SUMMARY OF SAFETY AND EFFECTIVENESS DATA
For a supplemental Premarket Approval Application

I. GENERAL INFORMATION

Device Generic Name:	Injectable Dermal Filler
Device Trade Name:	PERLANE® Injectable Gel
Applicant's Name and Address:	Medicis Aesthetics Holdings Inc. 8125 North Hayden Road Scottsdale, AZ 85258
Premarket Approval Application (PMA) Number:	P040024/S6
Date of Panel Recommendation:	None
Date of Notice of Approval to the Applicant:	May 2, 2007

The original PMA application P040024 for Restylane Injectable Gel was approved on March 25, 2005. The device is indicated for mid-to-deep implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds. Preclinical data from the original application is applicable to the current PMA supplement for the Perlane Injectable Gel and is therefore incorporated by reference. Please refer to the SSED for P040024 for additional supporting documentation. You may obtain a copy of the SSED via the CDRH website at http://www.fda.gov/cdrh/pmapage.html. Written requests for copies can be obtained from The Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852 under Docket # 05M-0118.

II. INDICATIONS FOR USE

PERLANE® 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.

III. CONTRAINDICATIONS

- PERLANE® is contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.
- PERLANE® contains trace amounts of gram positive bacterial proteins, and is contraindicated for patients with a history of allergies to such material.
- PERLANE® is contraindicated in patients with bleeding disorders.

- PERLANE® is contraindicated for implantation into anatomical spaces other than the dermis or superficial layer of the subcutis.

IV. WARNINGS AND PRECAUTIONS

Warnings and precautions can be found in the Perlane physician's labeling.

V. DEVICE DESCRIPTION

PERLANE® 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. The largest fraction of gel particles size is between 940 and 1090 microns.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Alternative therapies for cosmetic tissue augmentation include bovine collagen dermal fillers, human collagen dermal fillers, other hyaluronic acid-based dermal fillers, and autologous fat transfer. Other treatment options for the treatment of photo-damaged skin with its associated wrinkling and changes in texture and pigmentation include topical creams (containing e.g. retinoids), chemical peeling procedures or laser resurfacing. Deep wrinkles, folds, scars, and other depressed lesions are often treated with surgery (e.g. rhytidectomy).

VII. MARKETING HISTORY

PERLANE® was first approved for marketing and sale in November 1999 in the European Union including EES. In 2000, PERLANE® marketing approval was obtained in Australia, Brazil, Canada, Ecuador, Korea, Mexico, Peru, Russia and Singapore. In 2001, the product was approved in Bulgaria, Colombia, Czech Republic, Jordan, Philippines, Poland and Slovak Republic. During 2002, the product was approved in Estonia, Israel, Morocco, Panama, Ukraine and Uruguay. During the years 2003, 2004 and 2005 approval was obtained in Guatemala, India, Romania, Taiwan, Tunis and Thailand.

The device has not been withdrawn from marketing for any reason related to the safety or effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

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 5. 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 6 presents all investigator-identified adverse experiences 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 a commercially available hyaluronic acid dermal filler. In Study 31GE0002, 68 Swedish patients underwent injections with both PERLANE® and a commercially available bovine collagen dermal filler.

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 n (%)	Affected Daily Activity n (%)	Disabling 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] 1 n (%)	2-7 n (%)	8-13 n (%)	14 n (%)	Number of days[2] 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 timepoint 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 n (%)	Affected Daily Activity n (%)	Disabling 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] 1 n (%)	2-7 n (%)	8-13 n (%)	14 n (%)	Number of days[3] 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 timepoint 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 shows the number of adverse experiences identified by investigators at 72 hours after injection for Studies MA-1400-01 and MA-1400-02. Some patients had multiple adverse experiences or had the same adverse experience at multiple injection sites. No adverse experiences were of severe intensity.

Table 5. All Investigator-Identified Adverse Experiences (72 Hours)
Number of Events per Patient Per Study

Study Term	MA-1400-01		MA-1400-02	
	Number of Events 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 6 presents the number of patients and per patient incidence of all adverse experiences identified by investigators at visits occurring two or more weeks after injection.

Table 6. Investigator-Identified Adverse Experiences (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 Control (n=150) (%)	31GE0002 PERLANE® (n=68) (%)	31GE0002 Control (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 31GE 0002) with repeat administration of PERLANE® at 6 - 9 months following the initial correction, the incidence and severity of adverse experiences were similar in nature and duration to those recorded during the initial treatment sessions.

In all 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.

Potential Adverse Events:
In postmarket surveillance of RESTYLANE® in the U.S. and both RESTYLANE® and PERLANE® in other countries, presumptive bacterial infections, inflammatory adverse events, allergic adverse events, and necrosis have been reported. 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.

IX. SUMMARY OF PRECLINICAL STUDIES

The testing performed in the original application for Restylane (which has the same chemical composition as Perlane) supported the safety and effectiveness of Perlane. Because the size of PERLANE® gel particles differ from Restylane, additional studies were performed. Specifically, Perlane was not cytotoxic in MEM elution and colony assay tests, no signs of delayed contact (dermal) sensitization were observed in guinea pigs, no significant irritation reactions were observed after intracutaneous implantation in rabbits, no mutagenic response was observed in an Ames test and Perlane was not genotoxic in a mouse bone marrow micronucleus study or an *in vitro* chromosomal aberration test in mammalian cells. Tests of hyaluronic acid content, gel content, gel swelling factor, device extrusion force, device sterility, device pH and total extractable carbohydrate content demonstrated that the Perlane was stable for a 36 month storage period.

