SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Injectable Dermal Filler

Device Trade Name: Restylane® Injectable Gel

Applicant's Name and Address: Medicis Aesthetics Holdings, Inc.
8125 North Hayden Road
Scottsdale, AZ 85258

Date of Panel Recommendation: April 27, 2011

Premarket Approval Application (PMA) Number: P040024/s051

Date of FDA Notice of Approval: October 11, 2011

Expedited: Not applicable

The original PMA (PMA # P040024) was approved on March 25, 2005 for mid-to-deep dermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds. The SSED to support the indication is available on the CDRH website and is incorporated by reference here. The current supplement was submitted to expand the indication for Restylane Injectable Gel.

II. INDICATIONS FOR USE

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

Restylane is indicated for submucosal implantation in patients over the age of 21 for lip augmentation.

III. CONTRAINDICATIONS

- *Restylane* is contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.
- *Restylane* contains trace amounts of gram positive bacterial proteins, and is contraindicated for patients with a history of allergies to such material.
- *Restylane* is contraindicated for patients with bleeding disorders.
- *Restylane* is contraindicated for implantation in anatomical spaces other than the dermis or submucosal implantation for lip augmentation.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Restylane labeling.

V. DEVICE DESCRIPTION

Restylane is a gel of hyaluronic acid (HA) isolated from a *Streptococcus* species that is chemically crosslinked with BDDE, stabilized and suspended in phosphate buffered saline at pH = 7 and a concentration of 20 mg/mL. Restylane is a transparent, viscous, and sterile gel that is supplied in a disposable glass syringe. The product is approved in fill sizes of 0.4, 0.7, 1, or 2 mL. The syringe is co-packed in a blister together with sterile 29 G or 30G needle(s).

The HA has a molecular weight of about one million and is stabilized by adding a minimum amount of 1,4-butanediol diglicidyl ether to allow formation of a three-dimensional HA molecular network. The chemical stabilizing process does not change the polyanionic character of the polysaccharide chain.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Patients frequently seek correction of facial contour deformities that are: (1) age-related loss of facial fat or weakening of underlying supportive structures; (2) sun damage in non-pigmented skin; or, (3) related to specific diseases or their treatments that may cause facial wasting, scarring, or structural damage (e.g., prior surgery, anorexia, acne vulgaris, collagen vascular disease). Treatment of photo-damaged skin, with its associated wrinkling and changes in texture and pigmentation, is often accomplished by use of topical moisturizing creams (some of which may contain pharmaceuticals, such as sunscreens or retinoids), chemical or mechanical peeling procedures, or laser resurfacing. These methodologies typically affect epidermal quality but do not treat underlying structural issues. Deeper wrinkles, folds, scars, and other lesions are often treated with surgery (e.g., scar revision, blepharoplasty, face lift, rhytidectomy, permanent silastic implants). Other than implants, these methodologies have the advantage of reducing redundant skin but do not restore the youthful look associated with abundant soft tissue support. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

Restylane was first approved for marketing and sale in September 1996 in the European Union, Iceland, Liechtenstein and Norway (EES). The product has since been approved in several countries worldwide. Restylane was approved in the United States (U.S.) under PMA P020023 (submitted by Q-Med) on December 12, 2003, and under PMA P040024 (submitted by Medicis) on March 25, 2005. Restylane has not been removed from the marketplace for any reasons related to safety, effectiveness, patient or physician complaint, or dissatisfaction.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The safety of Restylane for lip augmentation was evaluated in three Pre-Market studies and Post Marketing Surveillance. Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

• Acne
• Aphthous Stomatitis
• Broken capillaries
• Burning Sensation
• Cheilitis
• Contusion (bruising/ ecchymosis)
• Death
• Dermatitis
• Device Dislocation
• Discolouration
• Erythema
• Extrusion Of Device
• Eye Disorders
• Fistula/Leakage
• Granuloma/Foreign Body Reaction
• Headache
• Herpes Simplex
• Hyperpigmentation
• Hypersensitivity (Allergic reaction and anaphylactic shock)
• Inflammation
• Infection/Abscess
• Ischemia/Necrosis
• Lip Blister
• Lip Discoloration
• Lip Disorder
• Lip Dry
• Lip Exfoliation
• Lip Pain
• Lip Swelling
• Lip Ulceration
• Mass Formation
• Muscle Disorders
• Nasopharyngitis
• Necrosis
• Numbness
• Oral Dysesthesia
• Pain
• Papules/Nodules
• Paraesthesia Oral

• Pruritus
• Rash
• Scar/Scab/Skin Atrophy
• Skin Exfoliation (includes sloughing of the skin, peeling, desquamation, and superficial desquamation.)
• Swelling
• Swollen Tongue
• Tenderness
• Urticaria

In the Pivotal Study (MA-1300-15) there were 5 *serious adverse events* reported in Restylane-treated patients, i.e., diverticulitis (n=1), pneumonia and pneumococcal infection (n=1), lumbar spinal stenosis (n=1) and transient ischemic attack (n=1).

In Pilot Study MA-1300-13k there were two serious adverse events. A death occurred when a patient (with a medical history indicating hypothyroidism) experienced cardiac arrest on Day 29 resulting from a thyroid neoplasm. Another subject (whose medical history included rheumatoid arthritis, peripheral neuropathy, and hyperlipidemia) was hospitalized for severe cellulitis of the left lower extremity that was refractory to antibiotic therapy. Both SAEs were considered unrelated to the study device.

For the specific adverse events that occurred in the clinical studies, please see Section X below.

IX. SUMMARY OF PRECLINICAL STUDIES

This supplement presented clinical data to support approval of a new indication for use. Because no change in product manufacture or specification was proposed, the supplement did not contain any manufacturing information or preclinical testing. Instead, the data previously presented in PMA P040024 were sufficient to support the new proposed indication for use.

X. SUMMARY OF PRIMARY CLINICAL STUDY

Medicis Aesthetics, Inc. performed three clinical studies to establish a reasonable assurance of safety and effectiveness for Restylane submucosal implantation for lip augmentation. Summaries of each study (i.e., 1) Pivotal Study MA-1300-15, 2) US Pilot Study MA-1300-13K and 3) Canadian Pilot Study MA-1300-14) are presented below.

- Pivotal Study (MA-1300-15)

A. Study Design

The trial was a multi-center, two-arm study with a 3:1 randomization to Treatment and No-Treatment cohorts. After treatment, patients attended clinical visits at 72 hours and 2, 4, 8, 12, 16, 20, 24 weeks after Restylane injection as well as 2 and 4 weeks after a Week 24 Restylane re-treatment. The Primary Effectiveness endpoint compared the differences in the live Blinded Evaluators' MFLS assessments at Week 8 post treatment with the Treating Investigators' baseline MLFS score. Separate upper and lower lip evaluations were performed (as co-primary endpoints)

and treatment success was defined as at least a one grade increase in MLFS for both the upper and lower lips. The proportion of Responders (i.e., at least a one grade increase from baseline to Week 8 MLFS score for both the upper and lower lips) were calculated using a Fisher's Exact Test.

