Restylane® Lyft with Lidocaine

Injectable Gel with 0.3% Lidocaine

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

Description

Restylane® Lyft with Lidocaine is a sterile gel of hyaluronic acid generated by *Streptococcus* species of bacteria, chemically cross-linked with BDDE, stabilized and suspended in phosphate buffered saline at pH=7 and concentration of 20 mg/mL with 0.3% lidocaine.

Indication

Restylane® Lyft with Lidocaine is indicated for implantation into the deep dermis to superficial subcutis for the correction of moderate to severe facial folds and wrinkles, such as nasolabial folds.

Restylane® Lyft with Lidocaine is indicated for subcutaneous to supraperiosteal implantation for cheek augmentation and correction of age-related midface contour deficiencies in patients over the age of 21.

Contraindications

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

Warnings

- Defer use of *Restylane® Lyft with Lidocaine* 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® Lyft with Lidocaine* have been observed as consisting mainly of short-term minor or moderate inflammatory symptoms starting early after treatment and with less than 2 weeks duration. Refer to the adverse reactions section for details.

- Introduction of Restylane® Lyft with Lidocaine into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction. Take extra care when injecting soft tissue fillers, for example inject the product slowly and apply the least amount of pressure necessary. Rare but serious adverse events associated with the intravascular injection of soft tissue fillers in the face have been reported and include temporary or permanent vision impairment, blindness, cerebral ischemia or cerebral hemorrhage, leading to stroke, skin necrosis, and damage to underlying facial structures. Immediately stop the injection if a patient exhibits any of the following symptoms, including changes in vision, signs of a stroke, blanching of the skin, or unusual pain during or shortly after the procedure. Patients should receive prompt medical attention and possibly evaluation by an appropriate health care practitioner specialist should an intravascular injection occur.

- As with all dermal filler procedures, *Restylane® Lyft with Lidocaine* should not be used in vascular rich areas. Use in these highly vascularized areas, such as glabella and nose, has resulted in cases of vascular embolization and symptoms consistent with ocular vessel occlusion, such as blindness, and with brain vessel occlusion resulting in cerebral infarction.

- 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® Lyft with Lidocaine* is packaged for single patient use. Do not resterilize. Do not use if package is opened or damaged.
- For the treatment of moderate to severe facial wrinkles and folds, the maximum recommended dose per treatment is 6.0 mL based on U.S. clinical studies. For cheek augmentation implantation and the treatment of age-related midface volume deficit in patients over the age of 21, the maximum recommended dose is also 6.0 mL per treatment. The safety of injecting greater amounts has not been established.
- The safety or effectiveness of *Restylane® Lyft with Lidocaine* for the treatment of anatomic regions other than nasolabial folds and midface area has not been established in controlled clinical studies.
- Long term safety and effectiveness of *Restylane® Lyft with Lidocaine* beyond one year have not been investigated in clinical trials.
- As with all transcutaneous procedures, *Restylane® Lyft with Lidocaine* implantation carries a risk of infection. Standard precautions associated with injectable materials should be followed.
- The safety and efficacy of *Restylane® Lyft with Lidocaine* for lip augmentation has not been established.
- The safety of *Restylane® Lyft with Lidocaine* 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® Lyft with Lidocaine* ®. Keloid formation was not observed in studies involving 709 patients (including 160 African-Americans and 76 other patients of Fitzpatrick Skin Types IV, V and VI). For additional information please refer to Studies MA-1400-02, MA-1400-01, 31GE0002, 31GE0101, and MA-1400-05 in the Clinical Trials Section. In study MA-1400-03 with *Restylane® Lyft with Lidocaine* and *Perlane®*, there were 51.7% (31/60) of patients with Fitzpatrick Skin Types IV, V, and VI and no reports of keloid formation.
- *Restylane® Lyft with Lidocaine* injection may cause hyperpigmentation at the injection site. In a clinical study of 150 patients with pigmented skin (of African-American heritage and Fitzpatrick Skin Types IV, V, and VI), the incidence of post-inflammatory hyperpigmentation was 6% (9/150). 50% of these events lasted up to six weeks after initial implantation. In study MA-1400-03 with *Perlane®* and *Restylane® Lyft with Lidocaine*, there were 51.7% (31/60) of patients with Fitzpatrick Skin Types IV, V, and VI and no reports of hyperpigmentation. In study MA-1400-05 with *Restylane® Lyft with Lidocaine*, there were 30.5% (61/200) of patients with Fitzpatrick Skin Types IV, V, and VI and no reports of hyperpigmentation.
- *Restylane® Lyft with Lidocaine* should be used with caution in patients on immunosuppressive therapy.
- Bruising or bleeding may occur at *Restylane® Lyft with Lidocaine* injection sites. *Restylane® Lyft with Lidocaine* 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® Lyft with Lidocaine* 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® Lyft with Lidocaine*, there is a possible risk of eliciting an inflammatory reaction at the implant site. This also applies if *Restylane® Lyft with Lidocaine* is administered before the skin has healed completely after such a procedure.
- Injection of *Restylane® Lyft with Lidocaine* into patients with a history of previous herpetic eruption may be associated with reactivation of the herpes.
- *Restylane® Lyft with Lidocaine* 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 Galderma Laboratories, L.P. at 1-855-425-8722. Glass is also 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® Lyft with Lidocaine* should not be mixed with other products before implantation of the device.
- Cheek augmentation or correction of age-related midface contour deficiencies in patients over the age of 21, with *Restylane® Lyft with Lidocaine* should only be performed by physicians who have appropriate experience and who are knowledgeable about the anatomy and the product for use in deep (subcutaneous and/or supraperiosteal) injection for cheek augmentation.
- In order to minimize the risks of potential complications, this product should only be used by health care practitioners who have appropriate training, experience, and who are knowledgeable about the anatomy at and around the site of injection.
- Health care practitioners are encouraged to discuss all potential risks of soft tissue injection with their patients prior to treatment and ensure that patients are aware of signs and symptoms of potential complications.

Adverse Experiences

Restylane® Lyft with Lidocaine is indicated for implantation into the deep dermis to superficial subcutis for the correction of moderate to severe facial folds and wrinkles, such as nasolabial folds and for subcutaneous to supraperiosteal implantation for cheek augmentation and correction of age-related midface contour deficiencies in patients over the age of 21. Adverse event information for *Restylane® Lyft with Lidocaine* use in the correction of moderate to severe facial folds and wrinkles, such as nasolabial folds is presented in Tables 1-10 and for cheek augmentation and correction of age-related midface contour deficiencies is presented in Tables 11-13.

***Restylane® Lyft with Lidocaine* for the correction of moderate to severe facial folds and wrinkles, such as nasolabial folds.**

There were five US studies that reported adverse events in support of the indication for treatment of moderate to severe facial folds and wrinkles, such as nasolabial folds.

In two U.S. studies (i.e., Study MA-1400-01 and Study MA-1400-02) involving 433 patients at 25 centers, the adverse outcomes reported in patient diaries during 14 days after treatment are presented in Tables 1–4. The physician diagnosed adverse events identified in these studies at 72 hours after injection are presented in Table 7. In Study MA-1400-01, 150 patients were injected with *Perlane®* on one side of the face and *Restylane®* on the other side of the face. In study MA-1400-02, 283 patients were randomized to receive either *Perlane®* or *Restylane®* injection on both sides of the face. Table 8 presents all investigator-identified adverse events recorded at study visits 2 weeks or more after injection in studies MA-1400-01, MA-1400-02, 31GE0101 and 31GE0002. In Study 31GE0101, 150 Canadian patients were injected with both *Perlane®* and Hylaform®. In Study 31GE0002, 68 Scandinavian patients underwent both *Perlane®* and Zyplast® injections.

In a fifth U.S. study (Study MA-1400-03) 60 patients at three centers randomly received *Restylane® Lyft with Lidocaine* injections on one side of the face and *Perlane®* injections on the

other side of the face. The adverse events reported in patient diaries during 14 days after treatment are presented in Tables 5 and 6. The physician-recorded adverse events identified in study MA-1400-03 at 14 days after injection are presented in Table 9.

