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.

Restylane® Lyft with Lidocaine is indicated for injection into the subcutaneous plane in the dorsal hand to correct volume deficit 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* is contraindicated for 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, erythema, bruising, itching, 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 generally with less than 2 weeks duration. Refer to the Adverse Experiences section for details.
- *Restylane® Lyft with Lidocaine* must not be implanted into blood vessels and should not be used in vascular rich areas. Localized superficial necrosis and scarring may occur after

injection in or near vessels, such as in the lips, nose, or glabella area. It is thought to result from the injury, obstruction, or compromise of blood vessels. Special caution should be taken if the patient has undergone a prior surgical procedure in the planned treatment area.

- 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.

- 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.

- Special care should be taken to avoid injection into veins or tendons in the hand. Injection into tendons may weaken tendons and cause tendon rupture. Injection into veins may cause embolization or thrombosis.

- Injection into the hand may cause adverse events that last for more than 96 days. In a clinical study, 24.7% of subjects had at least a 10 degree negative change in thumb flexion which persisted through the course of the 6-months duration study. Refer to adverse events sections for additional details.

- Injection of the dorsum of the hand may cause pain in extremity and peripheral swelling.

- Injection of Restylane Lyft in the hand and post-treatment behavior such as strenuous use or trauma to the hands may increase the risk for delayed onset AEs in the hand.

Precautions

- *Restylane® Lyft with Lidocaine* is packaged for single patient use. Do not resterilize. Do not use if package is opened or damaged.
- 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.
- 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.
- 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. For the treatment of dorsal hand volume deficit, the maximum recommended dose per hand is 3.0 mL based on U.S. clinical studies. The safety of injection greater amounts has not been established.

- 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.
- Correction of volume deficit in the dorsal hand 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 the subcutaneous plane.
- Safety of *Restylane® Lyft with Lidocaine* injected into the dorsum of the hand in patients under 22 years old has not been studied.
- The safety or effectiveness of *Restylane® Lyft with Lidocaine* for the treatment of anatomic regions other than nasolabial folds, midface area and dorsal hand has not been established in controlled clinical studies.
- The safety and effectiveness of cannula injection of *Restylane® Lyft with Lidocaine* for cheek augmentation and correction of age-related midface contour deficiencies have only been clinically evaluated in three brands of blunt-tip cannulas (DermaSculpt, Softfil, and TSK Steriglide) that were 25G-27G and 1.5 or 2 inches in length.
- 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 in controlled clinical studies.
- The safety of *Restylane® Lyft with Lidocaine* for use during pregnancy, in breastfeeding females or in patients under 22 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 (MA—1400-01) 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.

- Injection of *Restylane® Lyft Lidocaine* in patients with pre-existing tendency toward edema formation may be associated with prominent discoloration and excessive swelling due to fluid build-up.
- Injection of *Restylane® Lyft Lidocaine* too superficially or in facial areas with limited soft tissue support, thin skin or limited soft tissue cover, may result in contour irregularities and palpable lumps.
- *Restylane® Lyft with Lidocaine* should be used with caution in patients on immunosuppressive therapy.
- Use of *Restylane® Lyft with Lidocaine* in dorsal hand in patients with diseases, injuries or disabilities of the hand has not been studied. Care should be used in treating patients with autoimmune disease affecting the hand, hand implants, Dupuytren's contracture, history of hand tumor, vascular malformations, Raynaud's disease and patients at risk for tendon rupture.
- 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.
- Avoid injecting *Restylane® Lyft with Lidocaine* into areas in close proximity to permanent implants, as this could potentially aggravate latent adverse events or interfere with the aesthetic outcome of the treatment. Limited data is available on injecting *Restylane® Lyft with Lidocaine* into an area where an implant other than hyaluronic acid has been placed.
- Patients should minimize exposure of the treated area to excessive sun, UV lamp exposure and extreme temperatures at least until any initial swelling and redness has resolved.
- If epilation, UV irradiation or laser treatment, mechanical or 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.
- Lidocaine should be used with caution in patients receiving other local anesthetics or agents structurally related to amide-type local anesthetics e.g., certain anti-arrhythmics, since the systemic toxic effects can be additive.
- Lidocaine should be used cautiously in patients with epilepsy, impaired cardiac conduction, severely impaired hepatic function or severe renal dysfunction.
- Individual variation and treatment area may affect the bio-degradation of *Restylane® Lyft with Lidocaine*, in rare cases product remnants has been detected in tissue when the clinical effect has returned to baseline.
- *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. After use, syringes and needles/blunt cannula should be handled as potential biohazards. Disposal should be in accordance with accepted medical practice and applicable local, state, and federal requirements.
- *Restylane® Lyft with Lidocaine* should not be mixed with other products before implantation of the device.
- The safety or effectiveness of *Restylane® Lyft with Lidocaine* for the correction of moderate to severe facial folds and wrinkles, such as nasolabial folds and for correction of volume deficit in the dorsal hand, with a small bore, blunt tip cannula has not been established in controlled clinical studies.

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. It is also indicated for injection into the subcutaneous plane in the dorsal hand to correct volume deficit 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. Adverse event information for *Restylane® Lyft with Lidocaine* using a small bore, blunt-tip cannula for subcutaneous to supraperiosteal implantation for cheek augmentation and correction of age-related midface contour deficiencies in patients over the age of 21 is presented in Tables 14-16. Adverse event information for Restylane Lyft with Lidocaine use in the dorsal hand to correct volume deficit is presented in Tables 17-18.

***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 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	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

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®*.

Restylane® Lyft with Lidocaine **using a needle 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* using a needle 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.

Study conducted for the use of a small bore, blunt tip cannula for cheek augmentation and correction of midface contour deficiencies in patients over the age of 21.

Clinical study 43USC1633 was a multicenter, open-label, single-arm prospective study of cannula injection of *Restylane® Lyft with Lidocaine* for cheek augmentation and the correction of age related midface contour deficiencies. Three brands of cannula were evaluated (DermaSculpt, Softfil, and TSK Steriglide), and all were 25G-27G and 1½ or 2 inches in length.

The study was conducted at 4 sites in the U.S. with sixty (60) subjects enrolled and treated. The study included 33 subjects with Fitzpatrick skin types I, II, or III, and 27 subjects with skin types IV, V, or VI of which 14 were FST V or VI.

Safety was evaluated by collecting adverse events (AEs) throughout the study. A subject diary was used to document pre-defined, expected, post-treatment events (i.e., pain, tenderness, redness, bruising, swelling, and itching) reporting during the first two weeks after treatment at baseline and week 16 (optional re-treatment). Other safety assessments included evaluation by a qualified study staff member of midface firmness, symmetry, sensation, function, mass formation and product palpability.

The majority of subjects (91.7%, 55/60 subjects) reported no AEs/Treatment Emergent AEs (TEAEs) during the study period. Following initial treatment at baseline, a total of five TEAEs were reported by five of the 60 subjects enrolled (8.3%), and included, by preferred term: ear pain, influenza, arthropod bite, headache, and presyncope. There were no TEAEs reported after re-treatment at week 16.

TEAEs by severity are presented by MedDRA System Organ Class (SOC) and Preferred Term (PT) in Table 14. There was one severe TEAE (ear pain assessed as unrelated to injection product and/or injection procedure), and no serious AEs (SAEs) observed during the study.

Of the five TEAEs reported, only one was assessed as related to the product and/or injection procedure (mild presyncope); the event occurred and resolved on the same day as treatment.

Table 14. Summary of TEAEs by Severity: Safety Population					
		Initial treatment N=60		Optional re-treatment N=43	
Primary System Organ Class *Preferred Term*	Intensity	Events	Subjects n (%)	Events	Subjects n (%)
Ear and labyrinth disorders					
Ear pain	Total	1	1 (1.7%)	0	0 (0.0%)
	Mild	0	0 (0.0%)	0	0 (0.0%)
	Moderate	0	0 (0.0%)	0	0 (0.0%)
	Severe	1	1 (1.7%)	0	0 (0.0%)
Infections and infestations					
Influenza	Total	1	1 (1.7%)	0	0 (0.0%)
	Mild	1	1 (1.7%)	0	0 (0.0%)
	Moderate	0	0 (0.0%)	0	0 (0.0%)
	Severe	0	0 (0.0%)	0	0 (0.0%)
Injury, poisoning and procedural complications					
Arthropod bite	Total	1	1 (1.7%)	0	0 (0.0%)
	Mild	1	1 (1.7%)	0	0 (0.0%)
	Moderate	0	0 (0.0%)	0	0 (0.0%)
	Severe	0	0 (0.0%)	0	0 (0.0%)
Nervous system disorders					
Headache	Total	1	1 (1.7%)	0	0 (0.0%)
	Mild	1	1 (1.7%)	0	0 (0.0%)
	Moderate	0	0 (0.0%)	0	0 (0.0%)
	Severe	0	0 (0.0%)	0	0 (0.0%)
Presyncope	Total	1	1 (1.7%)	0	0 (0.0%)
	Mild	1	1 (1.7%)	0	0 (0.0%)
	Moderate	0	0 (0.0%)	0	0 (0.0%)
	Severe	0	0 (0.0%)	0	0 (0.0%)

% = (n/N)*100
Note: TEAE = Treatment Emergent AE.
Note: AEs are coded using MedDRA version 20.0.