A No Treatment cohort was the control, because there is no FDA approved therapy for lip augmentation. To maintain masking, Control subjects did not receive Restylane injections until Week 24. Patients were treated between July 20, 2009 and May 7, 2010. The database for this PMA supplement reflected data collected through June 1, 2010 and included 180 patients.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in Study MA-1300-15 was limited to patients who met the following inclusion criteria: males and non-pregnant or non-breast feeding females who were: 18-65 years old, seeking augmentation therapy for the lips, willing to comply with the requirements of the study, (including sequential photography or imaging), willing to abstain from any other facial plastic surgical or cosmetic procedure for 9 months and willing to give written informed consent. All female subjects agreed to use an acceptable form of birth control during the study period and take a urine pregnancy test at baseline and at the Week 24 visit. Additional study entry criteria related to patient skin type included:

- a MLFS score of 1 (very thin) or 2 (thin) on both upper and lower lips assessed at baseline for patients with Fitzpatrick I, II and III type skin; or

- a MLFS score of 1 (very thin) or 2 (thin) on either the upper and lower lip assessed at baseline for patients with Fitzpatrick IV, V and VI type skin.

Subjects were also permitted to have had facial cosmetic procedures outside the area of assessment (e.g., botulinum toxin above the orbital rim, etc.) either before or contemporaneously with lip augmentation.

Patients were excluded if they had: a history of allergy or hypersensitivity to injectable hyaluronic acid gel, a history or the presence of any disease which may result in changes in facial contour or edema of the face, (e.g., inflammation, infection, facial psoriasis, herpes zoster, acanthosis, cancer, precancer, actinic keratosis), prior use of a biodegradable or non-biodegradable tissue augmentation therapy or aesthetic facial surgical therapy below the level of the lower orbital rim, (in the preceding eight months), or plans for such substances/procedures during the study), the presence of any contraindication to the implant procedures, (e.g., use of platelet inhibiting agents or other anticoagulants, in a relevant period before study entry, a history of severe allergies or multiple allergies manifested by anaphylaxis or a history of a hypotensive crisis in response to radio-contrast media or other osmotic agent, the presence of any condition, which made the subject unable to complete the study per protocol or a concomitant condition that might confuse or confound study treatments or assessments), the presence of known allergies or hypersensitivity reactions to local topical anesthetics or nerve blocking agents, the presence of cancerous or precancerous lesions in the treatment area, prior surgery to the upper or lower lip, prior significant trauma, to the upper or lower lip resulting in formation of a scar, the presence of facial hair that could interfere with MLFS evaluation, a history of herpes labialis and an outbreak within four weeks of study entry or four or more outbreaks in the 12

months prior to study entry, the presence of mild, moderate, or severe abnormal rating for texture or firmness or detection of any abnormal lip structure, (e.g., a scar or lump), the presence of moderate or severe abnormal lip asymmetry, the presence of abnormal lip movement, with an inability to pronounce three or more of the preselected words, the presence of abnormal lip function, with inability to effectively suck water through a straw, the presence of abnormal lip sensation, with inability to feel a 0.4G monofilament or a cotton wisp at any site on the lip, the presence of any mass formation at screening, the current use of immunosuppressive therapy, a history of connective tissue diseases or participation in any interventional clinical research study within 30 days prior to randomization

2. Follow-up Schedule

All patients returned for follow-up examinations at 72 hours and 2, 4, 8, 12, 16, 20, 24 weeks after the last Restylane injection as well as 2 and 4 weeks after the Week 24 Restylane re-treatment.

Pre-Treatment evaluations included assessment of study entry criteria, medical history, lip fullness, lip texture, lip firmness and lip symmetry evaluations and patient photography.

Post-Treatment, the parameters measured were: a subject's 14 day treatment diary (after each injection) to record bruising, redness, swelling, pain tenderness, itching, a Treating Investigator assessment of safety outcomes at each visit and a staff member evaluation of abnormal lip texture, lip firmness, and lip symmetry, as well as abnormal lip movement, function, sensation and mass formation at each study visit, the Treating Investigator evaluation of lip fullness on the Medicis Lip Fullness Scale (MLFS) and a Global Aesthetic Improvement Scale (GAIS) after each visit, the Blinded Evaluator determination of MLFS scores at Weeks 8, 12, 16, 20, and 24 after the last treatment, a subject's assessment of GAIS after each visit and photographs at each visit. Adverse events and complications were also recorded at all visits.

3. Clinical Endpoints

The primary safety objective was to identify the incidence of all adverse events including subject adverse outcomes occurring during the first fourteen days after treatment (in a subject diary) as well as safety assessments (and adverse events) by the Treating Investigator at a 72 hour visit and visits at 2, 4, 8, 12, 16, 20, 24 weeks after the last treatment and at 2 and 4 weeks after the Week 24 re-treatment. Additional safety evaluations, performed by a qualified health care professional included lip assessments for texture, firmness, symmetry, product palpability, mass formation, lip movement, function, and sensation.

The primary effectiveness endpoint was whether Restylane was more effective than No Treatment (as determined by Blinded Evaluator) at 8 weeks after treatment compared to the baseline lip fullness assessment by the Treating Investigator. A Responder was defined as at least one grade increase from Baseline on the MLFS scale for both upper and lower lips. The MLFS is presented below in Table 1.

Table 2. Medicis Lip Fullness Scale

1	Very Thin
2	Thin
3	Medium
4	Full

5	Very Full

The following additional effectiveness endpoints were evaluated: 1) Blinded Evaluator MLFS score at Weeks 12, 16, 20, and 24, as well as 2 and 4 weeks after the Week 24 re-treatment, 2) Treating Investigators' MLFS scores at each time point after treatment, 3) Independent Photographic Reviewers' (IPR) assessment of MLFS score after study completion by three off-site reviewers who compared photos from Baseline and Weeks 4 – 24, 4) the Treating Investigators' GAIS assessment at each time point after treatment, 5) Subjects' GAIS assessment at each time point after treatment, 6) the degree of correlation between MLFS and GAIS scores by Treating Investigators, 7) the degree of correlation between Treating Investigators' MLFS and the Subject GAIS scores, 8) the agreement among the proportion of Responders determined by the MLFS and GAIS scales judged by the Treating Investigators, and 9) the Agreement among the MLFS for the Treating Investigator, Blinded Evaluator, and IPR assessments.

B. Accountability of PMA Cohort

180 patients enrolled and 116/135 (86%) Restylane and 39/45 (87%) Control subjects completed the study. No subject discontinued due to an adverse event. Subject accountability is displayed below in Table 2.

Table 2. Subject Accountability* Study MA-1300-15

	No Treatment n=45	Restylane n=135	Total n=180
Subjects Completing Study	39 (87%)	116 (86%)	155 (86%)
Withdrew from the study	6 (13%)	19 (14%)	25 (14%)
Primary Reason for Discontinuation			
Withdrew Consent	2 (4%)	8 (6%)	10 (6%)
Lost to Follow-up	3 (7%)	10 (7%)	13 (7%)
AER	0	0	0
Investigator Decision	0	1 (< 1%)	1 (< 1%)
Other	1 (2%)	0	1 (< 1%)

* Percentages reflect total number of subjects in the ITT population

C. Study Population Demographics and Baseline Parameters

Demographic characteristics were similar for the No Treatment and Restylane groups at baseline. The demographics of the entire study population are presented in Table 3 and Table 4 presents the demographics for patients with Fitzpatrick Skin Types IV and V.