Table 1. Maximum Intensity of Symptoms after Initial Treatment, Patient Diary (Study MA-1400-02)[1]

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

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

Table 2. Duration of Adverse Events after Initial Treatment, Patient Diary (Study MA-1400-02) [1]

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

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

Table 3. Maximum Intensity of Symptoms after Initial Treatment, Patient Diary (Study MA-1400-01)[1,2]

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

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

Table 4. Duration of Adverse Events after Initial Treatment, Patient Diary (Study MA-1400-01)[1,2]

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

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

Table 5. Maximum Intensity of Symptoms after Initial Treatment, Patient Diary (Study MA-1400-03)[1]										
	Restylane® Lyft with Lidocaine	*Perlane*	*Restylane® Lyft with Lidocaine* Patients				*Perlane* Patients			
	Total patients reporting symptoms n (%)	Total patients reporting symptoms n (%)	None	Tolerable[2]	Affected Daily Activity[2]	Disabling[2]	None	Tolerable[2]	Affected Daily Activity[2]	Disabling[2]
			n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Bruising	36 (60.0%)	33 (55.0%)	24 (40.0%)	32 (53.3%)	4 (6.7%)	0 (0.0%)	27 (45.0%)	29 (48.3%)	4 (6.7%)	0 (0.0%)
Redness	34 (56.7%)	31 (51.7%)	26 (43.3%)	31 (51.7%)	3 (5.0%)	0 (0.0%)	29 (48.3%)	29 (48.3%)	2 (3.3%)	0 (0.0%)
Swelling	42 (70.0%)	39 (65.0%)	18 (30.0%)	34 (56.7%)	8 (13.3%)	0 (0.0%)	21 (35.0%)	34 (56.7%)	5 (8.3%)	0 (0.0%)
Pain	28 (46.7%)	26 (43.3%)	32 (53.3%)	25 (41.7%)	3 (5.0%)	0 (0.0%)	34 (56.7%)	24 (40.0%)	2 (3.3%)	0 (0.0%)
Tenderness	50 (83.3%)	49 (81.7%)	10 (16.7%)	45 (75.0%)	5 (8.3%)	0 (0.0%)	11 (18.3%)	47 (78.3%)	2 (3.3%)	0 (0.0%)
Itching	16 (26.7%)	12 (20.0%)	44 (73.3%)	15 (25.0%)	1 (1.7%)	0 (0.0%)	48 (80.0%)	12 (20.0%)	0 (0.0%)	0 (0.0%)
Other[3]	3 (5.0%)	1 (1.7%)	NA	NA	NA	NA	NA	NA	NA	NA

[1]Missing values are not reported.
[2]Prospective definitions for: tolerable, affected daily activity and disabling were not provided in the diary or protocol.
[3] Other included symptoms of acne, lumpiness, and red/purple mark. Diary entries of hurts to swallow, lack of energy, feeling of sickness, achy, headache, and broken capillaries could not be associated with a particular product.

Table 6. Duration of Adverse Events after Initial Treatment, Patient Diary (Study MA-1400-03) [1]										
	Restylane® Lyft with Lidocaine	*Perlane*	*Restylane® Lyft with Lidocaine* Patients				*Perlane* Patients			
	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	36 (60.0%)	33 (55.0%)	6 (16.7%)	27 (75.0%)	3 (8.3%)	0 (0.0%)	5 (15.2%)	23 (69.7%)	4 (12.1%)	1 (3.0%)
Redness	34 (56.7%)	31 (51.7%)	9 (26.5%)	24 (70.6%)	0 (0.0%)	1 (2.9%)	9 (29.0%)	18 (58.1%)	3 (9.7%)	1 (3.2%)
Swelling	42 (70.0%)	39 (65.0%)	4 (9.5%)	33 (78.6%)	4 (9.5%)	1 (2.4%)	6 (15.4%)	29 (74.4%)	3 (7.7%)	1 (2.6%)
Pain	28 (46.7%)	26 (43.3%)	17 (60.7%)	11 (39.3%)	0 (0.0%)	0 (0.0%)	15 (57.7%)	11 (42.3%)	0 (0.0%)	0 (0.0%)
Tenderness	50 (83.3%)	49 (81.7%)	6 (12.0%)	40 (80.0%)	4 (8.0%)	0 (0.0%)	8 (16.3%)	35 (71.4%)	6 (12.2%)	0 (0.0%)
Itching	16 (26.7%)	12 (20.0%)	5 (31.3%)	10 (62.5%)	1 (6.3%)	0 (0.0%)	5 (41.7%)	7 (58.3%)	0 (0.0%)	0 (0.0%)
Other[2,4]	3 (5.0%)	1 (1.7%)	0 (0.0%)	3 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)

[1] Missing values are not reported.
[2] Events are reported as local events; because of the design (split-face) of the study, causality of the systemic adverse events cannot be assigned.
[3] Data are cumulated from up to two injection sites per patient with earliest and latest time point for any reaction provided.
[4] Other included symptoms of acne, lumpiness, and red/purple mark. Diary entries of hurts to swallow, lack of energy, feeling of sickness, achy, headache, and broken capillaries could not be associated with a particular product.

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

Table 7. All Investigator-Identified Adverse Events (72 Hours)
Number of Events per Patient per Study

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

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

Table 8. Investigator-Identified Adverse Events (2 Weeks or More After Implantation) (Number of Patients) (*Perlane* v. Specified Active Controls – All Studies)								
Study Term	MA-1400-01 *Perlane* (n=150) (%)	MA-1400-01 *Restylane* (n=150) (%)	MA-1400-02 *Perlane* (n=141) (%)	MA-1400-02 *Restylane* (n=142) (%)	31GE0101 *Perlane* (n=150) (%)	31GE0101 Hylaform (n=150) (%)	31GE0002 *Perlane* (n=68) (%)	31GE0002 Zyplast (n=68) (%)
Ecchymosis	7 (4.6%)	4 (2.7%)	15 (10.6%)	14 (9.9%)	6 (4.0%)	2 (1.3%)	0 (0%)	0 (0%)
Edema	0 (0%)	0 (0%)	3 (2.1%)	2 (1.4%)	14 (9.3%)	6 (4.0%)	4 (5.9%)	9 (13.2%)
Erythema	2 (1.3%)	2 (1.3%)	2 (1.4%)	1 (0.7%)	13 (8.7%)	8 (5.3%)	6 (8.8%)	8 (11.8%)
Tenderness	1 (0.7%)	0 (0%)	1 (0.7%)	0 (0%)	2 (1.3%)	0 (0%)	0 (0%)	0 (0%)
Pain	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)	13 (8.7%)	3 (2.0%)	0 (0%)	2 (2.9%)
Papule	0 (0%)	1 (0.7%)	1 (0.7%)	2 (1.4%)	11 (7.3%)	1 (0.7%)	1 (1.5%)	6 (8.8%)
Pruritus	0 (0%)	1 (0.7%)	0 (0%)	1 (0.7%)	2 (1.3%)	3 (2.0%)	3 (4.4%)	5 (7.4%)
Rash	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	0 (0%)	0 (0%)
Hyperpigmentation	7 (4.7%)	8 (5.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Injection site scab	0 (0%)	1 (0.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Skin exfoliation	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	0 (0%)

In two studies (i.e., 31GE0101 and 31GE0002) with repeat administration of *Perlane*® at 6–9 months following the initial correction, the incidence and severity of adverse events were similar in nature and duration to those recorded during the initial treatment sessions**.**

In all four studies, investigators reported the following local and systemic events that were judged unrelated to treatment and occurred at an incidence of less than 1%, i.e., acne; 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, renal stones, and uterine fibroids.

Table 9 shows the number of adverse events identified by investigators during Day 1 through Day 14 after injection in Study MA-1400-03.

Table 9. All Investigator-Identified Adverse Events (14 Days) Number of Events per Patient per Study		
Study Term	MA-1400-03	
	Number of Events *Restylane® Lyft with Lidocaine* (n=142)	Number of Events *Perlane* (n=141)
Ecchymosis	19	23
Edema	24	24
Erythema	25	25
Pain	14	14
Papule	1	1
Pruritus	9	5
Tenderness	30	30

Some patients had multiple adverse events or had the same adverse events at bilateral injection sites. No adverse events were of severe intensity. Patients were queried on adverse events on the day of injection and at the Day 14 visit.

Study MA-1400-03, included 47 subjects who had no prior cosmetic treatment and 13 subjects who had prior dermal filler treatment. There were no statistical differences in the proportion of subjects with adverse events who had prior treatment and those with no prior treatment.

Table 10. MA-1400-03—Related AE by prior procedure. By Subjects			
Prior procedure	Related AE		p-value*
	Yes	No	
Yes	9 (69.2%)	4	1.00
No	31 (66.0%)	16	

* Fisher's exact test

***Restylane® Lyft with Lidocaine* for cheek augmentation and correction of midface contour deficiencies in patients over the age of 21.**

One U.S. study reported adverse events in support of *Restylane® Lyft with Lidocaine* for the indication of cheek augmentation and correction of midface contour deficiencies.

