Perlane-L®
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
Perlane-L 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. The median particle size is between 750 and 1000 microns.

Indication
Perlane-L 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.

Contraindications
- *Perlane*-L is contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.
- *Perlane*-L contains trace amounts of gram positive bacterial proteins, and is contraindicated for patients with a history of allergies to such material.
- *Perlane*-L is contraindicated for patients with bleeding disorders.
- *Perlane*-L is contraindicated for implantation in anatomical spaces other than the dermis or superficial layer of the subcutis.
- *Perlane*-L should not be used in patients with previous hypersensitivity to local anesthetics of the amide type, such as lidocaine.

Warnings
- Defer use of *Perlane*-L at specific sites in which an active inflammatory process (skin eruptions such as cysts, pimples, rashes, or hives) or infection is present until the process has been controlled.
- Injection site reactions (e.g., swelling, redness, tenderness, or pain) to *Perlane*-L have been observed as consisting mainly of short-term minor or moderate inflammatory symptoms starting early after treatment and with less than 7 days duration. Refer to the adverse reactions section for details.
- *Perlane*-L must not be implanted into blood vessels. Localized superficial necrosis may occur after injection in or near dermal vessels, such as the glabellar area. It is thought to result from the injury, obstruction, or compromise of blood vessels.
- Delayed onset inflammatory papules have been reported following the use of dermal fillers. Inflammatory papules that may occur rarely should be considered and treated as a soft tissue infection.

Precautions
- *Perlane*-L is packaged for single patient use. Do not resterilize. Do not use if package is opened or damaged.
- Based on U.S. clinical studies patients should be limited to 6.0 mL per patient per treatment. The safety of injecting greater amounts has not been established.
- The safety or effectiveness of *Perlane*-L for the treatment of anatomic regions other than nasolabial folds has not been established in controlled clinical studies.
- Long term safety and effectiveness of *Perlane*-L beyond one year have not been investigated in clinical trials.
- As with all transcutaneous procedures, *Perlane*-L implantation carries a risk of infection. Standard precautions associated with injectable materials should be followed.
- The safety and efficacy of *Perlane*-L for lip augmentation has not been established.
- The safety of *Perlane*-L for use during pregnancy, in breastfeeding females or in patients under 18 years has not been established.
- Formation of keloids may occur after dermal filler injections including *Perlane*.® Keloid formation was not observed in studies involving 509 patients (including 150 African-Americans and 25 other patients of Fitzpatrick Skin Types IV, V and VI). For additional information please refer to Studies MA-1400-02, MA-1400-01, 31GE0002, and 31GE0101 in the Clinical Trials Section. In study MA-1400-03 with *Perlane*-L and *Perlane,* there were 51.7% (31/60) of patients with Fitzpatrick Skin Types IV, V, and VI and no reports of keloid formation.
- *Perlane*-L injection may cause hyperpigmentation at the injection site. In a clinical study of 150 patients with pigmented skin (of African-American heritage and Fitzpatrick Skin Types IV, V, and VI), the incidence of post-inflammatory hyperpigmentation was 6% (9/150). 50% of these events lasted up to six weeks after initial implantation. In study MA-1400-03 with *Perlane* and *Perlane*-L, there were 51.7% (31/60) of patients with Fitzpatrick Skin Types IV, V, and VI and no reports of hyperpigmentation
- *Perlane*-L should be used with caution in patients on immunosuppressive therapy.
- Bruising or bleeding may occur at *Perlane*-L injection sites. *Perlane*-L should be used with caution in patients who have undergone therapy with thrombolytics, anticoagulants, or inhibitors of platelet aggregation in the preceding 3 weeks.
- After use, syringes and needles should be handled as potential biohazards. Disposal should be in accordance with accepted medical practice and applicable local, state, and federal requirements.
- The safety of *Perlane*-L with concomitant dermal therapies such as epilation, UV irradiation, or laser, mechanical or chemical peeling procedures has not been evaluated in controlled clinical trials.
- Patients should minimize exposure of the treated area to excessive sun, UV lamp exposure and extreme cold weather at least until any initial swelling and redness has resolved.
- If laser treatment, chemical peeling or any other procedure based on active dermal response is considered after treatment with *Perlane*-L, there is a possible risk of eliciting an inflammatory reaction at the implant site. This also applies if *Perlane*-L is administered before the skin has healed completely after such a procedure.
- Injection of *Perlane*-L into patients with a history of previous herpetic eruption may be associated with reactivation of the herpes.
- *Perlane*-L is a clear, colorless gel without particulates. In the event that the content of a syringe shows signs of separation and/or appears cloudy, do not use the syringe and notify Medicis Aesthetics Inc. at 1-800-555-5115. Glass is 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.
- *Perlane*-L should not be mixed with other products before implantation of the device.

Adverse Experiences
There were five U.S. studies that reported adverse events.

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 *Perlane*-L 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 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 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.

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.

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.