Table 3. Patient Demographics for the Entire Study Population

Characteristic	No Treatment N=45	Restylane N=135	Total N=180
Age (years)			
N	45	135	180
Mean (SD)	47.2 (10.9)	47.8 (10.5)	47.6 (10.6)
Median	47.0	51.0	50.0
Range	25 – 65	18 – 65	18 - 65
Gender			
Male	0	1 (<1%)	1 (<1%)
Female	45 (100%)	134 (99%)	179 (99%)
Race			
American Indian /	1 (2%)	1 (<1%)	2 (1%)

Alaskan Native			
Black or African American	0	2 (1%)	2 (1%)
Native Hawaiian / Pacific Islander	0	1 (<1%)	1 (<1%)
Asian	0	0	0
White	41 (91%)	128 (95%)	169 (94%)
Other	3 (7%)	3 (2%)	6 (3%)
Ethnicity			
Not Hispanic or Latino	39 (87%)	122 (90%)	161 (89%)
Hispanic or Latino	6 (13%)	13 (10%)	19 (11%)
Fitzpatrick Skin Types			
I, II and III	35 (78%)	104 (77%)	139 (77%)
IV	10 (22%)	28 (21%)	38 (21%)
V	0	3 (10%)	3 (2%)
VI	0	0	0
Height (cm)			
Mean (SD)	164.0 (6.6)	163.4 (6.3)	163.5 (6.4)
Median	163.0	162.5	162.6
Range	149.9 – 177.8	149.9 – 180.3	149.9 – 180.3
Weight (kg)			
Mean (SD)	69.3 (11.7)	67.4 (15.9)	67.9 (15.0)
Median	67.6	63.5	63.5
Range	43.1 - 95.3	46.3 - 156.5	43.1 – 156.5
Baseline MLFS (upper lip)			
Very thin (1)	26 (58%)	82 (61%)	108 (60%)
Thin (2)	18 (40%)	52 (39%)	70 (39%)
Medium (3)	1 (2%)	1 (<1%)	2 (1%)
Full (4)	0	0	0
Very Full (5)	0	0	0
Baseline MLFS (lower lip)			
Very thin (1)	20 (44%)	44 (33%)	64 (36%)
Thin (2)	19 (42%)	78 (58%)	97 (54%)
Medium (3)	4 (9%)	9 (7%)	13 (7%)
Full (4)	2 (4%)	3 (2%)	5 (3%)
Very Full (5)	0	1 (<1%)	1 (<1%)

Table 4. Demographics for Fitzpatrick IV and V Skin Type Patients

Characteristic	No Treatment N=10	Restylane N=31	Total N=41
Age (years)			
Mean (SD)	43.9 (10.8)	42.5 (10.7)	42.9 (10.6)
Median	44.0	45.0	45.0
Range	28-60	20-57	20-60
Gender			
Male	0	0	0
Female	10 (100%)	31 (100%)	41 (100%)
Race			
American Indian / Alaskan Native	0	1 (3%)	1 (2%)
Black or African American	0	2 (6%)	2 (5%)
Native Hawaiian / Pacific Islander	0	0	0
Asian	0	0	0
White	7 (70%)	25 (81%)	32 (78%)
Other	3 (30%)	3 (10%)	6 (15%)

Ethnicity			
Not Hispanic or Latino	8 (80%)	22 (71%)	30 (73%)
Hispanic or Latino	2 (20%)	9 (29%)	11 (27%)
Fitzpatrick Skin Types			
IV	10 (100%)	28 (90%)	38 (93%)
V	0	3 (10%)	3 (7%)
VI	0	0	0
Height (cm)			
Mean (SD)	159.8 (3.9)	162.6 (5.9)	161.9 (5.6)
Median	160.0	162.6	162.6
Range	152.4 – 165.1	149.9-172.7	149.9-172.7
Weight (kg)			
Mean (SD)	64.0 (11.0)	66.3 (13.8)	65.7 (13.0)
Median	63.5	61.2	61.2
Range	47.6-83.9	52.3-115.7	47.6-115.7
Baseline MLFS (upper lip)			
Very thin (1)	5 (50%)	14 (45%)	19 (46%)
Thin (2)	4 (40%)	16 (52%)	20 (49%)
Medium (3)	1 (10%)	1 (3%)	2 (5%)
Full (4)	0	0	0
Very Full (5)	0	0	0
Baseline MLFS (lower lip)			
Very thin (1)	2 (20%)	4 (13%)	6 (15%)
Thin (2)	2 (20%)	14 (45%)	16 (39%)
Medium (3)	4 (40%)	9 (29%)	13 (32%)
Full (4)	2 (20%)	3 (10%)	5 (12%)
Very Full (5)	0	1 (3%)	1 (2%)
Characteristic	**No Treatment N=10**	**Restylane N=31**	**Total N=41**

Additional information on the Study Population:

The majority of subjects in the Restylane (79%) and No Treatment (69%) cohorts had a concomitant procedure during the study period. For the Restylane group, the most commonly reported concomitant procedure was cold compress therapy (76%) and laser therapy (7%).

Medical history was also similar for the No Treatment and Restylane treatment groups, with subjects reporting at least one medical history event (80% and 90% respectively), oral herpes (7% and 6%), acne (7% and 6%), drug hypersensitivity (27% and 23%), prior skin cosmetic procedure (7% and 23%), any prior medication (56% and 72%), and any concomitant medications (93% and 100%). Prior medications were taken by 72% of the Restylane group. The most commonly reported prior medications were acetylsalicyclic acid (2%), Anovlar (< 1%), fish oil (3%), levothyroxine (6%), thyroid (2%), ibuprofen (7%) and fluoxetine (5%). All of the Restylane subjects took concomitant meds during the study. These included anesthetics for topical use (6%), ibuprofen (15%), lidocaine and lidocaine HCl (39%), local anesthetics (18%), Octocaine with epinephrine (14%), paracetamol (21%), white soft paraffin (6%) and Xylocaine epinephrine 21%.

Injected Volume of Restylane:

The mean volume of Restylane injected for initial treatment session (including touch-up) was 2.9 mL. (A dose not exceeding 1.5 mL per upper lip and 1.5 mL per lower lip per treatment session was recommended.) Submucosal injection to the upper and lower lips was used for all subjects.

The most subjects underwent a combination of injection methods, (i.e., linear retrograde, linear antegrade and serial puncture). The mean length of time needed to treat both lips was 14.1 minutes (initial treatment) and 7.6 minutes (touch up visit).

The mean volume of Restylane injected during the Week 24 re-treatment session (including touch up) was 1.8 mL. No Treatment patients who received their first Restylane injection received a mean volume of 2.4 mL. For subjects receiving retreatment at Week 24, the mean length of time for the injection treatment was 9.5 minutes (for both lips) with 4.3 minutes required for touch up. For subjects in the No Treatment group, the median length of time needed to treat both lips initially (at Week 24) was 12.9 minutes with 7.7 minutes required for touch up.

The mean volume at initial treatment (including touch up) was 2.5 mL for patients with Fitzpatrick Skin Types IV and V and the mean length of time to perform the injection was 16.3 minutes and 9.9 minutes for the initial and touch-up treatments, respectively. The mean volume for retreatment and touch-ups at Week 24 was 1.4 mL for patients with Fitzpatrick Skin Types IV and V. The mean length of time to perform retreatment was 10.9 minutes with 4.9 minutes for touch up.

D. Safety and Effectiveness Results

1. Safety Results

172/180 subjects received their first treatment with Restylane at either Baseline/Day 0 or at Week 24. 93 subjects received a second series of treatments at Week 24. There were 26 TEAEs experienced by 17 No Treatment subjects and 795 TEAEs experienced by 149 Restylane subjects after their first treatment session. 267 TEAEs were experienced by 60 of subjects after their second Restylane treatment. The majority of the TEAEs were mild in intensity (i.e., 672/795 (85%) and 264/267 (99%), after the first and second treatments, respectively. The number of subjects and the number of TEAEs experienced by 5% or more of the study population are presented in Table 5.