X. SUMMARY OF CLINICAL STUDIES

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 subjects.

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.

U.S. Clinical Studies

MA-1400-02: Prospective, Randomized, Blinded, Controlled Clinical Study

Design	1:1 randomized, prospective study at 17 US 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 two weeks after initial treatment. Patients were partially blinded to treatment; live evaluating physicians were blinded to treatment and treating physicians were not blinded to treatment. 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 and point was wrinkle severity 12 weeks after optimal correction was achieved. Wrinkle severity was evaluated on a five-step validated Wrinkle Severity Rating Scale (WSRS) (*i.e.*, none, mild, moderate, severe, extreme) by a live evaluator blinded to treatment. Patient success was defined as maintaining at least a one point improvement on the WSRS at 12 weeks after optimal correction was achieved. The percent of patient successes were calculated for each treatment group. Each group was compared to its own baseline, with no comparison with PERLANE® to RESTYLANE.® Secondary: WSRS was 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 timepoint, if earlier, at which less than 50% of patients had at least a 1-grade response remaining in both nasolabial folds (NLFs). Safety assessments included: collection of patient symptoms in a 14-day diary; investigator evaluation of adverse experiences at 72 hours, and at 2, 6, 12, and 24 weeks; development of humoral or cell-mediated immunity; and the relationship of adverse experiences to injection technique.

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 7. 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 7: 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%) subjects displayed a pre-treatment antibody response against PERLANE,® (which was believed to be related to co-purifying *Streptococcus* capsule antigens). One subject also developed a measurable increase in antibody titer after PERLANE® injection. 4/16 (27%) patients with antibodies against PERLANE® had adverse experiences 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 experiences in the patients with a humoral response against PERLANE® were mild in severity. No severe events were noted and the subject 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 US 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 blinded to treatment assignment. Evaluations were performed by an independent live investigator 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 WSRS (*i.e.*, none, mild, moderate, severe, extreme) by an on-site blinded evaluator. Patient success was defined as maintaining at least a one point improvement on the WSRS at 12 weeks after optimal correction was achieved. The percent of patient successes was calculated for each group. Each treatment group was compared to its own baseline, with no comparison of PERLANE® to RESTYLANE.® Secondary: WSRS was assessed at other follow-up points (2, 6, and 24 weeks after optimal correction) by the treating 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 timepoint, if earlier, at which less than 50% of patients had at least a 1-grade response at both nasolabial folds. Safety assessments included: collection of patient symptoms in a 14-day diary; investigator evaluation of adverse experiences at 72 hours, and at 2, 6, 12, and 24 weeks; the development of humoral or cell-mediated immunity; and the relationship of adverse experiences 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 8 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 over baseline.

Table 8: 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%) subjects displayed a pre-treatment antibody response against PERLANE® (which was believed to be related to co-purifying *Streptococcus* capsule antigens). No subjects developed a measurable increase in antibody titer after PERLANE® injection. 0/6 (0%) patients with antibodies against PERLANE® had adverse experiences 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 experiences 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

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 a commercially available hyaluronic acid dermal filler. Patients were randomized to either PERLANE® or control 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 blinded; evaluating physicians were independent and blinded to treatment; treating physicians were partially blinded. 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 control 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 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 timepoints by patient. Safety assessments included: investigator evaluation of adverse experiences 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 9 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 9: Blinded Evaluator Wrinkle Severity Response Rates

Time point	Number of NLFs	No. of PERLANE® NLFs maintaining ≥ 1 Unit improvement on WSRS	No. of Control 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 10 shows the results for the within-patient investigator assessment of NLF on the WSRS.

Table 10: 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® is superior to Control n (%)	PERLANE® equal to Control n (%)	Control 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 subjects 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 a commercially available bovine dermal filler. Patients were randomized to either PERLANE® or Control 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 blinded; evaluating physicians were independent and blinded to treatment; treating physicians were partially blinded. A touch-up was allowed 2 weeks after the initial treatment. Retreatment 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 Control 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 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 Control 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 experiences 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 11. 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 subjects; the control-treated side experienced more improvement in 10.3% of the subjects.

Table 11: 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] McNermar's test

[2] Percent=n/Number of subjects in the ITT population at Month 6

[3] Percent=n/Number of subjects in the ITT population Month 9; includes only patients not retreated (n=43)

XI. CONCLUSIONS DRAWN FROM THE STUDIES

PERLANE® is effective at wrinkle correction based on the blinded live evaluator scores of wrinkle severity reduction which is further supported by investigator scores and patient scores and includes efficacy in subjects with deeply pigmented skin of African American heritage. Reasonable assurance of safety has also been demonstrated by the short duration of and generally mild/moderate severity of adverse events observed.

Therefore, it is reasonable to conclude that the benefits of use of the device for the target population outweigh the risk of illness or injury when used as indicated and in accordance with the directions for use.

XII. PANEL RECOMMENDATION

In accordance with the provisions of section 515c(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the General and Plastic Surgery Devices Panel, an FDA advisory committee, for review and recommendation

because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CDRH DECISION

FDA issued an approval order May 2, 2007.

The applicant's manufacturing facility was inspected and was found to be in compliance with the Quality System Regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for Use: See product prescribing information.

Hazard to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the labeling.

Postapproval Requirement and Restrictions: See the approval order.