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

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

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

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

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

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

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

- Hypersensitivity reactions ranging from moderate to severe mostly occurred within 1 to 2 days of implantation and up to 3 weeks. Reported symptoms included swelling; itching on chest and back; puffy, burning, watery, and itchy eyes; and shortness of breath. Treatments included steroids, diphenhydramine, unspecified intravenous medication, oxygen and various creams. An evaluation of patients who reported potential hypersensitivity reactions did not demonstrate any evidence of IgE or cell mediated immunologic reactions specifically directed at hyaluronic acid. Most hypersensitivity events resolved within 1 to 14 days with or without treatment.

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

Clinical Trials
The safety and effectiveness of *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 *Perlane*-L 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 *Perlane*-L was consistent with *Perlane.*

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	Tolerable[2]	Affected Daily Activity[2]	Disabling[2]	None	Tolerable[2]	Affected Daily Activity[2]	Disabling[2]
			n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Bruising	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	Tolerable[3]	Affected Daily Activity[3]	Disabling[3]	None	Tolerable[3]	Affected Daily Activity[3]	Disabling[3]
			n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Bruising	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]

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

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

Table 6. Duration of Adverse Events after Initial Treatment, Patient Diary (Study MA-1400-03)[1]

	Perlane-L	*Perlane*	*Perlane*-L 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. 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. 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%)

Table 9. All Investigator-Identified Adverse Events (14 Days) Number of Events per Patient per Study

Study Term	MA-1400-03	
	Number of Events *Perlane*-L (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.

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

90-39411-02

August 2011

U.S. Clinical Studies

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 11. 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 11. 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 12 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 12. 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*.

Non-U.S. Clinical Studies

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 *Perlane*-L to *Perlane* in 60 patients. Patients were randomized to *Perlane*-L 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* – *Perlane*-L) 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 *Perlane*-L 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 *Perlane*-L 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
Perlane-L 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 – *Perlane*-L 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 *Perlane*-L) 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 *Perlane*-L (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 – *Perlane*-L 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* – *Perlane*-L) 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**
	Perlane-L	*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 – *Perlane*-L side), ** One-sample T-test

At Day 14, patients showed improvement from baseline: 95% on the *Perlane*-L 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			
	Perlane-L		*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

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 13 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 13. 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 14 shows the results for the within-patient investigator assessment of NLF on the WSRS.

Table 14. 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 15. 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 15. 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)

HOW SUPPLIED
Perlane-L is supplied in a disposable glass syringe with a Luer-Lok® fitting. *Perlane*-L 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
Perlane-L 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 *Perlane*-L as this may damage or alter the product.

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

℞ only

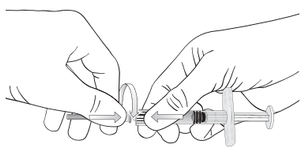
U.S. PATENT 5,827,937

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

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

DIRECTIONS FOR ASSEMBLY

ASSEMBLY OF 27 G TW AND 29 G TW NEEDLE TO SYRINGE
Use the thumb and forefinger to hold firmly around both the glass syringe barrel and the Luer-Lok adapter. Grasp the needle shield with the other hand. To facilitate proper assembly, both push and rotate firmly.



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

TREATMENT PROCEDURE

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

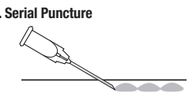
   Advise the patient of the necessary precautions before commencing the procedure.

   A consent form should be utilized.
2. Assess the patient's need for appropriate anesthetic treatment for managing comfort, i.e., topical anesthetic, local or nerve block.
3. The patient's face should be washed with soap and water and dried with a clean towel. Cleanse the area to be treated with alcohol or another suitable antiseptic solution.
4. Sterile gloves are recommended while injecting *Perlane*-L.
5. Before injecting, press rod carefully until a small droplet is visible at the tip of the needle.
6. *Perlane*-L is administered using a thin gauge needle (27 G TW x ½" or 29 G TW x ½"). The needle is inserted at an approximate angle of 30° parallel to the length of the wrinkle or fold. *Perlane*-L should be injected into the deep dermis to superficial layer of the subcutis. If *Perlane*-L is injected too superficially this may result in visible lumps and/or bluish discoloration.
7. Inject *Perlane*-L applying even pressure on the plunger rod. It is important that the injection is stopped just before the needle is pulled out of the skin to prevent material from leaking out or ending up too superficially in the skin.
8. Only correct to 100% of the desired volume effect. Do not overcorrect. With cutaneous deformities the best results are obtained if the defect can be manually stretched to the point where it is eliminated. The degree and duration of the correction depend on the character of the defect treated, the tissue stress at the implant site, the depth of the implant in the tissue and the injection technique.
9. Typical usage for each treatment session is specific to the site as well as wrinkle severity. In a prospective study of midface wrinkle correction, the median total dose was 3.0 mL. Based on U.S. clinical studies, the maximum recommended dose per treatment is 6.0 mL.

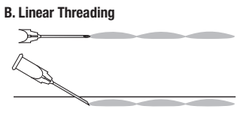
INJECTION TECHNIQUES

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

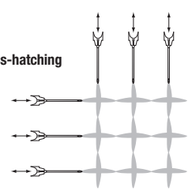
A. Serial Puncture



B. Linear Threading



C. Cross-hatching



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

STERILE NEEDLE(S)

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

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

To order call 877-520-0500.

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