Table 5. Incidence of Treatment Emergent Adverse Events Reported in 5% or Greater of the Study Population by Severity

System Organ Class	Severity	Treatment Group					
		No Treatment at Baseline n=45		First Restylane Treatment n= 172		Second Restylane Treatment n= 93	
		Events	Subjects	Events	Subjects	Events	Subjects
Any TEAE	Total	26	17 (38%)	795	149 (87%)	267	60 (65%)
	Mild	22	13 (29%)	672	96 (56%)	264	57 (61%)
	Moderate	4	4 (9%)	113	45 (26%)	3	3 (3%)
	Severe	0	0	10	8 (5%)	0	0
General Disorders and Administrative Site Conditions							
Pain	Total	1	1 (2%)	97	36 (21%)	51	19 (20%)
	Mild	1	1 (2%)	73	22 (13%)	50	18 (19%)
	Moderate	0	0	21	12 (7%)	1	1 (1%)
	Severe	0	0	3	2 (1%)	0	0
Swelling	Total	0	0	222	99 (58%)	101	51 (55%)
	Mild	0	0	186	78 (45%)	101	51 (55%)
	Moderate	0	0	36	21 (12%)	0	0
	Severe	0	0	0	0	0	0

Tenderness	Total	0	0	69	38 (22%)	29	16 (17%)
	Mild	0	0	60	31 (18%)	29	16 (17%)
	Moderate	0	0	9	7 (4%)	0	0
	Severe	0	0	0	0	0	0
Infections and Infestations							
Nasopharyngitis	Total	3	2 (4%)	9	9 (5%)	2	2 (2%)
	Mild	3	2 (4%)	8	8 (5%)	1	1 (1%)
	Moderate	0	0	1	1 (< 1%)	1	1 (1%)
	Severe	0	0	0	0	0	0
Injury, Poisoning and Procedural Complications							
Contusion	Total	0	0	130	75 (44%)	40	25 (27%)
	Mild	0	0	116	66 (38%)	40	25 (27%)
	Moderate	0	0	14	9 (5%)	0	0
	Severe	0	0	0	0	0	0
Nervous System Disorders							
Headache	Total	3	2 (4%)	17	12 (7%)	3	3 (3%)
	Mild	3	2 (4%)	17	12 (7%)	3	3 (3%)
	Moderate	0	0	0	0	0	0
	Severe	0	0	0	0	0	0
Skin and S.C. Tissue Disorders							
Erythema	Total	0	0	57	29 (17%)	19	10 (11%)
	Mild	0	0	57	29 (17%)	19	10 (11%)
	Moderate	0	0	0	0	0	0
	Severe	0	0	0	0	0	0
Skin Exfoliation	Total	0	0	21	14 (8%)	2	2 (2%)
	Mild	0	0	21	14 (8%)	2	2 (2%)
	Moderate	0	0	0	0	0	0
	Severe	0	0	0	0	0	0

The mean duration for TEAEs are presented in Table 6.

Table 6. Duration of Treatment Emergent Adverse Events Reported by 5% or Greater of the Study Population by Severity

System Organ Class		Treatment Group		
		No Treatment N=45	**First Treatment N=172**	**Second Treatment N=93**
Any TEAE	Number	17	147	59
	Mean (sd)	12.4 (12.9)	15.6 (14.4)	10.4 (10.4)
	Median	9.0	11.0	8.0
	Range	1 – 43	1 – 80	1 -73
General Disorders and Administrative Conditions				
Pain	Number	1	36	19
	Mean (sd)	9.0	4.6 (3.1)	3.4 (2.8)
	Median	9.0	4.0	2.0
	Range	9	1-17	1-11
Swelling	Number	0	96	51
	Mean (sd)	-	10.8 (8.1)	7.3 (4.6)
	Median	-	8.0	6.0
	Range	-	2-40	2-21
Tenderness	Number	0	38	16
	Mean (sd)	-	9.2 (5.8)	10.4 (9.7)
	Median	-	8.0	7.5
	Range	-	1-26	2-34

Infections and Infestations				
Nasopharyngitis	Number	2	9	2
	Mean (sd)	4.0 (1.4)	9.9 8.1)	10.5 (6.4)
	Median	4.0	6.0	10.5
	Range	3-5	3-27	6-15
Injury, Poisoning and Procedural Complications				
Contusion	Number	0	74	25
	Mean (sd)	-	8.6 (5.1)	6.6 (2.8)
	Median	-	8.0	7.0
	Range	-	2-36	2-12
Nervous System Disorder				
Headache	Number	2	12	3
	Mean (sd)	2.0 (1.4)	1.4 (0.7)	1.3 (0.6)
	Median	2.0	1.0	1.0
	Range	1-3	1-3	1-2
Skin and S.S. Tissue Disorder				
Erythema	Number	0	29	10
	Mean (sd)	-	5.3 (4.5)	4.4 (6.0)
	Median	-	5.0	3.0
	Range	-	1-22	1-21
Skin Exfoliation	Number	0	14	2
	Mean (sd)	-	5.2 (4.0)	11.0 (11.3)
	Median	-	4.0	11.0
	Range	-	1-16	3-19

The number of events and subjects reporting TEAEs in the lip area are presented in Table 7.

Table 7. Summary of Treatment Emergent Adverse Events in the Lip Area

System Organ Class	No Treatment n=45		1st Treatment n=172		2nd treatment n= 93	
	Events	Subjects	Events	Subjects	Events	Subjects
Any TEAE	3	3 (7%)	681	139 (81%)	254	57 (61%)
Congenital, Familial And Genetic Disorders						
Vascular Anomaly	0	0	1	1 (<1%)	0	0
Gastrointestinal Disorders						
Aphthous Stomatitis	0	0	1	1 (<1%)	0	0
Chapped Lips	0	0	1	1 (<1%)	0	0
Cheilitis	0	0	1	1 (<1%)	0	0
Hypoesthesia Oral	0	0	0	0	1	1 (<1%)
Lip Blister	0	0	2	1 (<1%)	0	0
Lip Discoloration	0	0	0	0	1	1 (<1%)
Lip Disorder	0	0	1	1 (<1%)	0	0
Lip Dry	0	0	2	1 (<1%)	0	0
Lip Exfoliation	0	0	5	3 (2%)	0	0
Lip Pain	0	0	5	3 (2%)	0	0
Lip Swelling	0	0	7	7 (4%)	0	0
Lip Ulceration	0	0	1	1 (< 1%)	0	0
Oral Dysesthesia	0	0	0	0	1	1 (< 1%)
Paraesthesia Oral	0	0	2	1 (<1%)	0	0
General Disorder and Administrative - Site Conditions						

Mass	0	0	6	5 (3%)	3	3 (3%)
Oedema	0	0	15	7 (4%)	2	1 (1%)
Pain	0	0	96	36 (21%)	51	19 (20%)
Swelling	0	0	221	99 (58%)	100	51 (55%)
Tenderness	0	0	69	38 (22%)	29	16 (17%)
Infections and Infestations						
Herpes Simplex	2	2 (4%)	2	2 (1%)	0	0
Oral Herpes	1	1 (2%)	8	7 (4%)	2	2 (2%)
Injury, Poisoning, and Procedural Complication						
Contusion	0	0	127	74 (43%)	40	25 (27%)
Laceration	0	0	1	1 (<1%)	0	0
Post Procedural Complication	0	0	1	1 (<1%)	0	0
Nervous System Disorders						
Burning Sensation	0	0	2	1 (<1%)	0	0
Paraesthesia	0	0	2	1 (<1%)	0	0
Skin and S.C. Tissue Disorder						
Acne	0	0	0	0	1	1 (<1%)
Blister	0	0	1	1 (<1%)	0	0
Ecchymosis	0	0	10	7 (4%)	0	0
Erythema	0	0	57	29 (17%)	19	10 (11%)
Pruritus	0	0	10	6 (3%)	2	1 (1%)
Rash	0	0	1	1 (< 1%)	0	0
Rash Papular	0	0	1	1 (< 1%)	0	0
Scab	0	0	1	1 (< 1%)	0	0
Skin Exfoliation	0	0	21	14 (8%)	2	2 (2%)

*Contusion is interchangeable with bruising and/or ecchymosis

There were 5 *serious adverse events* reported in this study. In the first Restylane treatment group they were: diverticulitis (n=1), pneumonia and pneumococcal infection (n=1), lumbar spinal stenosis (n=1) and transient ischemic attack (n=1). One patient in the No Treatment group became pregnant and was withdrawn before treatment.