Pre-defined, expected post-treatment events occurring after treatment were collected in a subject diary by day during a 14-day period, starting on the day of treatment. The table below lists the maximum intensity of events recorded in the initial treatment and optional re-treatment diaries for the right and left midface combined.

Almost all subjects (98.3%, 59/60 subjects) reported at least one diary symptom following initial treatment at baseline. For the optional re-treatment at week 16, the proportion of subjects reporting at least one diary symptom decreased to 74.4% (32/43 subjects).

The majority of all reported symptoms were assessed as tolerable by subjects in both initial and optional re-treatment diaries. The most commonly reported symptom was tolerable tenderness followed by tolerable swelling and tolerable pain. There were few reports of symptoms that affected daily activities, and no reports of disabling symptoms in either diary.

Table 15. Pre-Defined, Expected Post-Treatment Events Recorded in Subject Diary After Treatment by Maximal Intensity: Safety Population		
Subject Diary Symptoms	Initial treatment N=60	Optional re-treatment N=43
Right and left midface combined		
Maximum severity reported for any diary symptom	n (%)	n (%)
None	1 (1.7%)	11 (25.6%)
Tolerable	53 (88.3%)	31 (72.1%)
Affects daily activities	6 (10.0%)	1 (2.3%)
Disabling	0 (0.0%)	0 (0.0%)
Pain	60	43
None	24 (40.0%)	22 (51.2%)
Tolerable	34 (56.7%)	21 (48.8%)
Affects daily activities	2 (3.3%)	0 (0.0%)
Disabling	0 (0.0%)	0 (0.0%)
Tenderness	60	43
None	5 (8.3%)	12 (27.9%)
Tolerable	54 (90.0%)	30 (69.8%)
Affects daily activities	1 (1.7%)	1 (2.3%)
Disabling	0 (0.0%)	0 (0.0%)
Redness	60	43
None	34 (56.7%)	34 (79.1%)
Tolerable	25 (41.7%)	9 (20.9%)
Affects daily activities	1 (1.7%)	0 (0.0%)
Disabling	0 (0.0%)	0 (0.0%)
Bruising	60	43
None	42 (70.0%)	32 (74.4%)
Tolerable	18 (30.0%)	11 (25.6%)
Affects daily activities	0 (0.0%)	0 (0.0%)
Disabling	0 (0.0%)	0 (0.0%)
Swelling	60	43
None	22 (36.7%)	16 (37.2%)
Tolerable	36 (60.0%)	27 (62.8%)
Affects daily activities	2 (3.3%)	0 (0.0%)
Disabling	0 (0.0%)	0 (0.0%)
Itching	60	43
None	49 (81.7%)	39 (90.7%)
Tolerable	10 (16.7%)	4 (9.3%)
Affects daily activities	1 (1.7%)	0 (0.0%)
Disabling	0 (0.0%)	0 (0.0%)

% = (n/N)*100

The majority of all symptoms resolved in 7 days or less, as recorded in the initial treatment and optional re-treatment diaries, which is consistent to what has previously been reported for needle injections.

Table 16. Number of Days with Post-Treatment Events Recorded in the Subject Diary: Safety Population
Initial treatment (N=60)

	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	36 (60.0%)	13 (36.1%)	23 (63.9%)	0 (0.0%)	0 (0.0%)
Tenderness	55 (91.7%)	4 (7.3%)	45 (81.8%)	5 (9.1%)	1 (1.8%)
Redness	26 (43.3%)	14 (53.8%)	11 (42.3%)	1 (3.8%)	0 (0.0%)
Bruising	18 (30.0%)	3 (16.7%)	14 (77.8%)	1 (5.6%)	0 (0.0%)
Swelling	38 (63.3%)	8 (21.1%)	28 (73.7%)	2 (5.3%)	0 (0.0%)
Itching	11 (18.3%)	4 (36.4%)	7 (63.6%)	0 (0.0%)	0 (0.0%)
Optional re-treatment (N=43)					
	Number of days				
Location/ Adverse Event	Any[2)] n (%)	1 n (%)	2-7 n (%)	8-13 n (%)	14 n (%)
Pain	21 (48.8%)	8 (38.1%)	12 (57.1%)	0 (0.0%)	1 (4.8%)
Tenderness	31 (72.1%)	1 (3.2%)	29 (93.5%)	0 (0.0%)	1 (3.2%)
Redness	9 (20.9%)	4 (44.4%)	4 (44.4%)	0 (0.0%)	1 (11.1%)
Bruising	11 (25.6%)	3 (27.3%)	7 (63.6%)	0 (0.0%)	1 (9.1%)
Swelling	27 (62.8%)	7 (25.9%)	17 (63.0%)	2 (7.4%)	1 (3.7%)
Itching	4 (9.3%)	1 (25.0%)	2 (50.0%)	1 (25.0%)	0 (0.0%)

1) Percentages are based on the number of subjects receiving initial treatment.
2) Percentages are based on the number of subjects receiving re-treatment.
Note: Percentages for duration categories are based on the number of subjects reporting the symptom ("Any") for the specified location.
Note: Subjects were only required to complete 14 days of diary reporting.
Note: Two subjects had events recorded on day 14 of the diary. These events were followed to resolution by the investigator.

Midface safety assessments including firmness, sensation, device palpability, and function were normal for all subjects at all post-treatment evaluation time points. There were no reports of mass formation and no reports of asymmetry between left and right midface at study end.

***Restylane® Lyft with Lidocaine* for injection into the subcutaneous plane in the dorsal hand to correct volume deficit in patients over the age of 21.**

One U.S. study was conducted in support of *Restylane® Lyft with Lidocaine* for injection in the dorsal hand to correct volume deficit in patients over the age of 21.

Clinical study 43USH1501 was a prospective, multi-center, randomized, evaluator-blinded, paired (split-hand) study designed to evaluate the safety and efficacy of *Restylane® Lyft* with Lidocaine for injection in the dorsal hand to correct volume deficit in patients over the age of 21. The study was conducted at 5 investigational sites and included 89 patients who were injected with a Terumo 29G x ½" thin-walled sharp needle.

For needle subjects only, adverse events were recorded in subject diaries (28 days post-treatment) as well as by physician evaluations.

Subjects were asked to record symptoms of bruising, redness, swelling, pain, tenderness, itching, and impaired hand function in a 28-Day patient diary. Subject's scores for the severity of these

events are presented in Table 17 and durations are provided in Table 18. After the first injection, most events resolved within the first week and most reactions reported were mild.

Table 17. Maximum Intensity of Post-Treatment Injection Site Reactions Recorded in the Subject Diary (Safety Population)

	Initial Treatment			6 Month Treatment		
	Restylane® Lyft hand		Fellow Hand	Restylane® Lyft hand	Fellow Hand	
Event Severity	Treatment (N=89)[b]	Touch-Up (N=74)[b]	No Treatment[a] (N=89)[b]	Re-treatment (N=70)	Treatment (N=77)	Touch-Up (N=44)
Bruising						
Total	53 (60.2%)	37 (50.7%)	1 (1.1%)	29 (41.4%)	48 (62.3%)	17 (38.6%)
Mild	43 (48.9%)	32 (43.8%)	1 (1.1%)	23 (32.9%)	32 (41.6%)	13 (29.5%)
Moderate	10 (11.4%)	5 (6.8%)	0	6 (8.6%)	15 (19.5%)	4 (9.1%)
Severe	0	0	0	0	1 (1.3%)	0
Itching						
Total	12 (13.6%)	7 (9.6%)	0	8 (11.4%)	10 (13.0%)	10 (22.7%)
Mild	11 (12.5%)	6 (8.2%)	0	6 (8.6%)	6 (7.8%)	10 (22.7%)
Moderate	1 (1.1%)	1 (1.4%)	0	2 (2.9%)	4 (5.2%)	0
Severe	0	0	0	0	0	0
Pain						
Total	39 (44.3%)	26 (35.6%)	0	30 (42.9%)	42 (54.5%)	11 (25.0%)
Mild	30 (34.1%)	25 (34.2%)	0	20 (28.6%)	26 (33.8%)	8 (18.2%)
Moderate	8 (9.1%)	1 (1.4%)	0	10 (14.3%)	13 (16.9%)	2 (4.5%)
Severe	1 (1.1%)	0	0	0	3 (3.9%)	1 (2.3%)
Redness						
Total	63 (71.6%)	41 (56.2%)	0	42 (60.0%)	50 (64.9%)	20 (45.5%)
Mild	52 (59.1%)	39 (53.4%)	0	34 (48.6%)	33 (42.9%)	19 (43.2%)
Moderate	11 (12.5%)	2 (2.7%)	0	7 (10.0%)	16 (20.8%)	1 (2.3%)
Severe	0	0	0	1 (1.4%)	1 (1.3%)	0
Swelling						
Total	66 (75.0%)	43 (58.9%)	1 (1.1%)	31 (44.3%)	47 (61.0%)	22 (50.0%)
Mild	45 (51.1%)	34 (46.6%)	1 (1.1%)	18 (25.7%)	27 (35.1%)	16 (36.4%)
Moderate	19 (21.6%)	9 (12.3%)	0	12 (17.1%)	19 (24.7%)	5 (11.4%)
Severe	2 (2.3%)	0	0	1 (1.4%)	1 (1.3%)	1 (2.3%)
Tenderness						
Total	66 (75.0%)	49 (67.1%)	2 (2.3%)	41 (58.6%)	55 (71.4%)	26 (59.1%)
Mild	51 (58.0%)	42 (57.5%)	2 (2.3%)	28 (40.0%)	31 (40.3%)	21 (47.7%)
Moderate	14 (15.9%)	7 (9.6%)	0	11 (15.7%)	20 (26.0%)	4 (9.1%)
Severe	1 (1.1%)	0	0	2 (2.9%)	4 (5.2%)	1 (2.3%)
Impaired Function						