In the U.S. pivotal study (MA-1400-05) involving 200 patients at 12 centers, patients received *Restylane® Lyft with Lidocaine* in both the right and left midface at baseline or in the control group at Month 12. Subjects were asked to record symptoms of bruising, redness, swelling, pain, tenderness and itching in a 14-Day patient diary. Subject's scores for the severity of these events are presented in Table 11 and durations are provided in Table 12. The majority of events were mild considered tolerable and resolved in 2 – 7 days. Bruising tended to have a longer duration with the majority of subjects resolving between 8 and 14 days.

Table 11. MA-1400-05 Overall Summary of Selected Adverse Events* as Reported in Subject's Diary by Maximum Severity – Safety Population

	Treatment Group		
	No Treatment at Baseline (N=49)	**First Treatment with *Restylane®* *Lyft with Lidocaine* (N=199)**	**Second Treatment with *Restylane® Lyft with Lidocaine* (N=128)**
Right and Left Midface Combined (N=198)			
Maximum Severity Reported for any Diary Symptom	49	198	127
None	47 (96%)	3 (2%)	1 (<1%)
Tolerable	2 (4%)	146 (74%)	94 (74%)
Affects Daily Activities	0	45 (23%)	26 (20%)
Disabling	0	4 (2%)	6 (5%)
Pain (Including Burning)	49	198	127
None	48 (98%)	41 (21%)	28 (22%)
Tolerable	1 (2%)	134 (68%)	84 (66%)
Affects Daily Activities	0	22 (11%)	13 (10%)
Disabling	0	1 (<1%)	2 (2%)
Tenderness	49	198	127
None	49 (100%)	9 (5%)	10 (8%)
Tolerable	0	171 (86%)	104 (82%)
Affects Daily Activities	0	17 (9%)	12 (9%)
Disabling	0	1 (<1%)	1 (<1%)
Redness	49	198	127
None	49 (100%)	43 (22%)	27 (21%)
Tolerable	0	139 (70%)	88 (69%)
Affects Daily Activities	0	16 (8%)	10 (8%)
Disabling	0	0	2 (2%)
Bruising	49	198	127
None	49 (100%)	35 (18%)	28 (22%)
Tolerable	0	130 (66%)	79 (62%)
Affects Daily Activities	0	32 (16%)	16 (13%)
Disabling	0	1 (<1%)	4 (3%)
Swelling	49	198	127
None	49 (100%)	19 (10%)	18 (14%)
Tolerable	0	145 (73%)	94 (74%)
Affects Daily Activities	0	30 (15%)	11 (9%)
Disabling	0	4 (2%)	4 (3%)
Itching	49	198	127
None	48 (98%)	131 (66%)	92 (72%)
Tolerable	1 (2%)	63 (32%)	33 (26%)
Affects Daily Activities	0	3 (2%)	1 (<1%)
Disabling	0	1 (<1%)	1 (<1%)

Note: Percentages are based on the number of Subjects in the Safety Population with any non-missing assessment for location and parameter (if applicable).

Note: For right and left combined, the overall maximum severity is taken as the maximum of overall right severity and overall left severity. The combined maximum severity within symptom category is taken as the maximum of right severity and left severity within the symptom category.

* Selected Adverse Events are those that were pre-listed in the diary (bruising, redness, swelling, pain, tenderness, itching) and required a recording of "none" or the presence and extent. These diary recordings were handled separately from adverse events that were elicited from an interview about any medical occurrence that meets the definition of Adverse Event.

Table 12:	**Duration of Selected Adverse Events* as Reported in the Subject's Diary – Safety Population**				
	No Treatment at Baseline (N = 49)				
	Number of Days				
Location/ Adverse Event	**Any[1] n (%)**	**1 n (%)**	**2-7 n (%)**	**8-13 n (%)**	**14 n (%)**
Right and Left Midface Combined					
Pain (Including Burning)	1 (2%)	1 (100%)	0	0	0
Tenderness	0	0	0	0	0
Redness	0	0	0	0	0
Bruising	0	0	0	0	0
Swelling	0	0	0	0	0
Itching	1 (2%)	0	1 (100%)	0	0
	First Treatment with *Restylane® Lyft with Lidocaine* (N = 199)				
	Number of Days				
Location/ Adverse Event	**Any[1] n (%)**	**1 n (%)**	**2-7 n (%)**	**8-13 n (%)**	**14 n (%)**
Pain (Including Burning)	157(79%)	34 (22%)	109 (69%)	12 (8%)	2 (1%)
Tenderness	189(95%)	17 (9%)	112 (59%)	47 (25%)	13 (7%)
Redness	155(78%)	39 (25%)	96 (62%)	18 (12%)	2 (1%)
Bruising	163(82%)	10 (6%)	66 (40%)	70 (43%)	17 (10%)
Swelling	179(90%)	14 (8%)	132 (74%)	26 (15%)	7 (4%)
Itching	67(34%)	16 (24%)	42 (63%)	9 (13%)	0
	Second Treatment with *Restylane® Lyft with Lidocaine* (N=128)				
	Number of Days				
Location/ Adverse Event	**Any[1] n (%)**	**1 n (%)**	**2-7 n (%)**	**8-13 n (%)**	**14 n (%)**
Pain (Including Burning)	99 (77%)	17 (17%)	70 (71%)	10 (10%)	2 (2%)
Tenderness	117 (91%)	9 (8%)	71 (61%)	29 (25%)	8 (7%)
Redness	100 (78%)	19 (19%)	67 (67%)	11 (11%)	3 (3%)
Bruising	99 (77%)	5 (5%)	46 (46%)	35 (35%)	13 (13%)
Swelling	109 (85%)	15 (14%)	72 (66%)	20 (18%)	2 (2%)
Itching	35 (27%)	9 (26%)	19 (54%)	5 (14%)	2 (6%)

[1] Percentages are based on the number of subjects in the Safety population.

Note: Percentages for duration categories are based on the number of subjects reporting the symptom ("Any") for the specified location, unless otherwise noted.

Note: Second Treatment with *Restylane® Lyft with Lidocaine* column only includes diary summaries from subjects who actually received a second treatment at Month 12.

* Selected Adverse Events are those that were pre-listed in the diary (bruising, redness, swelling, pain, tenderness, itching) and required a recording of "none" or the presence and extent. These diary recordings were handled separately from adverse events that were elicited from an interview about any medical occurrence that meets the definition of Adverse Event.

Midface safety assessments, such as firmness, symmetry, function (movement), mass formation and sensation were evaluated at the screening visit, optional touch up visit, 2 week follow up visit, 4 week follow up visit, 2, 4, 6, 8 and 10 month follow up visits, and the 12 month follow up visit. In addition, midface safety assessments, such as firmness, symmetry, function, mass formation and sensation were evaluated at the following month 12 post treatment visits: optional touch up visit, 2 week post-treatment visit, 4 week post-treatment visit, and the 12 week post-

treatment visit. Device palpability was assessed at each scheduled visit listed above with the exception of the screening visit. One subject reported greater than mild for the midface safety assessments of firmness, symmetry, function, mass formation and abnormal device palpability. This subject reported a mild hematoma in the right cheek starting five days after the initial treatment that progressed to a moderate hematoma starting 26 days later and lasting 16 days. Reported treatment included antibiotics. The investigator believed that the hematoma was exacerbated by self-manipulation**.** There were no signs of inflammation in subjects reporting mild or moderate abnormality in the safety assessments of midface.

The physician diagnosed adverse events identified in this study are presented in Table 13. Of the 200 subjects enrolled in the study, 199 subjects received their first treatment with *Restylane® Lyft with Lidocaine* at either baseline/Day 0 or at Month 12, and 128 subjects received a second treatment at Month 12. Forty-nine percent (49%) of subjects receiving their first treatment reported a total of 269 TEAEs while 29% of subjects that received a second treatment reported a total of 77 TEAEs. The majority of these TEAEs were mild in intensity (212/269; 79%, and 70/77; 91%; first and second treatment respectively), and were transient in nature. The most common TEAEs occurring after initial treatment with *Restylane® Lyft with Lidocaine* were implant site haematoma (18%), implant site haemorrhage (5%), implant site pain (9%), implant site swelling (8%), and headache (7%). There was no increased risk with additional treatment with *Restylane® Lyft with Lidocaine®*.

Subjects with Fitzpatrick Skin Types IV, V and VI (n=61) and had safety results similar to the general study population.