The incidence (Table 8) and duration (Table 9) of adverse outcomes reported in the *Patient Diaries* are presented below.

Table 8. Intensity* of Adverse Outcomes Reported in the Subject Diary

	No treat pts (n=45)	1st treat pts (n=172)	2nd treat pts (n=93)	No Treatment				1st Restylane treatment				2nd Restylane treatment			
				N	T	A	D	N	T	A	D	N	T	A	D
Maximum Severity for any AER															
Upper lip	1	167 97.1%	86 92.5%	38 97%	1 3%	0	0	2 1%	90 53%	62 37%	15 9%	3 3%	59 66%	23 26%	4 4%
Lower lip	2	161 93.6%	79 84.9%	37 95%	2 5%	0	0	7 4%	98 58%	51 30%	12 7%	9 10%	54 61%	22 25%	3 3%
Bruising															
Upper lip	1	130 75.6%	54 58.1%	38 97%	1 3%	0	0	39 23%	97 57%	28 17%	5 3%	35 39%	44 49%	9 10%	1 1%
Lower lip	2	132 76.7%	48 51.6%	37 95%	2 5%	0	0	36 21%	107 64%	22 13%	3 2%	40 45%	40 45%	7 8%	1 1%
Redness															
Upper lip	0	126 73.3%	55 59.1%	39 100%	0	0	0	43 25%	115 68%	11 7%	0	34 38%	50 56%	2 2%	3 3%

Lower lip	1	120 69.8%	54 58.1%	38 97%	1 3%	0	0	48 29%	112 67%	8 5%	0	34 39%	49 56%	3 3%	2 2%
Swelling															
Upper lip	0	156 90.7%	85 91.4%	39 100%	0	0	0	3 2%	92 54%	64 38%	10 6%	4 4%	62 70%	20 22%	3 3%
Lower lip	0	158 91.9%	77 82.8%	39 100%	0	0	0	10 6%	102 61%	48 29%	8 5%	11 13%	54 61%	21 24%	2 2%
Pain (includes burning)															
Upper lip	0	143 83.1%	67 72.0%	39 100%	0	0	0	26 15%	111 66%	25 15%	7 4%	22 25%	51 57%	13 15%	3 3%
Lower lip	0	134 77.9%	62 66.7%	39 100%	0	0	0	34 20%	107 64%	20 12%	7 4%	26 30%	47 53%	13 15%	2 2%
Tenderness															
Upper lip	0	162 94.2%	78 83.9%	39 100%	0	0	0	7 4%	120 71%	38 22%	4 2%	11 12%	61 69%	14 16%	3 3%
Lower lip	1	152 88.4%	72 77.4%	38 97%	1 3%	0	0	16 10%	116 69%	32 19%	4 2%	16 18%	55 63%	15 17%	2 2%
Itching															
Upper lip	0	49 28.5%	19 20.4%	39 100%	0	0	0	120 71%	46 27%	3 2%	0	70 79%	18 20%	1 1%	0
Lower lip	0	48 27.9%	19 20.4%	39 100%	0	0	0	120 71%	45 27%	3 2%	0	69 78%	19 22%	0	0

*N= None; T= Tolerable; A=Affects Daily Activity; and D=Disabling

Table 9. Duration of Adverse Outcomes Reported in the Patient Diary

Location/AER	Total	1 day	2-7 day	8-13 day	> 14 days
No Treatment at Baseline n=45					
Upper Lip					
Bruising	1 (2%)	1 (100%)	0	0	0
Redness	0	0	0	0	0
Swelling	0	0	0	0	0
Pain (w/ burning)	0	0	0	0	0
Tenderness	0	0	0	0	0
Itching	0	0	0	0	0
Lower Lip					
Bruising	2 (4%)	2 (100%)	0	0	0
Redness	1 (2%)	1 (100%)	0	0	0
Swelling	0	0	0	0	0
Pain (w/ burning)	1 (2%)	1 (100%)	0	0	0
Tenderness	1 (2%)	1 (100%)	0	0	0
Itching	0	0	0	0	0

1st treatment at Baseline n=172					
Upper Lip					
Bruising	130 (76%)	8 (6%)	88 (68%)	31 (24%)	3 (2%)
Redness	126 (73%)	20 (16%)	86 (68%)	19 (15%)	1 (< 1%)
Swelling	166 (97%)	7 (4%)	95 (57%)	43 (26%)	21 (13%)
Pain (w/ burning)	143 (83%)	37 (26%)	94 (66%)	10 (7%)	2 (1%)
Tenderness	162 (94%)	15 (9%)	84 (52%)	45 (28%)	18 (11%)
Itching	49 (28%)	17 (35%)	27 (55%)	5 (10%)	0
Lower Lip					
Bruising	132 (77%)	11 (8%)	99 (75%)	19 (14%)	3 (2%)
Redness	120 (70%)	21 (18%)	84 (70%)	14 (12%)	1 (< 1%)
Swelling	158 (92%)	7 (4%)	93 (59%)	34 (22%)	24 (15%)
Pain (w/ burning)	134 (78%)	35 (26%)	86 (64%)	12 (9%)	1 (< 1%)
Tenderness	152 (88%)	10 (7%)	84 (55%)	39 (26%)	19 (13%)

Itching	48 (28%)	15 (31%)	29 (60%)	4 (8%)	0

2nd treatment at Baseline n=93					
Upper Lip					
Bruising	54 (58%)	6 (11%)	36 (67%)	12 (22%)	0
Redness	55 (59%)	13 (24%)	37 (67%)	5 (9%)	0
Swelling	85 (91%)	9 (11%)	53 (62%)	20 (24%)	3 (4%)
Pain (w/ burning)	67 (72%)	19 (28%)	42 (63%)	4 (6%)	2 (3%)
Tenderness	78 (84%)	5 (6%)	52 (67%)	14 (18%)	7 (9%)
Itching	19 (20%)	9 (47%)	10 (53%)	0	0
Lower Lip					
Bruising	48 (52%)	4 (8%)	36 (75%)	8 (17%)	0
Redness	54 (58%)	15 (28%)	34 (63%)	4 (7%)	1 (2%)
Swelling	77 (83%)	11 (14%)	50 (65%)	12 (16%)	4 (5%)
Pain (w/ burning)	62 (67%)	17 (27%)	40 (65%)	2 (3%)	3 (5%)
Tenderness	72 (77%)	4 (6%)	48 (67%)	14 (19%)	6 (8%)
Itching	19 (20%)	8 (42%)	11 (58%)	0	0

Additional safety assessments included evaluation of lip texture, firmness, symmetry, product palpability, mass formation, lip movement, function, and sensation, which were evaluated by a designated study staff member. Subjects were assessed for lip movement, function, and sensation at screening, 72 hours, and Weeks 2, 4, 8, 12, 16, 20, 24, after the initial treatment series as well as 72 hours, and 2 and 4 weeks after the Week 24 retreatment series.