Table 17. Maximum Intensity of Post-Treatment Injection Site Reactions Recorded in the Subject Diary (Safety Population)

	Initial Treatment			6 Month Treatment		
	Restylane® Lyft hand		Fellow Hand	Restylane® Lyft hand	Fellow Hand	
Event Severity	Treatment (N=89)[b]	Touch-Up (N=74)[b]	No Treatment[a] (N=89)[b]	Re-treatment (N=70)	Treatment (N=77)	Touch-Up (N=44)
Total	6 (6.8%)	3 (4.1%)	0	3 (4.3%)	8(10.4%)	1 (2.3%)

[a] Four subjects reported injection site reactions on the fellow hand during the no treatment phase.
[b] One subject did not hand in the diary from the Initial treatment (first treatment and touch-up)

Table 18. Number of Days with Post-Treatment Injection Site Reactions Recorded in the Subject Diary (Safety Population)

	Initial Treatment			6 Month Treatment		
	Restylane® Lyft hand		Fellow Hand	Restylane® Lyft hand	Fellow Hand	
Event Statistic	Treatment (N=89)	Touch-Up (N=74)	No Treatment [a] (N=89)	Re-treatment (N=70)	Treatment (N=77)	Touch-Up (N=44)
Bruising						
N	53	37	1	29	48	17
Mean	2.7	3.3	1.0	2.9	3.0	3.5
SD	1.66	3.54	N/A	1.58	1.69	1.87
Median	2.0	2.0	1.0	3.0	2.0	3.0
Min. to Max.	1 to 8	1 to 18	1 to 1	1 to 7	1 to 7	1 to 7
Itching						
N	12	7	0	8	10	10
Mean	1.7	1.6		4.4	3.1	2.0
SD	0.89	1.13		3.70	2.51	1.15
Median	1.0	1.0		3.5	3.0	2.0
Min. to Max.	1 to 3	1 to 4		1 to 11	1 to 9	1 to 4
Pain						
N	39	26	0	30	42	11
Mean	2.7	1.9		3.3	2.7	3.2
SD	3.40	1.18		5.02	2.12	3.12
Median	2.0	1.5		2.0	2.0	2.0
Min. to Max.	1 to 21	1 to 5		1 to 28	1 to 9	1 to 10
Redness						
N	63	41	0	42	50	20
Mean	2.2	2.7		2.1	2.5	2.6
SD	1.45	2.32		1.11	1.47	1.90
Median	2.0	2.0		2.0	2.0	2.0
Min. to Max.	1 to 7	1 to 12		1 to 6	1 to 7	1 to 9
Swelling						
N	66	43	1	31	47	22
Mean	3.4	4.3	2.0	5.0	3.3	3.3
SD	2.83	4.60	N/A	5.59	2.43	2.38
Median	3.0	3.0	2.0	3.0	3.0	3.0
Min. to Max.	1 to 16	1 to 21	2 to 2	1 to 28	1 to 15	1 to 11
Tenderness						
N	66	49	2	41	55	26
Mean	4.5	5.1	1.0	4.4	3.9	4.2
SD	5.70	5.46	0.00	4.91	2.72	3.59
Median	3.0	3.0	1.0	3.0	3.0	2.0
Min. to Max.	1 to 27	1 to 27	1 to 1	1 to 28	1 to 17	1 to 14
Impaired Function						
N	6	3	0	3	8	1
Mean	2.0	1.3		2.3	3.1	1.0
SD	1.55	0.58		1.15	1.73	N/A
Median	1.0	1.0		3.0	3.0	1.0
Min. to Max.	1 to 4	1 to 2		1 to 3	1 to 5	1 to 1

[a] Four subjects reported injection site reactions on the fellow hand during the no treatment phase.

Hand function safety assessments, including range of motion, functional dexterity, pinch and grip strength, and sensation were evaluated at all required study follow up visits. Passive and active range of motion testing in the fingers (extension) revealed negligible change. In the active flexion test for the thumb, there was slightly reduced flexion after treatment. There were 22 subjects out of

89 (24.7%) injected with needle that had at least 10-degree negative change of active flexion for thumb of the treated hand compared to baseline or non-treated hand that remain through the duration of the study. However, for 10 of these 22 subjects, a decrease in the non-treated (fellow) hand was also observed. A summary is provided in Table 19. There was no evidence of loss of sensation for any subject throughout the course of the study. Strength tests revealed no appreciable loss of strength for the grip and pinch strength tests.

Table 19: Active Flexion Range of Thumb Data for Subjects with at least 10-degree negative change

Patient ID	Start Visit of First Episode	Number of Episodes	Duration of Longest Episode (Days)
Patient 1	Week 16	1	76
Patient 2	Week 2 following touch-up	2	>141
Patient 3	Week 2 following touch-up	2	36
Patient 4	Week 2	3	>114
Patient 5	Week 2	2	104
Patient 6	Week 4	2	>176
Patient 7	Week 2	2	>186
Patient 8	Week 4 following touch-up	1	62
Patient 9	Week 2	1	>215
Patient 10	Week 16	1	37
Patient 11	Week 2	3	84
Patient 12	Week 2	2	70
Patient 13	Week 2	1	>189
Patient 14	Week 2	2	129
Patient 15	Week 16	1	52
Patient 16	Week 12	1	31
Patient 17	Week 20	1	30
Patient 18	Week 2	1	>1
Patient 19	Week 20	1	29
Patient 20	Week 4	1	18
Patient 21	Week 4 following touch-up	1	28
Patient 22	Week 2	1	21

Note: Episode duration is calculated as study day for first visit with no decrease in Active Flexion Range of Thumb after an episode, MINUS study day with first decrease in Active Flexion Range of Thumb.
Note: “>” indicates that there is no assessment with no decrease in Active Flexion Range of Thumb for an episode, and instead the last study day is used as stop day.

Results from subject assessment of the hand-specific impact on daily life activities using the unvalidated monolateral Michigan Hand Questionnaire (MHQ) showed a negligible effect on subject’s daily life activities. The majority of subjects responded with favorable answers to all questions at each study visit assessed (Baseline, Week 12, and Week 24). The majority of subjects

were dissatisfied with the appearance of their hands at Baseline with a shift in response to satisfaction at Weeks 12 and 24.

A total of 37 (41.6%) subjects experienced at least one Treatment Emergent Adverse Event (TEAE), in total 82 events. The majority of TEAEs were mild in intensity (N=66 mild, 16 moderate, and no severe). There were no SAEs related to the study product or procedure reported in this trial.

A summary of all Treatment Emergent Adverse Events (TEAEs) can be seen in Table 20.

Table 20. Treatment Emergent Adverse Events by Intensity and Preferred Term
(Safety Population N=89)

Preferred Term	Grade of Intensity			Number	Number of Subjects	
	Mild	Moderate	Severe	of Events	n	%
Vitreous detachment	1	.	.	1	1	1.1
Cyst rupture	1	.	.	1	1	1.1
Device failure	1	.	.	1	1	1.1
Facial pain	1	.	.	1	1	1.1
Influenza like illness	.	1	.	1	1	1.1
Peripheral swelling	4	2	.	6	4	4.5
Bronchitis	1	1	.	2	2	2.2
Chronic sinusitis	.	2	.	2	1	1.1
Gastroenteritis	1	.	.	1	1	1.1
Nasopharyngitis	2	.	.	2	2	2.2
Onychomycosis	1	.	.	1	1	1.1
Oral herpes	1	.	.	1	1	1.1
Sinusitis	2	.	.	2	2	2.2
Tooth infection	1	1	.	2	2	2.2
Upper respiratory tract infection	1	.	.	1	1	1.1
Animal scratch	1	.	.	1	1	1.1
Burns first degree	1	.	.	1	1	1.1
Contusion	1	2	.	3	2	2.2
Eye injury	1	.	.	1	1	1.1
Laceration	5	1	.	6	6	6.7
Limb injury	1	.	.	1	1	1.1
Nail injury	1	.	.	1	1	1.1
Scratch	7	.	.	7	6	6.7
Thermal burn	2	.	.	2	2	2.2
Blood cholesterol increased	1	.	.	1	1	1.1
Vitamin D deficiency	1	.	.	1	1	1.1
Back pain	.	1	.	1	1	1.1
Muscle spasms	1	.	.	1	1	1.1
Musculoskeletal pain	.	1	.	1	1	1.1
Pain in extremity	7	.	.	7	5	5.6
Rotator cuff syndrome	1	.	.	1	1	1.1
Basal cell carcinoma	1	.	.	1	1	1.1
Lobular breast carcinoma in situ	1	.	.	1	1	1.1
Thyroid neoplasm	1	.	.	1	1	1.1
Uterine leiomyoma	.	1	.	1	1	1.1
Migraine	1	.	.	1	1	1.1
Urinary tract infection	1	.	.	1	1	1.1
Uterine polyp	.	1	.	1	1	1.1
Cough	.	1	.	1	1	1.1
Actinic keratosis	2	.	.	2	1	1.1
Dermatitis contact	.	1	.	1	1	1.1
Eczema	1	.	.	1	1	1.1
Onycholysis	2	.	.	2	1	1.1
Photosensitivity reaction	1	.	.	1	1	1.1
Pruritus	2	.	.	2	1	1.1
Rash	2	.	.	2	2	2.2
Skin mass	1	.	.	1	1	1.1
Urticaria	1	.	.	1	1	1.1