Table 13. MA-1400-05 Summary of Treatment Emergent Adverse Events Occurring in ≥ 2% of Treated Subjects – Safety Population

	Treatment Group					
	No Treatment at Baseline (N=50)		First Treatment with *Restylane® Lyft with Lidocaine* (N=199)		Second Treatment with *Restylane® Lyft with Lidocaine* (N=128)	
	Events	Subjects[1]	Events	Subjects[1]	Events	Subjects[1]
Any TEAE	18	15 (30%)	269	97 (48.7%)	77	37 (28.9%)
General Disorders and Administration Site Conditions						
Implant Site Haematoma	0	0	52	36 (18%)	18	10 (8%)
Implant Site Haemorrhage	0	0	18	10 (5%)	22	9 (7%)
Implant Site Mass	0	0	6	5 (2.5%)	1	1 (0.8%)
Implant Site Pain	0	0	36	17 (9%)	10	6 (5%)
Implant Site Swelling	0	0	36	15 (8%)	6	4 (3%)
Infections and Infestations						
Nasopharyngitis	1	1 (2%)	4	4 (2%)	0	0
Upper Respiratory Tract Infection	0	0	4	4 (2%)	0	0
Nervous System Disorders						
Headache	3	3 (6%)	14	13 (7%)	1	1 (<1%)
Hypoaesthesia	0	0	5	4 (2%)	0	0

[1] A subject with more than one treatment emergent adverse event within a system organ class and/or preferred term is only counted once.

Note: For the No Treatment at Baseline group an adverse event is considered treatment emergent if the start date is on or after the Visit 2 (Day 0) date. For the First Treatment with *Restylane® Lyft with Lidocaine* group an adverse event is considered treatment emergent if the start

date is on or after the date of initial treatment injection and before the date of Month 12 injection. For the Second Treatment with *Restylane® Lyft with Lidocaine* group an adverse event is considered treatment emergent if the start date is on or after the date of the Month 12 injection.

Two subjects (1%, 2/199) reported four serious adverse events (SAEs) that were considered to be related to the device and/or the procedure. One subject reported implant site inflammation (late onset inflammatory reactions) in both cheeks at separate times. The second subject experienced implant site hematomas in the right cheek and implant site infection/abscess. Treatment of the SAEs included NSAIDs, antibiotics, incision and drainage and, hyaluronidase. All events resolved.

Approximately 3% of subjects had a delayed onset (> 21 days after treatment) of implant site erythema, implant site hematoma, implant site inflammation, implant site mass, implant site pain, implant site swelling, implant site warmth, induration, twitching or rosacea that occurred up to 138 days after treatment.

Adverse events associated with the use of the device and occurring in < 2% of subjects whether related or not related were sunken eyes, nausea, implant site infection/abscess, implant site inflammation, implant site mass, implant site warmth, implant site irritation, induration, muscle tightness, muscle twitching, pain in jaw, presyncope, 7th nerve paralysis, acne, needle track marks, rosacea, conjunctivitis, eyelid cyst, colitis ischemic, dental carries, gingival swelling, tooth ache, cyst, discomfort, injection site pain, general swelling, ulcer, acarodermatitis, bronchitis, eye infection, implant site cellulitis, influenza, oral herpes, pneumonia, soft tissue infection, arthropod sting, incision site pain, exposure to toxic agent, facial injury, ligament sprain, meniscus lesion, thermal burn, tooth fracture, type 2 diabetes, arthralgia, back pain, bursitis, myalgia, neck pain, pain in extremity, basal cell carcinoma, pancreatic carcinoma, metastatic carcinoma, carpal tunnel syndrome, abortion spontaneous, depression, prostatitis, pulmonary vascular disorder, dermatitis contact, rash, urticaria, neurectomy, and hypertension.

Post-Marketing Surveillance:

The adverse events received from post-marketing surveillance for the use of *Restylane® Lyft with Lidocaine* when used outside the US for cheek augmentation were infrequent and included mostly reports of swelling and mass/induration. Serious adverse events which occurred ≥ 5 times were the following, in descending order of frequency: implant site swelling, implant site abscess, implant site infection, implant site erythema, implant site mass purulent discharge, implant site nodule, medical device implantation (i.e. events reported as overcorrection, overfill, skin depression, or irregular skin).

The incidence of post market events potentially related to treatment with *Restylane® Lyft with Lidocaine* for all indications and that occurred in greater than 5 subjects included the following, in descending order of frequency: swelling, device ineffective, accidental exposure, mass/induration, nondermatological events, erythema, pain/tenderness, infection/abscess, bruising/abscess, bruising/bleeding, papules/nodules, inflammation, neurological symptoms, medical device implantation (i.e. events reported as overcorrection, overfill, skin depression, or irregular skin), injection site reactions, hypersensitivity, pruritus, discoloration, eye disorders, ischemia/necrosis, scar/scab/skin atrophy, procedural complications, herpes, device dislocation,

device misuse, and rash. Reported treatments have included systemic steroids or systemic antibiotics administered intravenously, orally or by injection. 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. Serious abscess formations have also been reported.

Vision abnormalities including blindness have been reported following injection of hyaluronic acid, with and without lidocaine, into the nose, glabella, periorbital areas, and/or cheek, with a time to onset ranging from immediate to 1 week following injection. Reported treatments include anticoagulant, epinephrine, aspirin, hyaluronidase, corticosteroid treatment, hyperbaric oxygen and surgery. Outcomes ranged from resolved to ongoing at the time of last contact. Events requiring medical intervention, and events where resolution information is not available were reported after injection of hyaluronic acid with or without lidocaine. In these cases, the product was injected into the highly vascularized areas of the glabella, nose, and periorbital area, which are outside the device indications for use (See Warnings section).

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.

Adverse reactions should be reported to Galderma Laboratories, L.P. at 1-855-425-8722.

Clinical Trials

Restylane® Lyft with Lidocaine is indicated for implantation into the deep dermis to superficial subcutis for the correction of moderate to severe facial folds and wrinkles, such as nasolabial folds and for subcutaneous to supraperiosteal implantation for cheek augmentation and correction of age-related midface contour deficiencies in patients over the age of 21. Clinical trial information for *Restylane® Lyft with Lidocaine* use in the correction of moderate to severe facial folds and wrinkles, such as nasolabial folds is presented in the section titled "U.S. Clinical Studies to support Perlane®/Restylane® Lyft with Lidocaine in the treatment of facial folds and wrinkles (nasolabial folds and oral commissures)" and for cheek augmentation and correction of age-related midface contour deficiencies is presented in the section titled "U.S. Clinical Study to support the use of Restylane® Lyft with Lidocaine in cheek augmentation and correction of midface contour deficiencies".

The safety and effectiveness of *Perlane®* in the treatment of facial folds and wrinkles (nasolabial folds and oral commissures) were evaluated in four prospective randomized controlled clinical studies involving 509 *Perlane*-treated patients.

Perlane® 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.

The safety and pain reduction effect of *Restylane*® *Lyft with Lidocaine* in the treatment of facial folds and wrinkles (nasolabial folds) was evaluated in a prospective randomized controlled clinical study involving 60 patients. The addition of lidocaine to *Perlane*® resulted in a statistically significant reduction in the pain experienced by the patients. The study also showed that the safety profile of *Restylane*® *Lyft with Lidocaine* was consistent with *Perlane*®.

U.S. Clinical Studies to support *Perlane*®/*Restylane*® *Lyft with Lidocaine* in the treatment of facial folds and wrinkles (nasolabial folds and oral commissures)

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 *Perlane*® and *Restylane*® following treatment to baseline condition. Patients were randomized to either *Perlane*® or *Restylane*® treatment. A touch-up was allowed 2 weeks after initial treatment. Patients were partially masked; evaluating physicians were independent and masked; treating physicians were unmasked. Effectiveness was studied with 6 months follow-up. Safety was studied with 6 months follow-up.
Endpoints	Effectiveness Primary: The difference in effect of *Perlane*® 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 was calculated for each treatment group. Each group was compared to its own baseline, with no comparison of *Perlane*® to *Restylane*®. 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 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 events at 72 hours, and at 2, 6, 12, and 24 weeks; development of humoral or cell-mediated immunity; and the relationship of adverse events to injection technique.
Outcomes	**Demographics:** The study enrolled 283 (i.e., 141 *Perlane*® and 142 *Restylane*®) patients with moderate to severe NLF wrinkles. The patients were predominantly healthy ethnically diverse females. Bilateral NLFs and oral commissures were corrected in most patients with 1.9 mL to 4.6 mL of *Perlane*®. The greatest amount used in any patient was 9.0 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 *Perlane*® and control (*Restylane*®) are presented in Table 14. In the primary effectiveness assessment at 12 weeks, 87% of the *Perlane*® and 77% of the control patients had maintained at least a 1 point improvement over baseline.