Lip texture was judged via the criteria presented in Table 10.

Table 10. Lip Texture Scoring Criteria

Normal	Abnormal		
	Mild	Moderate	Severe
Texture of the lip was even without visible undulations or excessive coarseness beyond that expected for stated age.	The lip showed a single area of textural irregularity (a small papule, area of excess smoothness, focal absence of perpendicular lines) that could be visualized only with close inspection.	The lip showed more than one area of textural irregularity (a small papule, area of excess smoothness, focal absence of perpendicular lines) that could be visualized only with close inspection. or The lip showed one area of textural irregularity (less than ¼ of the lip area) at a conversational distance.	The lip showed two or more areas of textural irregularity (a small papule, area of excess smoothness, focal absence of perpendicular lines) that could be visualized at a conversational distance. or The lip showed one area of textural irregularity (more than ¼ of the lip area) at conversational distance.

The designated study staff member scored one Restylane subject as "severe abnormal lower lip texture" at Week 4 after treatment. By Week 8, the lower lip texture was scored as normal. During the same Week 4 visit, the subject scored their lip appearance as improved from baseline on the GAIS. No other subjects experienced severe abnormal lower lip texture.

Lip firmness was judged via the criteria presented in Table 11.

Table 11. Lip Firmness Scoring Criteria

Normal	Abnormal

	Mild	Moderate	Severe
Lip was supple when compressed laterally and surface distorted readily with minimal pressure. Pressure with a narrow diameter instrument (cotton-tipped applicator, toothpick etc) caused a focal depression in the surface of the lip. Upon palpation, lip was absent of abnormal structures such as scars or lumps; normal product feel without being visible.	Lip was slightly firm with lateral compression or required slightly greater than normal pressure to distort the surface. Upon palpation, an abnormal structure such as a scar or lump was felt, but was not visible.	Lip was firm with lateral compression or required distinctly greater than normal pressure to distort the surface or pressure with a narrow diameter instrument (cotton-tipped applicator or toothpick) caused a broader depression in the surface of the lip. Upon palpation, an abnormal structure such as a scar or lump was felt and was visible.	Lip was very firm with lateral compression or requires significantly greater than normal pressure to distort the surface. Upon palpation, an abnormal structure such as a scar or lump was felt and was visually distracting.

23% of subjects exhibited mild abnormal lip firmness during the study. One subject exhibited moderate lip firmness which resolved in less than 2 weeks. No subjects experienced severe abnormal upper or lower lip firmness at any time point. Lip swelling was commonly reported after Restylane injection, which may have contributed to the incidence of abnormal upper and lower lip firmness scores.

Lip symmetry was judged with the criteria presented in Table 12.

Table 12. Lip Symmetry Scoring Criteria

Normal	Abnormal		
	Mild	Moderate	Severe
One side of the lip balanced or mirrored the other side.	One side of the lip showed a 1 mm or less difference in height or a 1 mm or less difference in the length of the vermilion at repose.	One side of the lip showed a 1.1 mm to 2 mm difference in height or a 1.1 to 2 mm difference in the length of the vermilion at repose.	One side of the lip showed a greater than 2 mm difference in height or a greater than 2 mm difference in the length of the vermilion at repose.

Severe lip asymmetry occurred in 16/180 (8.9%) of the patients during the study and generally this severe asymmetry resolved in four weeks or less. GAIS scores at the corresponding or next closest visit indicated that all subjects with severe asymmetry judged themselves as improved or better.

Lip movement was tested by the ability to pronounce a preselected series of words. In three cases subjects were unable to pronounce all the words. One subject in the No Treatment group and one subject in the Restylane group at Week 24 failed to pronounce all the words even though they had passed the test during all previous visits. One additional subject in the Restylane group could not pronounce all the words at the Week 4 visit that occurred after the re-treatment series at Week 24.

Lip function was tested by assessing a subject's ability to suck liquid through a straw. All subjects were able to complete this activity at all times points during the study.

Lip sensation was tested via: 1) the monofilament test (i.e., a subject's ability to feel the sensation of a 0.4G monofilament at three points on the upper lip and three points on the lower lip) and 2) the cotton wisp test (i.e., a subject's ability to feel the sensation of a cotton wisp at three points on the upper lip and three points on the lower lip). Two patients did not pass this test. One Restylane-treated patient did not have sensation in the middle of the lower lip at Week 12. This patient had no other sensation problems at other time points during the study. A second Restylane-treated patient had a lack of sensation in the upper middle lip at Week 16 only.

Device palpability was assessed at each post treatment visit. The majority (i.e., 61% - 100%) of Restylane subjects experienced a palpable implant through the Week 24 visit. Device palpability decreased over time. For example, at Week 8 the device was palpable (with an expected feel) for 92% of treated upper lips and 89% of treated lower lips. By Week 24, device palpability was palpable in 61% and 62% of the treated upper and lower lips, respectively. An unexpected feel of the product was observed in 3% of the Restylane patients. Such assessments occurred between the 72 hours post treatment visit and Week 4 (both initial and retreatment at the Week 24 visit).

While one Restylane subject developed a mass formation two weeks after the second treatment at Week 24 (that returned to normal two weeks later after an upper lip cyst was drained), there were no "nodule" adverse events reported for any subject, and only one subject reported "rash papular" on the upper lip. There were also five subjects that reported eight events of lump/lumps during the study. The events occurred within 15 days or less from the time of an injection and resolved before the end of the study.

Assessing of Repeat Injections - For 98% of the subjects, treatment at Week 24 was no more difficult then the initial treatment sessions. For two subjects the second injection series was more difficult. In both cases the presence of previous dermal filler complicated injection. For these two subjects, neither reported pain as an adverse event during treatment, and both assessed their upper and lower lips as improved or better on the GAIS at the following visit.

Regarding subjects who chose not to get a second treatment at Week 24, there were 23 subjects who did not receive retreatment at 6 months. Seven patients cited continued efficacy of the first treatment, four subjects cited a previous side effect, and two patients claimed other reasons and the reasons for 10 other patients were unknown. For the four subjects who declined retreatment, the patient diagnosed-adverse outcomes judged as affecting daily activity or disabling were: pt# 1) bruising, swelling, and tenderness, pt# 2) bruising and swelling, and pt # 3) bruising, itching, pain, swelling, and tenderness. The fourth patient cited a low tolerance for pain and the previous procedure was too painful. Patients who declined re-treatment for unknown reasons experienced the following patient-diagnosed adverse outcomes that affected daily activity or were disabling: pt #1) swelling, tenderness, pain, pt# 2) swelling, tenderness, pain, pt# 3) bruising, swelling, tenderness, pain, pt # 4) swelling, tenderness, pain, redness, and pt#5) swelling, tenderness, pain. Five subjects who declined retreatment for unknown reasons had no patient-diagnosed adverse outcomes that affected daily activity or were disabling.