Adverse events that occurred in >2.5% of the study population consisted of peripheral swelling [4 subjects (4.5%)], laceration [6 subjects (6.7%)], scratch [(6 subjects (6.7%)], and pain in extremity [5 subjects (5.6%)] with the majority of TEAEs being mild in intensity (N=66 mild, 16 moderate, and no severe).

Of the 37 subjects reporting a TEAE, 7 subjects (7/89 [7.9%]) reported TEAEs classified as related to the product and/or injection procedure (with 13 total related events). For the 89 subjects in the Safety population, three hand-specific related TEAEs were reported in 3 subjects (3/89, 3.4%) after first treatment (first treatment in the randomized hand) and included peripheral swelling (2/89, 2.2%), and skin mass (1/89, 1.1%). In the second treatment (treatment in fellow [non-randomized] hand), 5 hand-specific related TEAEs were reported in 3 subjects (3/77, 3.9%) and included peripheral swelling (2/77, 2.6%), pain in extremity (2/77, 2.6%), and pruritis (1/77, 1.3%). Four hand-specific related TEAEs were reported in 2 subjects (2/70, 2.9%) in the 3rd treatment (Re-treatment at 24 weeks).

Of the 7 subjects with product/injection procedure related TEAEs, 4 subjects received medical treatment. Treatment included NSAIDS, oral antihistamines, topical and oral corticosteroids, hyaluronidase, and antibiotics.

Five of these 7 subjects experienced delayed onset (>21 days) related TEAEs and 2 additional subjects reported delayed onset related AEs after exit from the study The delayed adverse events were mild to moderate and included swelling, nodules, tenderness, itching, tingling, and erythema. Four of these subjects received treatment as mentioned above. All events were followed to resolution. A summary of all Delayed Treatment Emergent Adverse Events (TEAE) can be seen in Table 21.

Table 21. Delayed Onset Treatment Emergent Adverse Events (TEAE)

	FST	Injection method	AE start day rel. last trt	AE duration	Severity Intensity	Reported AE term	Treatment of the AE
Patient 1	TYPE III	Needle	113	89	MILD	SINGLE SUB-CUTANEOUS NODULE	None
Patient 2	TYPE III	Needle	28	5	MILD	ITCHING ON THE DORSUM OF THE LEFT HAND	None
			28	5	MILD	ITCHING ON THE DORSUM OF THE RIGHT HAND	None
			28	5	MILD	SWELLING TO THE DORSUM OF THE LEFT HAND	None
			28	5	MILD	SWELLING TO THE DORSUM OF THE RIGHT HAND	None
			28	5	MILD	TENDERNESS TO THE DORSUM OF THE LEFT HAND	None
			28	5	MILD	TENDERNESS TO THE DORSUM OF THE RIGHT HAND	None
Patient 3	TYPE III	Needle	48	51	MODERATE	SWELLING TO THE DORSUM OF THE LEFT HAND	Ibuprofen, Chloreniramine Maleate, Hydrocortisone Cream, Medrol Dose Pack, Hyaluronidase, Bethamethasone Dipropinate

Table 21. Delayed Onset Treatment Emergent Adverse Events (TEAE)							
	FST	Injection method	AE start day rel. last trt	AE duration	Severity Intensity	Reported AE term	Treatment of the AE
			20	51	MODERATE	SWELLING TO THE DORSUM OF THE RIGHT HAND	Ibuprofen, Chloreniramine Maleate, Hydrocortisone Cream, Medrol Dose Pack, Hyaluronidase, Bethamethasone Dipropinate
Patient 4	TYPE III	Needle	71	96	MILD	PROLONGED SWELLING OF THE DORSUM OF THE RIGHT HAND	Ibuprofen
Patient 5	TYPE V	Needle	151	49	MILD	SWELLING TO THE DORSUM OF THE LEFT HAND	Benadryl Cream, Hydrocortisone Cream, Methlypredisolone, Sulfamethoxazole, Hyaluronidase, Ice
Patient 6*	TYPE II	Needle	300	136	MILD	GRANULOMA	None
Patient 7*	TYPE IV	Needle	210	4	MODERATE	SWELLING	Medrol Dose Pack

*Indicates the adverse event reported post-study exit.

Cannula Cohort (Hand) Results

A cohort study with cannula injection of *Restylane Lyft with Lidocaine* was performed on 25 subjects (24 FST I-IV subjects and 1 FST V-VI subjects) in two U.S. sites. The benefits and risks of injecting *Restylane Lyft with Lidocaine* using a cannula for the hand indication have not been established. The study was not designed or powered to assess the safety and effectiveness of the use of cannula or to compare its performance to the use of a needle. Preliminary results indicate that cannula use was associated with higher number of TEAEs, delayed adverse events and negative change in the active flexion for thumb as compared to needle injections. However, it was not possible to control or adjust for important potential confounders such as injection techniques, cannula size, and physician's skills.

Rates of TEAE were higher in the cannula cohort (41 events in 17 of 25 cannula-injected subjects, 17/25 = 68.0%) compared to those rates observed in subjects who received *Restylane Lyft with Lidocaine* administered with needle (82 events in 37 of 89 needle-injected subjects, 37/89 = 41.6%). When the device was injected with needle (N=89) 12 hand-specific related TEAEs were reported and 3 of them were related to the 1st treatment (3 events occurred in 3 subjects, 3/89 = 3.3%) compared with Cannula injection (N=25) where 15 hand-specific related TEAEs in 7 subjects were reported related to the 1st treatment (15 events occurred in 7 subjects, 7/25 = 28%).

Regarding delayed adverse events, there appeared to be higher rates of delayed AE in the subjects who received *Restylane Lyft with Lidocaine* with cannula compared to those who received needle. In 13 subjects with delayed AEs (> 21 day after treatment), 6 subjects who had Needle injection had delayed AE (6/89 = 6.7%) and 7 subjects who received Cannula injection experienced delayed AE (7/25 = 28%).

Regarding negative change in the active flexion for thumb, there were 22 subjects out of 89 (24.7%) injected with the needle that had at least a 10-degree negative change of action flexion for thumb of the treated hand compared to baseline or non-treated hand that remain through the duration of the study.However, for 10 of these 22 subjects, a decrease in the non-treated (fellow) hand was also

observed. There were 9 subjects out of 25 (36%) injected with the cannula that had at least a 10-degree negative change of action flexion for the thumb of the treated hand compared to baseline or non-treated hand that remain through the duration of the study. However, for 1 of these 9 subjects, a decrease in the non-treated (fellow) hand was also observed.

Post-Marketing Surveillance:

The adverse event reports received from post-marketing surveillance (from voluntary reporting and published literature) for the use of *Restylane® Lyft with Lidocaine* and *Perlane®* for all indications (including cheek) included reports of swelling/oedema or inflammatory reactions immediate or delayed onset, up to several weeks after treatment. The following events were also reported: short duration of effect, mass formation including lumps or bumps, induration, pain or tenderness, erythema, bruising/hematoma, presumptive bacterial infections and abscess formation, papules or nodules, inflammation, injection site reactions including burning sensation, warmth and irritation, discoloration/hyperpigmentation, neurological symptoms including hypoaesthesia, paraesthesia and facial nerve paralysis, hypersensitivity, angioedema, ischemia and necrosis due to unintentional intravascular injection or embolisation, eye disorders including eye pain, eye swelling, eye irritation, increased lacrimation, eyelid ptosis and visual impairment such as blurred vision, reduced visual acuity and blindness, pruritus, atrophy/scarring, device dislocation, rash, effusion/discharge, granuloma/foreign body reaction, acne, blisters/vesicles, symptoms of reactivation of herpes infection, urticaria, capillary disorder such as telangiectasia, extrusion of device, dermatitis, muscle disorders such as muscle twitching and muscle weakness, encapsulation and other dermatological events including dry skin, skin wrinkling, skin exfoliation and localized alopecia, and non-dermatological events including headache, discomfort, malaise, pyrexia, dizziness, sinusitis, dyspnoea, fatigue, influenza like illness, insomnia, nausea and anxiety.