Table 14. Blinded Evaluator Wrinkle Severity Response Scores

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

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

Antibody Testing:
15/141 (10.6%) patients displayed a pre-treatment antibody response against *Perlane*®, (which was believed to be related to co-purifying *Streptococcus* capsule antigens). One patient also developed a measurable increase in antibody titer after *Perlane*® injection. 4/16 (27%) patients with antibodies against *Perlane*® had adverse events at the injection site, which was similar to the local adverse event rate observed in the entire *Perlane*® population (i.e., 49/141 (35%)). With the exception of one moderate bruising event, all the adverse events in the patients with a humoral response against *Perlane*® were mild in severity. No severe events were noted and the patient who developed an antibody response after *Perlane*® injection did not experience any adverse event at the injection site. Immediate type skin testing demonstrated that no patient developed IgE to *Perlane*®. Post-exposure histopathology of skin biopsies of an implant site on each patient demonstrated that no patient developed cell-mediated immunity to *Perlane*®.

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 *Perlane*® and *Restylane*® following treatment to baseline condition in 150 patients with pigmented skin and predominantly African-American ethnicity. Patients were randomized to either *Perlane*® or *Restylane*® treatment in a "within-patient" model of augmentation correction of bilateral nasolabial folds (NLFs) and oral commissures with one treatment assigned to one side and the other treatment to the other side. A touch-up was allowed 2 weeks after initial treatment. Patients and treating physicians were partially masked. Evaluations were performed by live investigator assessment for the primary analysis. Effectiveness was studied with 6 months follow-up. Safety was studied with 6 months follow-up.
Endpoints	Effectiveness Primary: The difference in effect of *Perlane*® 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 patients success was calculated for each group. Each treatment group was compared to its own baseline, with no comparison of *Perlane*® to *Restylane*®. 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 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 events at 72 hours, and at 2, 6, 12, and 24 weeks; the development of humoral or cell-mediated immunity; and the relationship of adverse events to injection technique.
Outcomes	**Demographics:** The study enrolled 150 patients with moderate to severe NLF wrinkles. The patients were predominantly healthy African-American females.

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

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

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

Efficacy:

The results of the live blinded evaluator assessment of wrinkle severity for *Perlane*® and control (*Restylane*®) are presented in Table 15 and are based on the Intent-to-Treat analysis. In the primary effectiveness assessment at 12 weeks, 92% of the *Perlane*-treated and 93% of the *Restylane*-treated NLF maintained at least a 1 point improvement over baseline.

Table 15. Live Evaluator Wrinkle Severity Response Scores

Time point	No. of patients	No. of *Perlane* Pts. maintaining ≥ 1 Unit Improvement on WSRS	95% *Perlane* Confidence Interval	No. of *Restylane* Pts. maintaining ≥ 1 Unit Improvement on WSRS	95% *Restylane* Confidence Interval
6 weeks	148	140 (95%)	90-99 %	142 (96%)	92-99%
12 weeks	149	137 (92%)	87-97%	139 (93%)	89-98%
24 weeks	147	104 (71%)	63-77%	08 (73%)	66-81%

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

Antibody Testing:

6/150 (4%) patients displayed a pre-treatment antibody response against *Perlane*® (which was believed to be related to co-purifying *Streptococcus* capsule antigens). No patients developed a measurable increase in antibody titer after *Perlane*® injection. 0/6 (0%) patients with antibodies against *Perlane*® had adverse events at the injection site as compared to the local adverse event rate observed in the entire *Perlane*® population (i.e., 14/150 (9%)). All the adverse events in the patients with a humoral response against *Perlane*® were mild in severity. Immediate type skin testing demonstrated that no patient developed IgE to *Perlane*®. Post-exposure histopathology of skin biopsies of an implant site on each patient demonstrated that no patient developed cell-mediated immunity to *Perlane*®.

MA-1400-03: Randomized, Blinded, Controlled Clinical Study

Design	1:1 randomized, prospective study at 3 U.S. centers, which compared the safety, tolerability, and pain reduction of *Restylane® Lyft with Lidocaine* to *Perlane®* in 60 patients. Patients were randomized to *Restylane® Lyft with Lidocaine* or *Perlane®* treatment in a "within-patient" model of bilateral nasolabial folds (NLFs) correction, with one treatment assigned to one side and the other treatment to the remaining side. Patients and treating physicians were blinded; evaluating physicians were independent and blinded. The study included 51.7% of patients with darker skin types based on classification of Fitzpatrick Skin Types IV, V, or VI (36.7% Skin Type IV and 15.0% Skin Type V or VI). Pain was assessed by each patient for each treatment site independently on the Visual Analog Scale (VAS) at the end of injection and at 15-minute intervals for 60 minutes post-treatment. Patient assessment of appearance using the Global Aesthetic Improvement Scale (GAIS) (Very much improved / much improved / improved / no change / worse) was performed at the Day 14 visit. Safety was studied with 14-day follow-up.
Endpoints	Primary: The proportion of patients that had a within-patient difference in the VAS (*Perlane - Restylane® Lyft with Lidocaine*) of at least 10 mm at injection together with a 95% confidence interval. The objective was to show that the confidence interval lay above 50%. Secondary: The proportion of patients that had a within-patient difference in VAS of at least 10 mm at post-injection time points (15, 30, 45 and 60 minutes after injection) together with a 95% confidence interval, the mean VAS by treatment and within-patient difference in VAS at each time point, the comparison of VAS between *Restylane® Lyft with Lidocaine* and *Perlane®*, at each time point, and patient assessment on GAIS by treatment. Safety assessments included: collection of patient symptoms in a 14-day diary and investigator evaluation of adverse events at 14 days.

Outcomes

Demographics:

The study enrolled 60 patients with moderate to severe NLF wrinkles. The patients were predominantly healthy ethnically diverse females.

Gender – Female: 56 (93.3%); Male: 4 (6.7%)

Ethnicity – White: 39 (65.0%); Hispanic or Latino: 16 (26.7%); African American: 5 (8.3%)

Fitzpatrick Skin Type- Type I-III; 29 (48.3 %); Type IV: 22 (36.7%); Type V and VI: 9 (15.0%)

Volume:
The mean volume of *Restylane® Lyft with Lidocaine* per wrinkle was 1.11 mL. The mean volume of *Perlane®* per wrinkle was 1.10 mL.

Volume Injected per Wrinkle (mL) (Study MA-1400-03)

Treatment	Volume (mL)					
	n	Mean	Std	Min	Median	Max
Restylane® Lyft with Lidocaine per NLF	60	1.11	0.49	0.50	1.00	3.00
Perlane per NLF	60	1.10	0.49	0.50	1.00	3.00
Difference within patient*	60	-0.01	0.14	-0.50	0.00	0.50

* *Perlane* volume - *Restylane® Lyft with Lidocaine* volume
Abbreviations: n = number of patients; std = standard deviation; Min = minimum; Max = maximum

Primary: The primary efficacy analysis for pain reduction showed that 95.0% of patients had a within-patient difference in VAS (*Perlane®* minus *Restylane® Lyft with Lidocaine ®*) of at least 10 mm at the time of injection. The primary objective was met, since statistically more than 50% of patients had at least 10 mm lower VAS score on the side treated with *Restylane® Lyft with Lidocaine* (confidence interval was 86.1 to 99.0). At 15 minutes post injection, 56.7% still had a within-patient difference in VAS of at least 10 mm.

Treatment Difference (Δ) in VAS (*Perlane* Side – *Restylane® Lyft with Lidocaine* Side) – ITT Population (Study MA-1400-03)

Time po nt	No. of patients with assessments**	Number of patients with Δ > 10 mm			
		n	%	95% LCL	95% UCL
Treatment*	60	57	95.0	86.1	99.0
15 Minutes	60	34	56.7	43.2	69.4
30 Minutes	60	24	40.0	27.6	53.5
45 Minutes	60	11	18.3	9.5	30.4
60 Minutes	60	5	8.3	2.8	18.4

* Primary endpoint
** Denominator (N), % = 100*n/N; UCL=upper confidence limit; LCL=lower confidence limit

Secondary: Both pain scores decreased over time, but the mean within-patient difference on VAS (*Perlane – Restylane® Lyft with Lidocaine*) was statistically significantly larger than zero at all time points (at injection and at 15, 30, 45 and 60 minutes post-injection).