The incidence of *herpes infections* in Study MA-1300-15 are presented in Table 13. During the study 11 subjects received concomitant antiviral medication and ten of these subjects had an associated adverse event of oral herpes or herpes simplex. One subject (No Treatment group) received antiviral medication (i.e., Valtrex) for two days a week after signing the informed

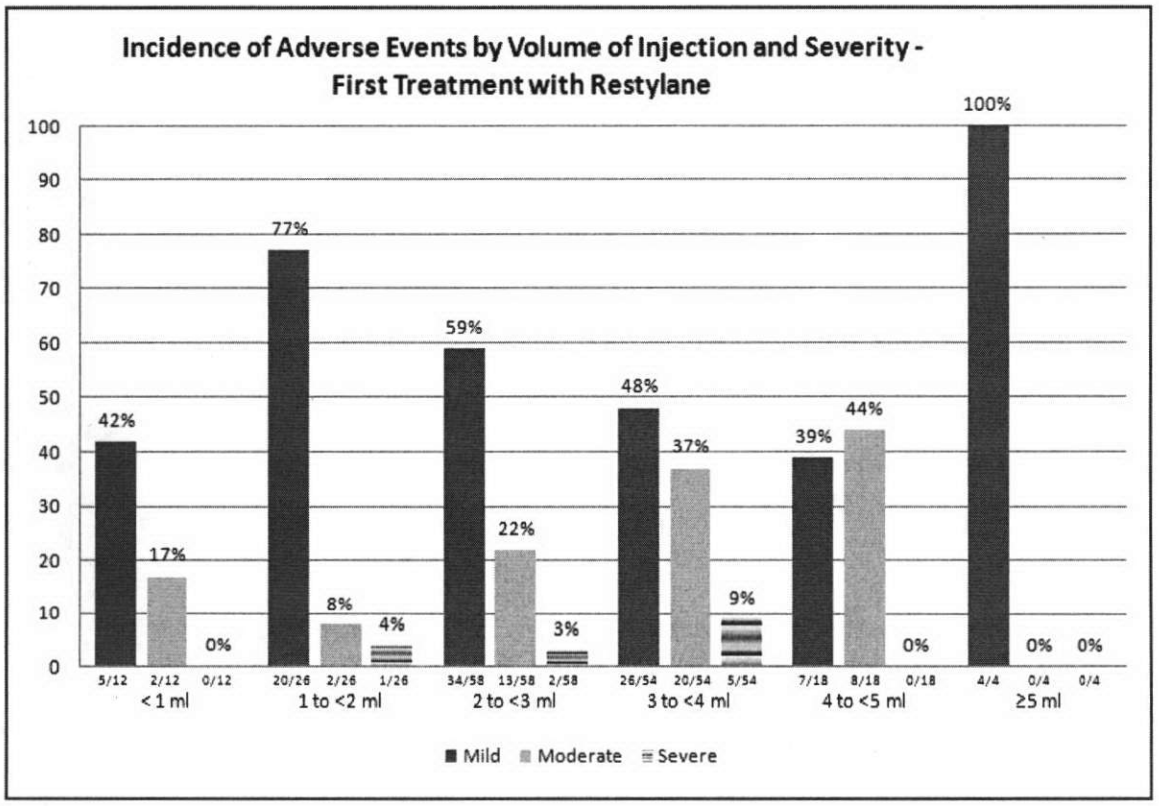
consent, but no associated adverse event was reported. Three additional subjects experienced oral herpes or herpes simplex adverse events, but did not use antiviral medication.

Table 13. Summary of Herpes Infections – Safety Population

	Treatment Group					
System Organ Class/ Preferred Term	**No Treatment at Baseline (N=45)**		**First Treatment with *Restylane* (N=172)**		**Second Treatment with *Restylane* (N=93)**	
	Events	**Subjects**	**Events**	**Subjects**	**Events**	**Subjects**
Infections and Infestations						
Herpes Simplex	2	2 (4%)	2	2 (1%)	0	0
Oral Herpes	1	1 (2%)	8	7 (4%)	2	2 (2%)

The *relationship between volume injected and adverse event occurrence* is presented below in Table 14.

Table 14. Relationship Between Injected Dose and Adverse Event Occurrence



In this study injection of greater than 1.5 mL per lip (upper or lower), per treatment session resulted in an increase in the occurrence of the number of moderate and severe injection site reactions.

2. Effectiveness Results

Primary Effectiveness Endpoint Results:

22

Analysis of the primary endpoint included subjects with a baseline MLFS score of 1 or 2 (i.e., 134/135 and 122/135, upper and lower lips, respectively for Restylane and 44/45 and 39/45 upper and lower lips, respectively, for No Treatment. The results of the primary effectiveness endpoint are presented in Table 15.

Table 15. Proportion of MLFS Responders Measured by the Blinded Evaluator

Assessment/Time point	Treatment Group	# Subjects in ITT	# (%) responders	p-value
Upper Lip				
Week 8	Restylane	134	127 (94.8%)	
	No Treatment	44	16 (36.4%)	
	Difference	--	58.4%	< 0.001
Lower Lip				
Week 8	Restylane	122	115 (94.3%)	
	No Treatment	39	15 (38.5%)	
	Difference	--	(55.8%)	< 0.001
Upper and Lower Lip Combined				
Week 8	Restylane	135	125 (92.6%)	
	No Treatment	45	13 (28.9%)	
	Difference		(63.7%)	< 0.001

* A Responder was defined as a 1 grade or more change from baseline on the MLFS (i.e., 1=very thin, 2=thin, 3=medium, 4-full 5-very full).
Subjects with a missing Blinded Evaluator assessment at 8 week were imputed using the hot deck method.
Only subjects with a baseline score of 1 or 2 were included in the analyses.

The proportion of Responders (i.e., at least a one grade increase from baseline to Week 8 MLFS score for both the upper and lower lips) were calculated using a Fisher's Exact Test. Subjects who did not have a Week 8 assessments had their data imputed using a hot deck procedure. Additional sensitivity analyses were conducted by imputing missing data with the subject's baseline MLFS value as well as with their last observation carried forward.

Secondary Effectiveness Endpoints Outcomes

The following additional effectiveness endpoints were evaluated with regard to Restylane's effectiveness in lip augmentation.

Table 16 presents a summary of the *absolute change in MLFS from Baseline for Upper and Lower Lips at Week 8.*

Table 16. Summary of MLFS Change from Baseline (Blinded Evaluators' Assessment) for Upper and Lower Lips at Week 8 – ITT Population

Assessment/ Time Point	Statistic	No Treatment (N=45)		Restylane (N=135)	
		Observed	Change from Baseline	Observed	Change from Baseline
Upper Lip					
Week 8	n	39	39	121	121
	Mean (S.D.)	1.9 (1.0)	0.5 (0.8)	3.4 (1.0)	2.1 (1.0)
	Median	2.0	0.0	3.0	2.0
	Min, Max	1,4	0, 3	1, 5	-1, 4
	P-value	--	--	--	<0.001
Lower Lip					
Week 8	n	35	35	111	111

	Mean (S.D.)	1.9 (0.8)	0.4 (0.6)	3.4 (0.9)	1.8 (0.9)
	Median	2.0	0.0	3.0	2.0
	Min, Max	1, 3	0, 2	1, 5	-1, 4
	P-value	--	--	--	<0.001

A Blinded Evaluator determination of MLFS score was performed at Weeks 12, 16, 20, and 24, as well as 2 and 4 weeks after the Week 24 re-treatment. Success was defined as at least one grade increase from Baseline to the measurement time point for both the upper and lower lips. The statistical difference in the proportion of Restylane and No Treatment Responders (based on the MLFS scores) was evaluated using Fisher's exact tests. The difference in the proportion of Restylane and No Treatment MLFS Responders was significant at all time points, when upper and lower lips were evaluated separately or combined. Table 17 presents the Blinded Evaluators' MLFS scores from Weeks 12- 24 when upper and lower lip outcome measures were combined.