When required, treatments for these events included ice, massage, warm compress, nitroglycerine paste, corticosteroids, antibiotics, anticoagulants, antihistamines, analgesics, antiviral agents, diuretic agents, aspiration/incision and drainage, surgery or enzymatic degradation (with hyaluronidase) of the product.

Adverse events received from post-marketing surveillance for *Restylane® Lyft with Lidocaine* and *Perlane®* used for cheek augmentation was in line with the reports listed above for all indications. In rare cases, a late onset (weeks to months) and recurrent inflammation was reported post injection. Concurrent localized events/symptoms were nodules or lumps, infection, and redness, swelling and pain. The treatments of these events included hyaluronidase, antibiotics, corticosteroids, analgesics, incision and drainage.

Reports of serious adverse events for *Restylane® Lyft with Lidocaine* and *Perlane®* are rare. The most commonly reported serious adverse events were infection/abscess, ischemia/necrosis, visual impairment, hypersensitivity/allergic reactions, scarring, inflammation, and granuloma including cases of mass/induration. Concurrent serious events/symptoms included: swelling, pain/tenderness, erythema, neurological symptoms such as paresthesia and hypoesthesia, bruising, discoloration, papules/nodules, and overcorrection, overfill and irregular skin.

Serious infections/abscesses were reported with a time to onset ranging from one day to two months following the injection. Most of the patients were recovered or recovering at the time of last contact. The treatments included antibiotics, analgesics, corticosteroids and hyaluronidase.

Serious hypersensitivity reactions were reported in most cases with a time to onset ranging from immediately to few weeks post injection. Most of the events were recovering or recovered at the time of last contact. The treatment included analgesics, antihistamine, antibiotics, and corticosteroids.

Serious granuloma/foreign body reaction including mass/induration, were reported with a time to onset ranging from one day to a year or longer. The outcomes were mostly recovered or recovering at the time of last contact. The treatment included analgesics, antihistamine, antibiotics, corticosteroids and excisions. Biopsies have been taken in some cases, but the majority of cases are non-biopsy confirmed.

Serious inflammation was reported with a time to onset from one to two weeks post injection. Most events were recovered or recovering at the time of last contact. Rare cases of inflammation with delayed onset up to several weeks or months post injection has been observed; particularly if the patient experienced local trauma, facial/dental infection, or local infection. The treatment included analgesics, antibiotics, and corticosteroids.

Vascular occlusion resulting in ischemia/necrosis and vision disturbances including blindness have been reported following injection of any soft tissue filler in the face especially in the nose, glabella, periorbital areas, nasolabial folds and cheek, with a time to onset ranging from immediate to a few weeks following injection. Vascular compromise may occur due to an inadvertent intravascular injection or as a result of vascular compression associated with implantation of any injectable product. This may manifest as blanching, discoloration, necrosis or ulceration at the implant site or in the area supplied by the blood vessels affected; or rarely as ischemic events in other organs due to embolisation. Isolated rare cases of ischemic events affecting the eye leading to visual loss, and the brain resulting in cerebral infarction, following facial aesthetic treatments have been reported.

Reported treatments include anticoagulant, epinephrine, aspirin, hyaluronidase, corticosteroid treatment, analgesics, antibiotics, local wound care, drainage, hyperbaric oxygen and surgery. Outcome of the events ranged from resolved to ongoing at the time of last contact. In many of the events requiring medical intervention, the patient 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).

Injection site bruising, swelling, erythema and pain mostly non-serious generally occurred within 1-2 days after treatment usually resolving within 1 to 4 weeks. Some occurrences have persisted for up to 6 months. Most instances of discoloration including hyperpigmentation, sometimes described as a blue or brown color, 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.

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. *Restylane® Lyft with Lidocaine* is also indicated for injection into the subcutaneous plane in the dorsal hand to correct volume deficit 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)." Clinical trial information 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". Clinical trial information for correction of volume deficit in the dorsal hand is presented in the section titled “U.S. Clinical Study to support the use of *Restylane® Lyft* with Lidocaine for injection in the dorsal hand to correct volume deficit.”

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 22. 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 22. 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 23 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 23. 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%	108 (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 point	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 24 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 24. 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 25 shows the results for the within-patient investigator assessment of NLF on the WSRS. **Table 25. 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 26. 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 26. 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* using a needle 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:

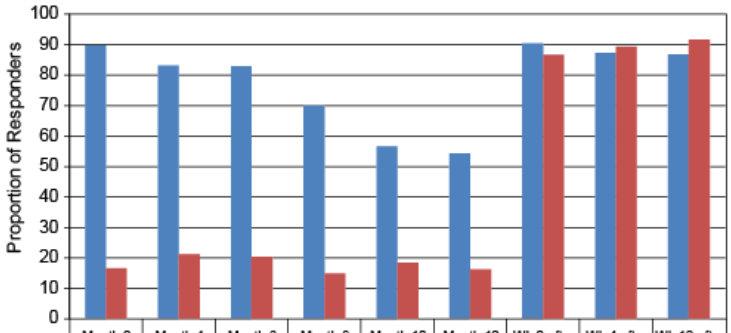
The results of the blinded evaluator assessment of midface fullness (MMVS) for *Restylane® Lyft with Lidocaine* and no treatment control are presented in Table 27. In the primary effectiveness assessment at Month 2, 88.7% of the *Restylane® Lyft with Lidocaine* and 16.0% of the no treatment control patients had at least a 1 point improvement over baseline. Similar results were seen for the treating investigator's assessment of MMVS.

Table 27. 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.

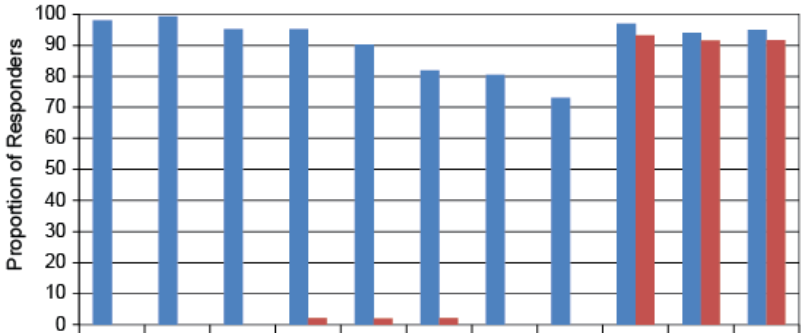
Note: The Proportion of Responders is calculated as the number of Responders at the visit of interest divided by the number of subjects in the ITT population for the specified treatment group with a non-missing assessment for the specified visit.

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.

U.S. Clinical Study to assess the adverse events of *Restylane® Lyft with Lidocaine* in conjunction with the use of a small blunt tip cannula (in the range of 25G-27G) for cheek augmentation and the correction of age related midface contour deficiency in patients over the age of 21.

43USC1633: Multicenter, Open-Label, Prospective Study

Design	This was a multicenter, open-label, prospective study of cannula injection of *Restylane® Lyft with Lidocaine* in 60 subjects seeking cheek augmentation and the correction of age related midface contour deficiency. The study included 33 subjects with Fitzpatrick skin types I, II, or III, and 27 subjects with skin types IV, V, or VI of which 14 were FST V or VI. After treatment at baseline, a 72 hour phone call and follow-up visits at 2, 4, 8 and 16 weeks were scheduled. At the 16-week visit after all study procedures for the visit were completed, subjects received an optional additional treatment if optimal aesthetic improvement was not maintained. If the optional additional treatment was provided, subjects were contacted via phone at 72 hours post-treatment and scheduled for an on-site visit two weeks post-treatment. Safety was evaluated by collecting AEs throughout the study. A subject diary was used to document pre-defined, expected, post-treatment events (i.e., pain, tenderness, redness, bruising, swelling, and itching) reporting during the first two weeks after treatment at baseline and week 16 (optional re-treatment). Other safety assessments included evaluation by a qualified study staff member of midface firmness, symmetry, sensation, function, mass formation and product palpability. Effectiveness was evaluated by the investigator using the GAIS and the MMVS, and by the subject using the GAIS and FACE-Q questionnaire.
Endpoints	**Primary:** The primary objective of the study was to assess the AEs of *Restylane® Lyft with Lidocaine* in conjunction with the use of a small blunt tip cannula for cheek augmentation and the correction of age related midface contour deficiency. Safety objectives included: • incidence, intensity, and duration of all AEs as collected throughout the study and incidence, intensity and duration of pre-defined, expected, post-treatment events reported during the first two weeks after treatment as recorded in the subject diary. • safety assessments of midface firmness, symmetry, sensation, mass formation and product palpability as evaluated by designated study staff. **Secondary:** The secondary objectives were to evaluate the effectiveness of *Restylane® Lyft with Lidocaine* used in conjunction with a small blunt-tip cannula for cheek augmentation and the correction of age related midface contour deficiency. Effectiveness objectives included: • proportion of responders defined as “Improved” or better on the GAIS as assessed by the investigator at weeks 2, 4, 8 and 16. • proportion of responders defined as “Improved” or better on the GAIS as assessed by the subject at weeks 2, 4, 8 and 16.