Patients' Mean VAS Assessments of Pain by Time Point (Study MA-1400-03)

Time point	VAS pain by treatment (mm)		VAS difference (mm)*	*p*-value**
	Restylane® Lyft with Lidocaine	*Perlane*		
Treatment	15.2	49.6	34.4	<0.001
15 Minutes	4.7	21.3	16.5	<0.001
30 Minutes	3.2	12.8	9.6	<0.001
45 Minutes	2.4	7.4	5.0	<0.001
60 Minutes	2.3	5.7	3.4	0.002

* Within-patient difference (*Perlane* side – *Restylane® Lyft with Lidocaine* side), ** One-sample T-test

At Day 14, patients showed improvement from baseline: 95% on the *Restylane® Lyft with Lidocaine* side of the face and 96.7% on the *Perlane®* side of the face.

Global Aesthetic Improvement Scale (GAIS) Evaluation at the Day 14 Visit (Study MA-1400-03)

Category	GAIS			
	Restylane® Lyft with Lidocaine		*Perlane*	
	n	**%**	n	**%**
Very Much Improved (4)	24	40.0	24	40.0
Much Improved (3)	18	30.0	19	31.7
Improved (2)	15	25.0	15	25.0
No Change (1)	3	5.0	2	3.3
Worse (0)	0	0.0	0	0.0

Non-U.S. Clinical Studies

31GE0101: Prospective, Randomized, Blinded, Controlled Clinical Study

Design	1:1 randomized, prospective study at 6 Canadian centers, which compared the safety and effectiveness of *Perlane*® and Hylaform®. Patients were randomized to either *Perlane*® or Hylaform® in a "within-patient" model of augmentation correction of bilateral nasolabial folds (NLFs) 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 were partially masked; evaluating physicians were independent and masked; treating physicians were partially masked. Effectiveness was studied with 6 months follow-up. Safety was studied with 6 months follow-up.
Endpoints	Effectiveness Primary: The difference in effect of *Perlane*® as compared to Hylaform® on the visual severity of the NLFs, as assessed by a Blinded Evaluator at 6 months after baseline. The primary evaluation parameter was a five-step validated Wrinkle Severity Rating Scale (WSRS) score (absent, mild, moderate, severe, extreme) by the Blinded Evaluator at 6 months. Success was defined as maintaining at least a one point improvement of the NLF on the WSRS at 6 months after optimal correction was achieved. The percent of successful NLFs after *Perlane*® and control treatments were compared, as well as a within-patient matched analysis (McNemar's Test). Secondary: Wrinkle Severity Rating Scale (WSRS) was assessed at other follow-up points (2 weeks and 3, 4.5, and 6 months after optimal correction) by the Blinded Evaluator and the patient. Global Aesthetic Improvement (GAI): very much improved /much improved / improved / no change / worse, assessed at same time points by patient. Safety assessments included: investigator evaluation of adverse events at all time points.
Outcomes	**Demographics:** The study enrolled 150 patients with moderate to severe nasolabial fold wrinkles. The patients were predominantly healthy white females. The study was completed by 140 of 150 patients at six months and additional safety data were available in 122 of 150 patients at 9 months. Gender – Female: 140 (93%); Male: 10 (7%) Ethnicity – White: 142/150 (95%); Non-caucasian: 8/150 (5%)

Efficacy:

The results of the blinded evaluator assessments are presented in Table 16 and are based on an Intent-to-Treat (ITT) analysis. At 6 months, 113/150 (75%) of the *Perlane*-treated NLFs maintained at least a single point improvement on the WSRS compared to 57/150 (38%) of the control-treated NLFs.

Table 16. Blinded Evaluator Wrinkle Severity Response Rates

Time point	Number of NLFs	No. of *Perlane* NLFs maintaining ≥ 1 Unit Improvement on WSRS	No. of Hylaform NLFs maintaining ≥ 1 Unit Improvement on WSRS
3 months	150	131 (87%)	94 (63%)
4.5 months	150	110 (73%)	69 (46%)
6 months	150	113 (75%)	57 (38%)

Table 17 shows the results for the within-patient investigator assessment of NLF on the WSRS.

Table 17. Evaluating Investigator's Assessment of NLF Severity; Score Change From Pre-Treatment Until 3, 4.5, and 6 Months After Last Treatment

Mos. after last treatment	*Perlane* superior to Hylaform n (%)	*Perlane* equal to Hylaform n (%)	Hylaform superior to *Perlane* n (%)	*p*-value*
3	95 (63.3%)	46 (30.7%)	9 (6.0%)	p< 0.001
4.5	87 (58.0%)	54 (36.0%)	9 (6.0%)	p< 0.001
6	96 (64.0%)	42 (28.0%)	12 (8.0%)	p< 0.001

* McNemar's test with %=n/N, where N=number of patients in the ITT population

31GE0002: Prospective, Randomized, Blinded, Controlled Clinical Study

Design	1:1 randomized, prospective study at 2 Scandinavian centers, which compared the safety and effectiveness of *Perlane*® and Zyplast®. Patients were randomized to either *Perlane*® or Zyplast® in a "within-patient" model of augmentation correction of bilateral nasolabial folds (NLFs) with one treatment assigned to one side and the other treatment to the other side. Patients were partially masked; evaluating physicians were independent and masked; treating physicians were partially masked. A touch-up was allowed 2 weeks after the initial treatment. Re-treatment was allowed at 6 or 9 months. Effectiveness was studied with 9 months follow-up. Safety was studied with 12 months follow-up.
Endpoints	Effectiveness Primary: Superiority of correction of the NLF by *Perlane*® as compared to Zyplast® based on the visual severity of the NLF, as assessed by a Blinded Evaluator at 6 months after optimal correction was achieved. The primary evaluation parameter was a five-step validated Wrinkle Severity Rating Scale (WSRS) score (absent, mild, moderate, severe, extreme) by the Blinded

	Evaluator at 6 months. NLF success was defined as maintaining at least a one point improvement on the WSRS at 6 months after optimal correction was achieved. The within patient comparison of *Perlane*® and control treatments was evaluated in a matched analysis (McNemar's Test). Secondary: Superiority of correction of the NLF by *Perlane*® or Zyplast® based on the visual severity of the NLFs, as assessed by a Blinded Evaluator at 9 months after baseline. Safety assessments included: investigator evaluation of adverse events at all time points.
Outcomes	**Demographics:** The study enrolled 68 patients with correctable NLF wrinkles. The patients were predominantly healthy white females. Gender – Female: 65 (96%); Male: 3 (4%) Ethnicity – White: 68/68 (100%) **Efficacy:** The results of the blinded evaluator assessments are presented in Table 18. At the primary effectiveness time point of 6 months, the *Perlane*-treated NLF experienced more improvement from baseline (judged by the WSRS) in 50% of the patients; the control-treated side experienced more improvement in 10.3% of the patients.

Table 18. Evaluating Investigator's Assessment; Difference in the Severity Rating Scale From Pre-Treatment Until 2, 4, 6, and 9 Months After Baseline

Time point	*Perlane* NLF is superior to control NLF n (%)	*Perlane* NLF is equal to control NLF n (%)	Control NLF is superior to *Perlane* NLF n (%)	*p*-value[1]
2 months[2]	32 (47.1%)	28 (41.2%)	8 (11.8%)	0.0001
4 months[2]	38 (55.9%)	25 (36.8%)	5 (7.4%)	0.0001
6 months[2]	34 (50.0%)	27 (39.7%)	7 (10.3%)	0.0003
9 months[3]	21 (48.8%)	16 (37.2%)	6 (14.9%)	0.0039

1. McNemar's test
2. Percent = n/Number of patients in the ITT population at Month 6
3. Percent = n/Number of patients in the ITT population at Month 9; includes only patients not re-treated (n=43)

U.S. Clinical Study to support the use of *Restylane® Lyft with Lidocaine* in cheek augmentation and correction of midface contour deficiencies.

