, 12, 16, 20 and 24 weeks.



Safety:

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 TEAE 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.

Lip safety assessments, such as lip texture, firmness, symmetry, movement, function, sensation, mass formation, and device palpability were evaluated at the screening visit, as appropriate, and at follow up visits. None of the lip assessments were remarkable or presented any safety concerns providing further evidence that Restylane is well tolerated for soft tissue augmentation in the lips.

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.

Rx only

U.S. PATENT 5,827,937

Manufactured for
Medicis Aesthetics Inc.
7720 N. Dobson Road
Scottsdale, AZ 85256
U.S.A.
Phone: 1-866-222-1480

Manufactured by
Q-Med AB
Seminariegatan 21
SE-752 28 Uppsala
Sweden

Made in Sweden

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All other trademarks are the property of their respective owners.

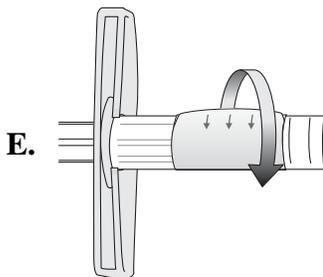
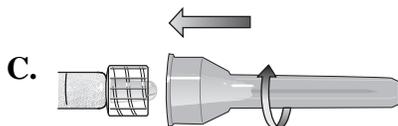
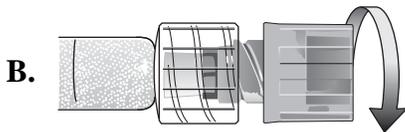
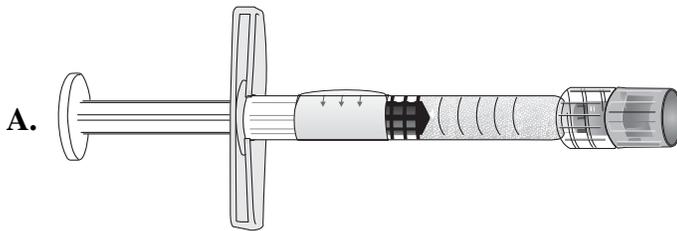
DIRECTIONS FOR ASSEMBLY

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.

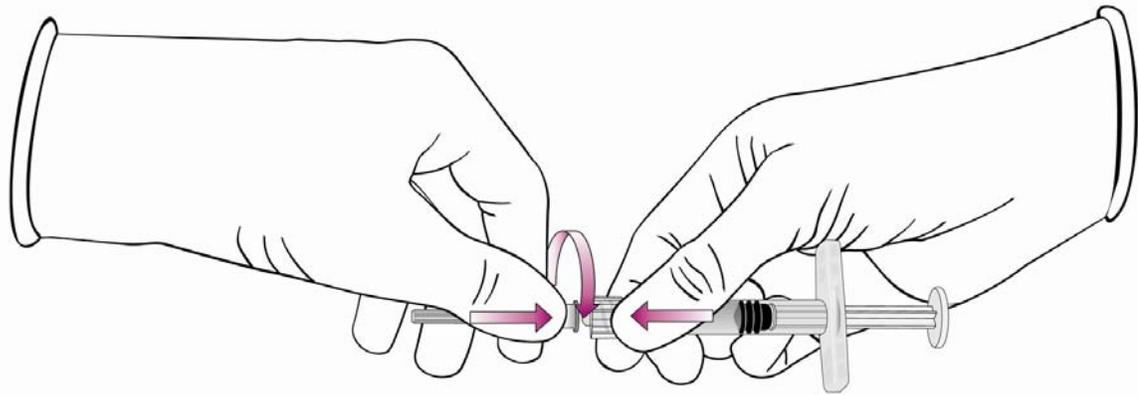
See pictures A through E.

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.



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

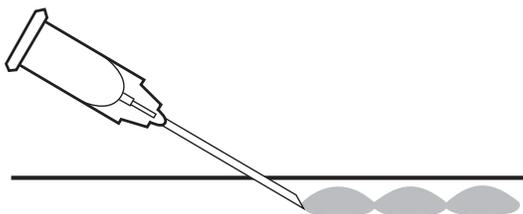
1. It is necessary to counsel the patient and discuss the appropriate indication, risks, benefits and expected responses to the *Restylane* treatment.
Advise the patient of the necessary precautions before commencing the procedure.
2. Assess the patient's need for appropriate anesthetic treatment for 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, ~~or~~ fold, or lip. For the nasolabial folds, *Restylane* should be injected into the mid to deep dermis. For the lips, *Restylane* should be injected into the submucosal layer or other depth as determined to be appropriate for the patient by the physician; care should be taken to avoid intramuscular injection. If *Restylane* is injected too

- superficially this may result in visible lumps and/or bluish discoloration.
- 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.
 - 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.
 - 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.

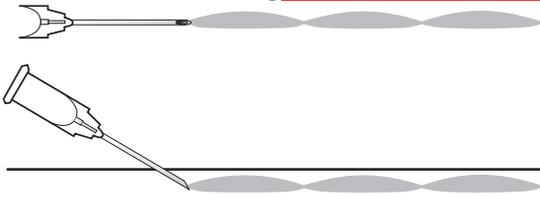
INJECTION TECHNIQUES

- Restylane* can be injected by a number of different techniques that depend on the treating physician's experience and preference, and patient characteristics.
- 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.
- 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.
- Serial threading is a technique that utilizes elements of both approaches.
- 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.
- 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.

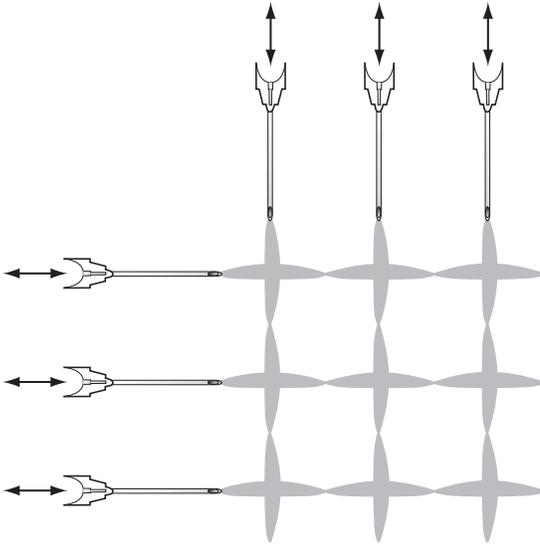
F. Serial Puncture



G. Linear Threading (includes retrograde and antegrade)



H. Cross-hatching



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 superficial bone 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 needs 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 a few days.

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.

Revised: ~~August-November~~ 2010

90-18250-~~XX~~