	• proportion of responders defined as at least one point increase from baseline on both sides of the face using the MMVS as assessed by the investigator at weeks 2, 4, 8 and 16. • proportion of subjects in each response category of the FACE-Q Satisfaction with Outcome Scale at week 8.
Outcomes	**Subject Accountability:** Sixty (60) subjects were enrolled, and 59 completed the study at week 16. At the week 16 visit, subjects could have received an optional additional treatment if optimal aesthetic improvement was not maintained. There were 43 subjects that received the optional re-treatment, and continued in the study an additional two weeks. One subject was lost to follow up and was withdrawn prior to study completion. No subject discontinued due to an AE. **Demographics:** Most subjects were female and White (87%, and 72%, respectively), and the majority identified as not being of Hispanic or Latino decent (88%). The study included 33 subjects (55%) with FST I, II, or III, and 27 subjects (45%) with skin types IV, V, or VI; of which 14 (23 %) were FST V or VI. At baseline, the majority of subjects had moderate right and left midface volume loss. **Extent of Exposure:** All subjects received treatment with *Restylane® Lyft with Lidocaine* in the right and left cheeks at baseline. At week 16, subjects were offered optional re-treatment if the optimal aesthetic improvement was not maintained. In this study, 25G and 27G cannulas were used by the investigators to administer treatment. The brands used were TSK Steriglide, DermasSculpt, and Softfil, and the cannulas were 1.5 inches/40 mm or 2 inches/50mm in length. The mean total volume injected into the right and left midface combined was 3.0 mL for the initial treatment at baseline, and 1.6 mL for the optional re-treatment at week 16. For the right midface, the mean total volume injected was 1.4 mL at baseline and 0.8 mL at week 16. For the left midface, the mean total volume injected at these time points was 1.5 mL and 0.8 mL, respectively. **Safety Results (for tabulated data, see Section Adverse Experiences):** The majority of subjects (91.7%, 55/60 subjects) reported no AEs/TEAEs during the study period. Following initial treatment at baseline, a total of five TEAEs were reported by five of the 60 subjects enrolled (8.3%), and included, by preferred term: ear pain, influenza, arthropod bite, headache, and presyncope. There were no TEAEs reported after re-treatment at week 16. There was one severe TEAE (ear pain assessed as unrelated to injection product and/or injection procedure), and no serious AEs (SAEs) observed during the study. Of the five TEAEs reported, only one was assessed as related to the product and/or injection procedure (mild presyncope); the event occurred and resolved on the same day as treatment. Pre-defined, expected post-treatment events occurring after treatment were collected in a subject diary by day during a 14-day period, starting on the day of treatment.

Almost all subjects (98.3%, 59/60 subjects) reported at least one diary symptom following initial treatment at baseline. For the optional re-treatment at week 16, the proportion of subject reporting at least one diary symptom decreased to 74.4% (32/43 subjects).

The majority of all reported symptoms were assessed as tolerable by subjects in both initial and optional re-treatment diaries. The most commonly reported symptom was tolerable tenderness followed by tolerable swelling and tolerable pain. There were few reports of symptoms that affected daily activities, and no reports of disabling symptoms in either diary.

The majority of all symptoms resolved in 7 days or less as recorded in the initial treatment and optional re-treatment diaries.

Midface safety assessments including firmness, sensation, device palpability, and function were normal for all subjects at all post-treatment evaluation time points. There were no reports of mass formation and no reports of asymmetry between left and right midface at study end.

Effectiveness Results:
The investigator evaluated the degree of improvement from baseline in the appearance of the subject's midface fullness using the GAIS at each post-baseline visit, performed separately for the right and left midface sides. The investigator referred to the subject's baseline archival photographs (obtained prior to injection of the implants at baseline) to aid in the assessment. A responder was defined as "Improved" or better from baseline.

The results of the investigator GAIS assessments demonstrated improvement for all or almost all subjects (ranging from 98.3% to 100.0%) at each post-baseline time point. The results were consistent for the right and left midface sides separately.

Investigator GAIS Over Time – Right and Left Midface Combined: ITT Population

Time Point	No of Subjects	No of Responders	Proportion of Responders	95% Confidence Interval
Week 2	60	60	100.0	94.0, 100.0
Week 4	57	57	100.0	93.7, 100.0
Week 8	59	58	98.3	90.9, 100.0
Week 16	59	58	98.3	90.9, 100.0
2 weeks after Week 16 re-treatment [1)]	43	43	100.0	91.8, 100.0

1) Visit was only required for subjects who received re-treatment at week 16.
Note: GAIS = Global Aesthetic Improvement Scale.
Note: Responder is defined as a subject with a GAIS rating of "Improved", "Much improved" or "Very much improved".
Note: The proportion of responders is calculated as the number of responders at the visit divided by the number of subjects for the specified visit.
Note: Exact 95% confidence limits based on the binomial distribution are used.

Independent of the investigator, subjects also rated the global aesthetic improvement of their midface fullness, relative to pretreatment appearance, using the GAIS at each post-baseline time point. For the right and left midface combined, the vast majority of subjects assessed themselves as improved or better from baseline at each post-baseline time point, with the proportion of responders ranging from 91.5% to 100%. The results were consistent for the right and left midface sides

separately.

Subject GAIS Over Time – Right and Left Midface Combined: ITT Population				
Time Point	No of Subjects	No of Responders	Proportion of Responders	95% Confidence Interval
Week 2	60	57	95.0	86.1 99.0
Week 4	57	55	96.5	87.9, 99.6
Week 8	59	54	91.5	81.3, 97.2
Week 16	59	54	91.5	81.3, 97.2
2 weeks after Week 16 re-treatment [1)]	43	43	100.0	91.8, 100.0

1) Visit was only required for subjects who received re-treatment at week 16.
Note: GAIS = Global Aesthetic Improvement scale.
Note: Responder is defined as a subject with a GAIS rating of "Improved", "Much improved" or "Very much improved".
Note: The proportion of responders is calculated as the number of responders at the visit divided by the number of subjects for the specified visit.
Note: Exact 95% confidence limits based on the binomial distribution are used.

The investigator rated the subject's right and left midface separately for severity of volume deficit or midface contour deficiency using the 4-point MMVS. Scoring of the midface was based on a visual live assessment at defined time points, and not in comparison to the baseline appearance. A responder was defined as at least a one point improvement from the baseline MMVS score.

The MMVS responder rate over time for the right and left midface combined was at or near 100% at each post-baseline time point through week 8. At week 16 the MMVS responder rate decreased to 83.1%, but returned to 100% two weeks following re-treatment. Similar results were demonstrated for the right and left midface separately.

MMVS Over Time – Right and Left Midface Combined: ITT Population				
Time Point	No of Subjects	No of Responders	Proportion of Responders	95% Confidence Interval
Week 2	60	59	98.3	91.1, 100.0
Week 4	57	55	96.5	87.9, 99.6
Week 8	59	59	100.0	93.9, 100.0
Week 16	59	49	83.1	71.0, 91.6
2 weeks after Week 16 re-treatment [1)]	43	43	100.0	91.8, 100.0

1) Visit was only required for subjects who received re-treatment at week 16.
Note: MMVS = Medicis Midface Volume Scale.
Note: Responder is defined as a subject with an improvement of at least one grade in MMVS from baseline.
Note: The proportion of responders is calculated as the number of responders at the visit divided by the number of subjects for the specified visit.
Note: Exact 95% confidence limits based on the binomial distribution are used.

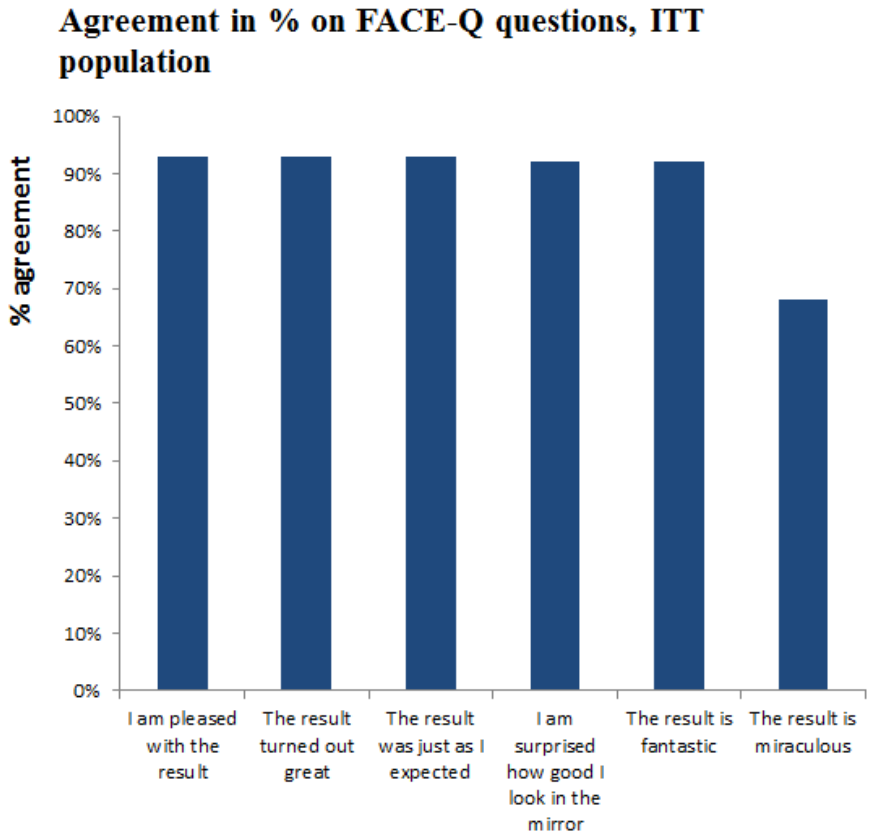
The FACE-Q Questionnaire was used to assess treatment outcome from the subject's perspective. At week 8, subjects indicated their level of agreement or disagreement on several questions related to how they felt about the treatment received at baseline.