MA-1400-05: Prospective, Randomized, Blinded, Controlled Clinical Study

Design	This was a 3:1 randomized, prospective study at 12 U.S. centers, which compared the safety and effectiveness of *Restylane® Lyft with Lidocaine* to a no treatment control in subjects seeking cheek augmentation. A touch-up was allowed 2 weeks after initial treatment. Patients were re-treated at Month 12 and patients originally randomized to the no treatment group received their initial treatment at Month 12. Blinded evaluating physicians

	were independent and masked; treating physicians were unmasked. Safety and Effectiveness was studied monthly through Month 12 and 12 weeks after the Month 12 re-treatment/treatment. Injections were performed with the supplied 29 G TW x ½" needle.
Endpoints	Effectiveness Primary: The proportion of responders with at least a one grade increase from the baseline assessment of the Medicis Midface Volume Scale (MMVS) for BOTH the right and left sides of the face at Month 2 as assessed by the blinded evaluator. The MMVS was a four point validated scale to assesses the fullness of the midface from Fairly Full (1) to Substantial Loss of Fullness (4). The proportion of responders was calculated for each treatment group and compared using Fisher's Exact Tests. Secondary: MMVS assessed at other follow-up points (2, 4, 6, 8, 10, and 12 months after optimal correction and 2, 4, and 12 weeks after the 12 Month treatment) by the blinded evaluator and the investigator. Satisfaction with treatment as assessed by the subject and the investigator using the Global Aesthetic Improvement Scale (GAIS). Additional assessment of patient satisfaction was assessed with the FACE-Q scale. The GAIS and FACE-Q scales were not validated at the time of the study. Safety assessments included: collection of patient symptoms in a 14-day diary; investigator evaluation of adverse events; and midface safety assessments (firmness, symmetry, movement, function, sensation, mass formation, and device palpability).

Outcomes	**Demographics:** The study enrolled 200 patients (150 *Restylane® Lyft with Lidocaine* and 50 no treatment) seeking cheek augmentation. Overall, the mean age for study subjects was 52.9 ± 7.6 years. The study included 61 subjects (31%) of Fitzpatrick skin types IV, V, or VI with 21 subjects of Fitzpatrick Skin Types V (17 subjects) and VI (4 subjects). Baseline MMVS were similar between the right and left midface with a majority of subjects (60% and 62%, respectively) having a MMVS score of 3 (moderate loss of fullness with slight hollowing below malar prominence). Gender – Female: 183 (92%); Male: 17 (9%) Ethnicity – White: 178 (89%); African American: 10 (5%), Asian: 3 (2%), American Indian/Alaskan Native 1 (<1%), Other: 8 (4%) Injection volumes averaged 6.227 mL (initial + touch-up at 2 weeks; right and left midface combined). **Efficacy:** The results of the blinded evaluator assessment of midface fullness (MMVS) for *Restylane® Lyft with Lidocaine* and no treatment control are presented in Table 19. In the primary effectiveness assessment at Month 2, 88.7% of the *Restylane® Lyft with Lidocaine* and 16.0% of the no treatment control patients had at least a 1 point improvement over baseline. Similar results were seen for the treating investigator's assessment of MMVS.

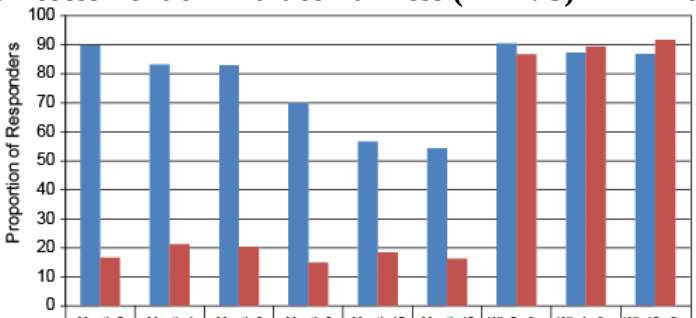
Table 19. Proportion of Responders Measured by the Blinded Evaluator's Assessment of Midface Fullness (MMVS) at Month 2

Timepoint	*Restylane® Lyft with Lidocaine*	No Treatment	P-Value[2]
Right and Left Midface Combined			
Month 2[1]	133 (88.7%)	8 (16.0%)	< 0.001

1 Primary endpoint N = Subjects with a missing blinded evaluator assessment at Month 2 for a midface are imputed using the hot deck method.

2 Fisher's Exact Test

Figure 1: Proportion of Responders Measured by the Blinded Evaluator's Assessment of Midface Fullness (MMVS) - ITT Population



	Month 2	Month 4	Month 6	Month 8	Month 10	Month 12	Wk 2 after 12-Mo Tx†	Wk 4 after 12-Mo Tx†	Wk 12 after 12-Mo Tx†
Restylane® Lyft with Lidocaine (n=150)	89.7* 131/146	83.2* 119/143	83.0* 117/141	70.0* 98/140	56.6* 81/143	54.3* 75/138	90.4 113/125	87.3 117/134	86.8 118/136
No Treatment (n=50)	16.7 8/48	21.3 10/47	20.4 10/49	14.9 7/47	18.4 9/49	16.3 8/49	86.7 39/45	89.4 42/47	91.7 44/48

**The difference between Restylane Lyft with Lidocaine and no treatment was statistically significant (P<.001) at each time point between month 2 and month 12 after treatment.*

†All subjects (both 'Restylane® Lyft with Lidocaine and 'No Treatment') were treated with Restylane® Lyft with Lidocaine by the Week 2 after 12-Month, Week 4 after 12-Month, and Week 12 after 12-Month visits. Wk = Week; Mo = Month; Tx = Treatment

Note: All subjects treated at the Month 12 Treatment visit received an injection with Restylane® Lyft with Lidocaine. This was the first treatment for the 'No Treatment' subjects and the second treatment for the 'Restylane® Lyft with Lidocaine' subjects.

Note: Response is defined as improvement of at least one grade in MMVS assessments from the baseline Blinded Evaluator's value to the Blinded Evaluator's assessment for the week of interest.

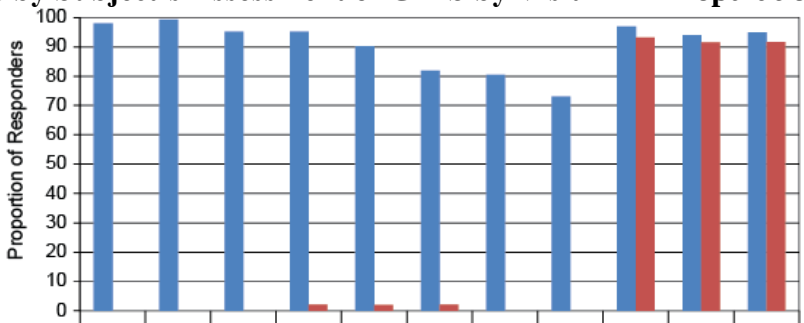
Note: The Proportion of Responders is calculated as the number of Responders at the visit of interest divided by the number of subjects in the ITT population for the specified treatment group with a non-missing assessment for the specified visit.

Note: P-values for the difference in proportions in Restylane® Lyft with Lidocaine and No Treatment are based on the Fisher's Exact test.

Note: 95% Confidence Intervals are two-sided confidence intervals calculated using the exact binomial distribution.

The results of the subject's satisfaction with the aesthetic improvement in midface fullness (GAIS) for *Restylane® Lyft with Lidocaine* and no treatment control are presented in Figure 2. Subjects were satisfied with treatment with 98% reporting improvement at 2 weeks after treatment and satisfaction seen in 73% of subjects after 12 months.

Figure 2: Right and Left Midface Combined: Proportion of Responders Measured by Subject's Assessment of GAIS by Visit – ITT Population



	Week 2	Week 4	Month 2	Month 4	Month 6	Month 8	Month 10	Month 12	Wk 2 after 12-Mo Tx†	Wk 4 after 12-Mo Tx†	Wk 12 after 12-Mo Tx†
Restylane® Lyft with Lidocaine (n=150)	98.0* 146/149	99.3* 145/146	95.2* 138/145	95.2* 138/145	90.3* 130/144	81.8* 117/143	80.4* 115/143	73.0* 103/141	96.9 123/127	94.0 125/133	95.0 134/141
No Treatment (n=50)	0 0/46	0 0/48	0 0/48	2.1 1/47	2.0 1/49	2.1 1/47	0 0/49	0 0/49	93.2 41/46	91.5 43/47	91.7 44/48

*The difference between Restylane Lyft with Lidocaine and no treatment was statistically significant (*P*<.001) at each time point between week 2 and month 12 after treatment.

†All subjects (both 'Restylane® Lyft with Lidocaine and 'No Treatment') were treated with Restylane® Lyft with Lidocaine by the Week 2 after 12-Month, Week 4 after 12-Month, and Week 12 after 12-Month visits. Wk = Week; Mo = Month; Tx = Treatment

Note: GIAS = Global Aesthetic Improvement Scale

Note: All subjects treated at the Month 12 Treatment visit received an injection with Restylane® Lyft with Lidocaine. This was the first treatment for the 'No Treatment' subjects and the second treatment for the 'Restylane® Lyft with Lidocaine' subjects.

Note: Response is defined as a score of 1 ('improved') or better on the GAIS scale at the time point of interest.