The sum of the subject's FACE-Q scores was converted to a Rasch-transformed total score according to the FACE-Q manual; the higher total score indicated greater subject satisfaction. As presented in following table, the mean total score was 77.3. The FACE-Q Satisfaction with Outcome used in the study did not evaluate a change from baseline (ie, before treatment is received). Therefore, baseline scores were not assessed.

FACE-Q Satisfaction with Outcome, Rasch-transformed Total Score at Week 8: ITT population	
FACE-Q Total Score	Total N=59
Week 8	
Mean (SD)	77.3 (23.5)
Median	78.0
Min, Max	0.0, 100.0

Note: FACE-Q – Satisfaction with Outcome Rasch-transformed total score is calculated according to the FACE-Q manual. The scale has a minimum score of 0 and maximum score of 100, with higher scores indicating better satisfaction.

Additionally, a majority of subjects agreed with all of the FACE-Q questions, with greater than 90% of subjects agreeing with five of the six questions.



Note: Agreement includes subjects who reported ‘somewhat agree’ or ‘definitely agree’.
Note: FACE-Q – Satisfaction with Outcome.

U.S. Clinical Study to support the use of *Restylane® Lyft with Lidocaine* for injection into the subcutaneous plane in the dorsal hand to correct volume deficit in patients over the age of 21.

43USH1501: Prospective, Multi-Center, Randomized, Blinded, Controlled Clinical Study

Design	A prospective, multi-center, randomized, evaluator-blinded, paired (split-hand) study designed to evaluate the safety and effectiveness of *Restylane® Lyft with Lidocaine* for injection using a 29 G TW x ½" needle in the dorsal hand to correct volume deficit in subjects over the age of 21. 90 subjects were treated at 5 investigational sites.
Endpoints	The primary effectiveness endpoint was responder rate at Week 12 based on the blinded-evaluator assessment using the MHGS. A responder was defined as a hand with at least 1 point improvement from Baseline on the MHGS. The secondary efficacy endpoints included response rates at Weeks 16, 20, and 24 based on blinded-evaluator live assessments of MHGS, Central Independent Photographic Reviewer's (CIPR) assessment of improvement at Weeks 12, 16, 20, and 24, and aesthetic improvement as assessed by subjects and the treating investigator separately using the Global Aesthetic Improvement Scale (GAIS) at Week 4, at Week 4 following touch-up, Weeks 12, 16, 20, Week 24 prior to treatment, Week 28, and Week 32. Other assessments included a subject questionnaire for satisfaction and perceived improvement of hand function, and the Michigan Hand Outcomes Questionnaire (Brief MHQ) for assessment of impact on normal daily activities. The primary safety objective of study 43USH1501 was to define the incidence of all TEAEs, including safety assessments made by the treating investigator at all visits and subject complaints reported during the first 4 weeks after treatment as recorded in the subject diary. Hand functionality was assessed through active and passive range of motions assessments (extension and flexion for index-, middle-, ring-, small finger and thumb), sensation test, functional dexterity test, and strength test (grip strength, key pinch strength, palmar pinch strength, and tip pinch strength) at all physical visits.
Outcomes	**Demographics** In total, 92 subjects were randomized in the study of which 90 received treatment. One subject did not have at least 1 post-treatment safety assessment and was excluded from the safety analysis leaving a total of 89 subjects in the safety population. Four subjects in the safety population did not meet the inclusion criteria for MHGS; therefore, 85 subjects were included in the ITT population. Overall, the mean age for study subjects was 55.7 ± 9.13 years. The study enrolled 82 females (96.5%) and 3 males (3.5%). The majority of subjects were not Hispanic or Latino (89.4% and 10.6% respectively). The study enrolled the following races: White – 71 (83.5%); Black or African American – 5 (5.9%); Native Hawaiian or Other Pacific Islander – 4 (4.7%); and Other – 5 (5.9%). The study included Fitzpatrick skin types: I – 4 (4.7%); II – 21 (24.7%), III – 39

(45.9%); IV – 12 (14.1%); V – 7 (8.2%); and VI – 2 (2.4%).

The majority of subjects had a baseline MHGS score 2, 3, or 4.

The mean volume of total injection for the initial treatment including touch-up in the randomized hand was 3.07 mL. Mean volume was similar at Baseline treatment (2.13 mL) and the first treatment of the fellow hand (2.05 mL at 6 months). All injections were subcutaneous.

Effectiveness

Results of the primary efficacy analysis, response rate at Week 12 based on MHGS evaluated by the Blinded Evaluator demonstrated the superiority of *Restylane® Lyft with Lidocaine* to no treatment. The difference in responder rates at Week 12 was 64.7%, with 85.9% and 21.2% considered responders for *Restylane® Lyft with Lidocaine* and no treatment, respectively.

The results of the primary efficacy analysis, response rate at Week 12 based on MHGS evaluated by the Blinded Evaluator, which was compared between Restylane® Lyft with Lidocaine and no treatment, demonstrated the superiority of Restylane® Lyft with Lidocaine to no treatment ($p<0.0001$).

Table 28. Summary of Primary Efficacy Endpoint: Responder Rate at Week 12 (ITT Population)

Restylane Lyft with Lidocaine (N=85) Responder[a] at Week 12			
Active Treatment Group (N=85)	**Fellow Hand [Control] (N=85)**	**Difference in Responder Rate**	**p-value[b]**
85.9%	21.20%	64.7%	<0.0001

[a] A responder is defined as having at least 1-point improvement from baseline on the MHGS by the blinded-evaluator assessment.
[b] P-value calculated using McNemar's test.

The first secondary efficacy endpoint, responder rates at Weeks 16, 20, and 24 based on MHGS evaluated by the Blinded Evaluator, demonstrated the superiority of *Restylane® Lyft with Lidocaine* to no treatment.

Table 29. Summary of Responder Rates at Weeks 16, 20, and 24 (ITT Population)			
Restylane Lyft with Lidocaine (N=83*) Responder[a] at Week 16			
Active Treatment Group (N=83)	**Fellow Hand [Control] (N=83)**	**Difference in Responder Rate**	**p-value[b]**
91.6%	19.3%	72.3%	<0.0001
Restylane Lyft with Lidocaine (N=82*) Responder[a] at Week 20			
Active Treatment Group (N=82)	**Fellow Hand [Control] (N=82)**	**Difference in Responder Rate**	**p-value[b]**
82.9%	25.6%	57.3%	<0.0001
Restylane Lyft with Lidocaine (N=83*) Responder[a] at Week 24			
Active Treatment Group (N=83)	**Fellow Hand [Control] (N=83)**	**Difference in Responder Rate**	**p-value[b]**
75.9%	30.1%	45.8%	<0.0001

[a] A responder is defined as having at least a 1-point improvement from baseline on the MHGS by the treatment blinded evaluator.
[b] p-value calculated using McNemar's test.
* N reflects number of subject observations at each timepoint.

The second secondary efficacy endpoint was a CIPR's assessment of hand improvement at Weeks 12, 16, 20, and 24 that demonstrated an increased improvement in the treatment hand compared to the fellow hand at all study visits.

Table 30. Summary of Central Independent Photographic Reviewer's Assessment of Hand Improvement (ITT Population)				
Restylane Lyft (N=85)	**Week 12**	**Week 16**	**Week 20**	**Week 24**
Improvement				
N	84	83	82	83
No	10 (11.9%)	12 (14.5%)	25 (30.5%)	12 (14.5%)
Yes	74 (88.1%)	71 (85.5%)	57 (69.5%)	71 (85.5%)
Fellow Hand				
Improvement				
N	84	83	82	83
No	68 (81.0%)	66 (79.5%)	69 (84.1%)	65 (78.3%)
Yes	16 (19.0%)	17 (20.5%)	13 (15.9%)	18 (21.7%)

The third secondary endpoint, the GAIS, was summarized using dichotomized categories for the following timepoints: Week 4, Week 4 following touch-up, Weeks 12, 16, and 20, Week 24, and Weeks 28 and 32. Subject and Investigator evaluations yielded similar results in the treatment hand at Week 24 (92.8%; 95.2%).