Note: The Proportion of Responders is calculated as the number of Responders at the visit of interest divided by the number of subjects in the ITT population for the specified treatment group with a non-missing assessment for the specified visit.

Note: *P*-values for the difference in proportions in Restylane® Lyft with Lidocaine and No Treatment are based on the Fisher's Exact test.

Note: 95% Confidence Intervals are two-sided confidence intervals calculated using the exact binomial distribution.

With regard to the photographic assessment of MMVS conducted by an Independent Photographic Reviewer (IPR), the between-group difference in the proportion of responders from baseline for the right and left midface combined was statistically significant ($p<0.05$) in favor of *Restylane® Lyft with Lidocaine* treatment at all visits except the Month 2 visit. The proportion of responders from baseline in the *Restylane® Lyft with Lidocaine* group as assessed by the IPR was 80.8% at Month 2, 80.0% at Month 4, 78.6% at Month 6, 79.7% at Month 8, 81.7% at Month 10, and 75.7% at Month 12. In the no treatment group the proportion of right and left midface combined responders was 69.6% at Month 2, 60.0% at Month 4, 54.2% at Month 6, 63.0% at Month 8, 63.8% at Month 10, and 57.4% at Month 12.

HOW SUPPLIED

Restylane® Lyft with Lidocaine is supplied in a disposable glass syringe with a Luer-Lok® fitting. *Restylane® Lyft with Lidocaine* is co-packed with sterilized needle(s) as indicated on the carton, either 27 G Thin Wall (TW) x ½", or 29 G TW 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® Lyft with Lidocaine 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® Lyft with Lidocaine* as this may damage or alter the product.

Do not use if the package is damaged. Immediately return the damaged product to Galderma Laboratories, L.P.

Rx only

U.S. Patent 5,827,937;8,455,459

Manufactured for
Galderma Laboratories, L.P.
14501 North Freeway
Fort Worth, TX 76177
U.S.A.
Phone: 1-855-425-8722

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

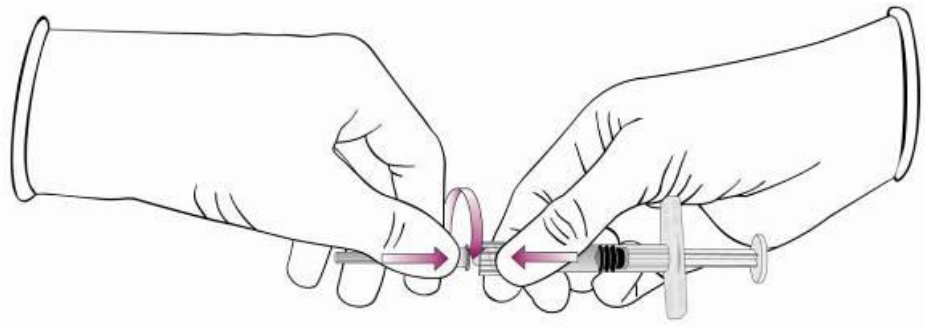
Restylane® and *Perlane®* are registered trademarks Galderma S.A. or its affiliates.

All other trademarks are the property of their respective owners.

DIRECTIONS FOR ASSEMBLY

ASSEMBLY OF 27 G TW and 29 G TW 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® Lyft with Lidocaine* treatment.

   Advise the patient of the necessary precautions before commencing the procedure.

   A consent form should be utilized.

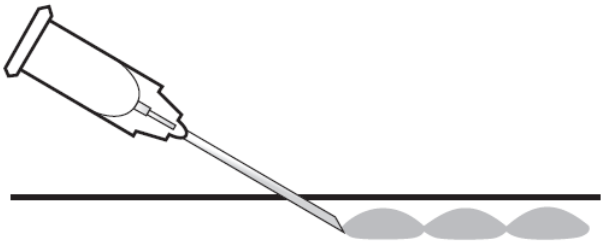
2. Assess the patient's need for appropriate anesthetic treatment for managing comfort, i.e., topical anesthetic, local or nerve block.
3. The patient's face should be washed with soap and water and dried with a clean towel. Cleanse the area to be treated with alcohol or another suitable antiseptic solution.
4. Sterile gloves are recommended while injecting *Restylane® Lyft with Lidocaine.*
5. Before injecting, press plunger rod carefully until a small droplet is visible at the tip of the needle.

6. After insertion of the needle, and just before injection, the plunger rod should be withdrawn slightly to aspirate and verify that the needle is not intravascular.
7. *Restylane® Lyft with Lidocaine* is administered using a thin gauge needle. *Restylane® Lyft with Lidocaine* is supplied with two 29 G TW x ½" needles (1 mL size) or three 27 G TW x ½" needles (2 mL fill size). The physician should use at their discretion the appropriate needle depending on the intended use of the product. The needle is inserted at an approximate angle of 30º parallel to the length of the wrinkle or fold. *Restylane® Lyft with Lidocaine* should be injected into the deep dermis to superficial layer of the subcutis for the treatment of moderate to severe facial folds and wrinkles (such as nasolabial folds) and for subcutaneous to supraperiosteal implantation for cheek augmentation and correction of age-related midface contour deficiencies in patients over the age of 21. If *Restylane® Lyft with Lidocaine* is injected too superficially this may result in visible lumps and/or bluish discoloration.
8. Inject *Restylane® Lyft with Lidocaine* 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.
9. 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.
10. For the treatment of moderate to severe facial wrinkles and folds, the maximum recommended dose per treatment is 6.0 mL based on U.S. clinical studies. For the treatment of age-related midface volume deficit, the maximum recommended dose is also 6.0 mL per treatment. The safety of injecting greater amounts has not been established.

INJECTION TECHNIQUES

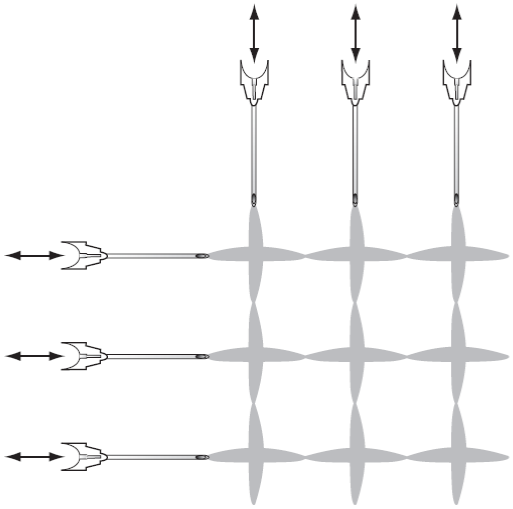
1. *Restylane® Lyft with Lidocaine* can be injected by a number of different techniques that depend on the treating physician's experience and preference, and patient characteristics.
2. **Serial puncture** (A) involves multiple, closely spaced injections along wrinkles or folds. Although serial puncture allows precise placement of the filler, it produces multiple puncture wounds that may be undesirable to some patients.
3. **Linear threading** (B) 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).
4. Serial threading is a technique that utilizes elements of both approaches.
5. **Cross-hatching** (C) 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.

A. Serial Puncture



B. Linear Threading

C. Cross-hatching



6. **Note! The correct injection technique is crucial for the final result of the treatment.**

   Dissection of the sub-epidermal plane with lateral movement of the needle, rapid flows (>0.3 mL/min), rapid injection or high volumes may result in an increase in short-term episodes of bruising, swelling, redness, pain, or tenderness at the injection site.

7. When the injection is completed, the treated site should be gently massaged so that it conforms to the contour of the surrounding tissues. If an overcorrection has occurred, massage the area firmly between your fingers or against an underlying 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. Blanching may represent a vessel occlusion. If normal skin coloring does not return, do not continue with the injection. Treat in accordance with the American Society for Dermatologic Surgery guidelines, which include hyaluronidase injection [1]

9. If the wrinkle needs further treatment, the same procedure should be repeated until a satisfactory result is obtained. Additional treatment with *Restylane® Lyft with Lidocaine* 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® Lyft with Lidocaine* is provided with a needle that does not contain engineered injury protection. Administration of *Restylane® Lyft with Lidocaine* 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

Galderma Laboratories, L.P. and its distributor, McKesson Specialty, are your only sources for FDA-approved *Restylane® Lyft with Lidocaine*. Purchasing from any other agent is illegal.

To order, call 1-855-425-8722

Revised: June 2015

90-39411-03

[1]Alam M, Gladstone H, Kramer EM, et al. ASDS guidelines of care: injectable fillers. *Dermatol Surg.* 2008;34(suppl 1):S115-S148.