	The fourth secondary efficacy endpoint evaluated the patient's satisfaction with Restylane® Lyft with Lidocaine and assessed at Week 12 based upon a 13-item questionnaire using a 5-point Likert Response Scale (1=Strongly Agree, 2=Agree, 3=Neither agree or disagree, 4=Disagree, 5=Strongly Disagree). Responses to each item were transformed into percent agreement (percentage of subjects with a score of 1 or 2) and are presented descriptively. Overall, the majority of subjects were satisfied with the appearance of the treated hand compared to the untreated (77/84; 91.7%), agreed that the treatment result looks natural (80/84; 95.2%), felt their treated hand appeared more attractive (74/84; 88.1%) and youthful (75/84; 89.3%), would recommend treatment to a friend (71/84; 84.5%) and would undergo repeat treatment in the future (65/84; 77.4%).

HOW SUPPLIED

Restylane® Lyft with Lidocaine is supplied in a disposable glass syringe with a luer-lock 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 or if expiry date or lot number is missing or illegible. Immediately return the damaged product to Galderma Laboratories, L.P.

Rx only

U.S. Patent 5,827,937; 8,455,459; 8,778,909; 8,357,795; 8,450,475; 8,822,676

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SE-752 28 Uppsala
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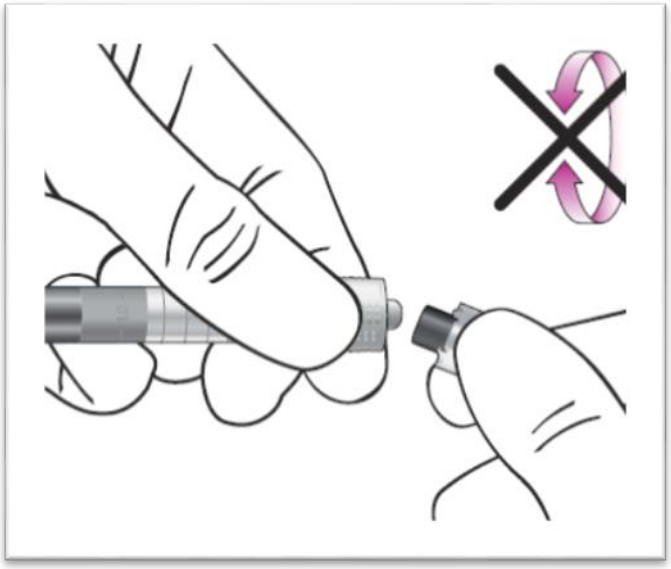
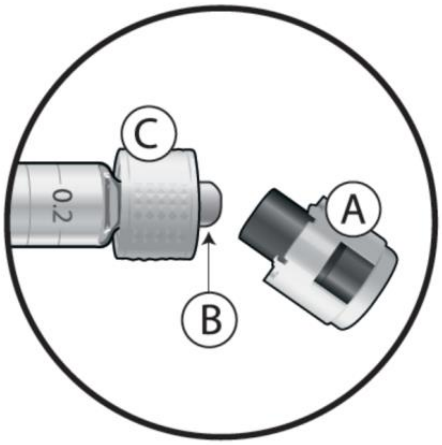
DIRECTIONS FOR ASSEMBLY

For safe use of *Restylane® Lyft with Lidocaine*, it is important that the needle is properly assembled.

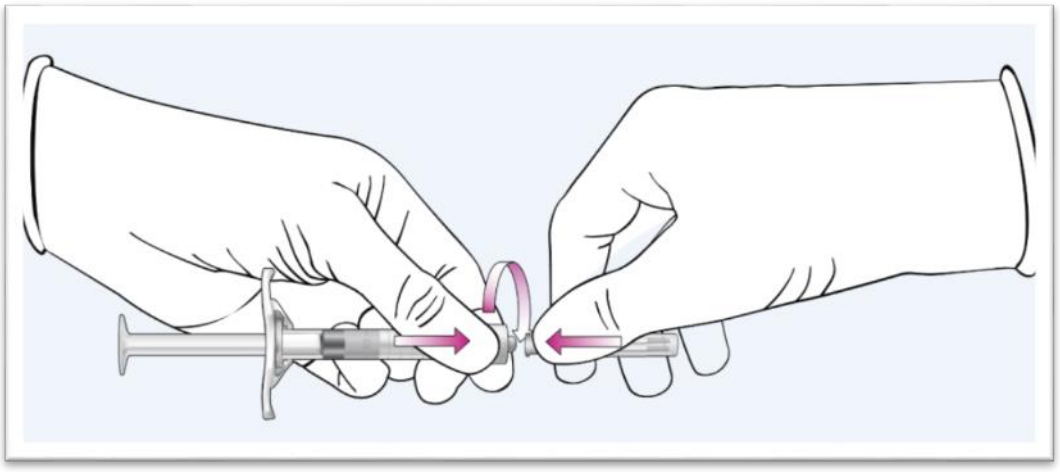
Use your thumb and forefinger to hold firmly around both the syringe barrel and the luer-lock adapter part (C) of the closure system.
With your other hand, take hold of the white cap (A) at the end of the closure system and gently tilt back and forth carefully until cap disconnects and can be pulled off (seal will be broken).
Do not rotate.
Do not touch the syringe tip (B) to keep it sterile.





ASSEMBLY OF NEEDLE TO SYRINGE

Use the thumb and forefinger to hold firmly around both the glass syringe barrel and the luer-lock adapter (C). Grasp the needle shield with the other hand. To facilitate proper assembly, both push and rotate firmly clockwise. Make sure the needle is screwed on all the way so that the needle shield touches the luer-lock adapter (C). To remove the needle shield, hold the syringe and the luer-lock adapter. With your other hand hold the needle shield and pull straight out. Do not rotate.



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.
    a. Advise the patient of the necessary precautions before commencing the procedure.
    b. 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 or hands 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.
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 in the nasolabial folds. For cheek augmentation and the correction of age related midface contour deficiency, a thin gauge needle or a blunt tip cannula (recommended cannula gauge sizes 25-27G with cannula length of 1.5 or 2 inches) can be used. *Restylane® Lyft with Lidocaine* is supplied with 29 G TW x ½" needles or 27 G TW x ½" needles. The physician should use at their discretion the appropriate needle depending on the intended use of the product. When using a needle, 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. When using a cannula for cheek augmentation and the correction of age related midface contour deficiency, after preparation as described above, an entry point is made in the skin with an incision needle of appropriate size. Inject slowly.
8. When treating the dorsal hand, *Restylane® Lyft with Lidocaine* can be administered using the supplied needles. With the needle, small boluses should be inserted in the dorsum of the hand in the subcutaneous plane. Small bolus injections or the linear retrograde injection technique can be used to deposit small volumes as needed. Rapid flow or rapid injection should be avoided.
9. Inject *Restylane® Lyft with Lidocaine* applying even pressure on the plunger rod. It is important that the injection is stopped just before the needle/cannula is pulled out of the skin to prevent material from leaking out or ending up too superficially in the skin. Do not apply excessive pressure to the syringe at any time. If resistance is encountered, the needle/

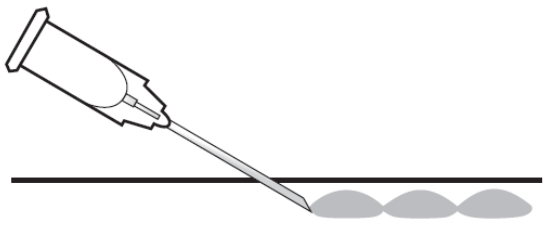
cannula should be partially withdrawn and repositioned, or fully withdrawn and checked for function and replaced if needed.

10. 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.
11. 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. For the treatment of volume deficit in the dorsal hand, the maximum recommended dose per hand is 3.0 mL per treatment. The safety of injecting greater amounts has not been established.

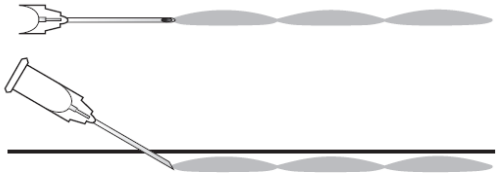
INJECTION TECHNIQUES

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** (only recommended for needle) (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/cannula 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/cannula has been fully inserted and is being withdrawn, it can also be performed while advancing the needle/cannula ("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.

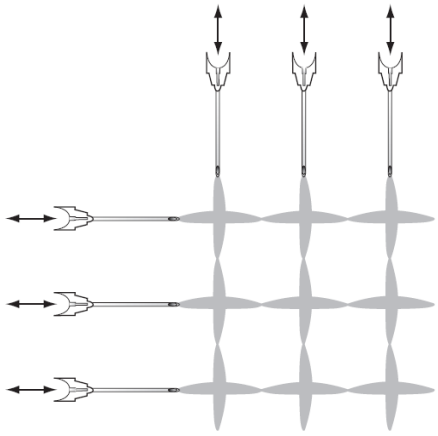
A. Serial Puncture (only recommended for needle)



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. It is recommended to change needle/cannula for each new treatment site.

8. When the injection is completed for the treatment of moderate to severe facial wrinkles and folds or age-related midface volume deficit, 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.

   When the injection is completed for the treatment of the dorsal hand, the hand should be balled into a fist and a lubricating agent, such as ultrasound gel or petrolatum ointment, should be applied. A deep thorough massage should be performed to smooth out the filler and push product into any remaining valleys or voids.

9. 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]

10. If the wrinkle, midface or dorsal hand 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.

11. 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.

12. 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

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