Table 17. Proportion of MLFS Responders from Baseline in Upper and Lower MLFS as Measured by the Blinded Evaluator

Assessment/Time point	Treatment Group	# Subjects in ITT	# pts w/ non-missing data	# (%) responders* responders+	p-value
Upper and Lower Lip Combined					
Week 12 (Secondary)	Restylane	135	121	109 (90.1%)* (80.7%)+	
	No Treatment	45	38	14 (36.8%)* (31.1%)+	
	Difference	--		**(53.2%)*** **(49.6)+**	< 0.001*
Week 16 (Secondary)	Restylane	135	120	101 (84.2%)* (74.8)+	
	No Treatment	45	39	14 (35.9%)* (31.1%)+	
	Difference	--		**(48.3%)*** **(43.7)+**	< 0.001*
Week 20 (Secondary)	Restylane	135	116	87 (75%)* (64.4%)+	
	No Treatment	45	39	13 (33.3%)* (28.9%)+	
	Difference	--		**(41.7%)*** **(35.5%)+**	< 0.001*
Week 24 (Secondary)	Restylane	135	115	80 (69.6%)* (59.3%)+	
	No Treatment	45	38	14 (36.8%)* (31.1%)+	
	Difference	--		**(32.7%)*** **(28.2%)+**	< 0.001*

*The proportion of responders is calculated as the number of responders at the visit divided by the number of subjects with non-missing data.

+The proportion of responders is calculated as the number of responders at the visit divided by the total number of subjects in the ITT (i.e., missing subjects are considered failures).

3. Subgroup Analyses

Outcomes patients with Fitzpatrick Skin Types IV and V

41 subjects with Fitzpatrick Type IV and V skin were enrolled in the study and ten were initially randomized to No Treatment. 39 patients received a single Restylane treatment series at Baseline or at the Week 24 visit and 22 patients received a Restylane re-treatment series at Week 24. Table 18 summarizes the TEAEs experienced in 5% or greater of patients with Fitzpatrick Skin Types IV and V.

Table 18. Incidence of Treatment Emergent Adverse Events Reported by 5% or Greater of the Patients with Fitzpatrick Skin Types IV and V

System Organ Class	No Treatment n=10		1st Treatment n=39		2nd treatment n= 22	
	Events	Subjects	Events	Subjects	Events	Subjects
Any TEAE	4	3 (30%)	165	34 (87%)	75	19 (86%)
Blood and Lymphatic System Disorders						
Lymphadenopathy	0	0	0	0	1	1 (5%)
Gastrointestinal Disorders*						
Lip Discolouration	0	0	0	0	1	1 (5%)
General Disorder and Administrative - Site Conditions						
Mass	0	0	3	2 (5%)	0	0
Pain	0	0	8	5 (13%)	7	4 (18%)
Swelling	0	0	51	26 (67%)	32	17 (77%)
Tenderness	0	0	13	8 (21%)	9	5 (23%)
Infections and Infestations						
Herpes Simplex	0	0	2	2 (5%)	0	0
Influenza	0	0	2	2 (5%)	0	0
Nasopharyngitis	2	1 (10%)	2	2 (5%)	0	0
Sinusitis	0	0	3	3 (8%)	0	0
Upper Respiratory Tract Infection	1	1 (10%)	0	0	0	0
Injury, Poisoning, and Procedural Complication						
Contusion**	0	0	30	17 (44%)	13	8 (36%)
Nervous System Disorders						
Headache	1	1(10%)	7	4 (10%)	2	2 (9%)
Psychiatric Disorders						
Depression	0	0	0	0	1	1 (5%)
Reproductive System and Breast Disorders						
Dysmenorrhoea	0	0	1	1 (3%)	1	1 (5%)
Respiratory, Thoracic and Mediastinal Disorders						
Oropharyngeal Pain	0	0	0	0	1	1 (5%)
Skin and S.C. Tissue Disorder						
Erythema	0	0	13	8 (21%)	7	4 (18%)
Skin Exfoliation***	0	0	7	4 (10%)	0	0

*TEAEs that include "lip" in the preferred term were coded to the system organ class Gastrointestinal Disorders, whereas TEAEs that included only the symptom (i.e., pain, swelling, tenderness) in the preferred term were coded to the system organ class General Disorders and Administrative Site Conditions

**Contusion is interchangeable with bruising and/or ecchymosis

***Includes sloughing of the skin, peeling, desquamation, and superficial desquamation

Outcomes patients aged 18-21 years old

In Study MA-1300-15, one 18 year old, one 19 year old and two 20 year old patients were enrolled in the study and randomized to Restylane treatment. Three of the four subjects were retreated at Week 24. The mean volume of Restylane injected was similar to the overall patient population. Similarly, the TEAEs reported in these 4 patients were similar to the overall study population.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Additional clinical data include safety assessments in two Pilot Studies of lip augmentation and analysis of both the sponsor's global postmarketing safety database and Manufacturer and User Facility Device Experience database (MAUDE).

- U.S. Pilot Study, MA-1300-13k, "Prospective, Open-Label, Single Center, Blinded-Evaluator, Pilot Study of the Safety and Efficacy of Restylane® in the Restoration of Soft Tissue Volume of the Lips"

Clinical Study Design:

Clinical Study MA-1300-13k was an open-label, single center, blinded-evaluator trial conducted at one center with 20 subjects. The study did not include randomization of patients to a Control cohort.

Inclusion and Exclusion Criteria:

The study population: 1) were healthy adults (18 to 75 years old non-inclusive without concomitant medical conditions) and, if female of childbearing potential, non-pregnant and non-breast feeding, 2) were willing to comply with procedures, including sequential photography, 3) were willing to abstain from any other facial plastic surgical or cosmetic procedures for the first 12 weeks of the study and 4) may have had facial cosmetic procedures outside the area of assessment either before or contemporaneously with augmentation. Subjects excluded from the study: 1) had presence of any disease on entry which may have resulted in changes in facial contour or edema of the face during the course of the study or use of any biodegradable tissue augmentation therapy in the preceding eight months or implantation of any non-biodegradable soft tissue augmentation product, 2) had known hypersensitivity to Restylane, 3) had not yet completed recovery from or planned to have a facial procedure, 3) had the presence of any contraindication to the operative procedures including use of platelet inhibiting agents or other anticoagulant in a relevant period before study entry, 4) had a history of severe allergies manifested by a history of anaphylaxis or a history or presence of multiple severe allergies such as anaphylaxis or a hypotensive crisis in response to radiocontrast media, 5) had use of any tissue augmenting therapy or aesthetic facial surgical therapy below the level of the lower orbital rim within six (6) months prior to randomization, 6) had any condition which made the subject unable to complete the study per protocol, 7) had known allergies or hypersensitivity reactions to local topical anesthetics, 8) had cancerous or pre-cancerous lesions in the area to be treated, or 9)

had use of any investigational drugs or any other medical devices under investigation within 30 days before entry.

Study Plan:

Eligibility criteria and pre-treatment 2D and 3D images were assessed at Baseline. Each eligible subject was treated with Restylane to optimal lip augmentation as agreed upon by the physician and subject. Safety assessments included recording all systemic and local adverse experiences at each post-treatment study visit (i.e., 72 hours and Weeks 2, 6, 12 and 24 after treatment). Subjects also received a diary for daily recording of anticipated adverse outcomes (i.e., pain, tenderness, erythema, edema, ecchymosis, pruritus, and mass formation (nodule, cyst and abscess)) for the first two weeks after treatment. Subjects also assessed lip palpability at 72 hours, and Weeks 2, 6, 12, and 24 weeks after treatment. All technical or medical problems with the administration of injections were also recorded.

Patient Demographics:

19/20 patients completed the study. The patient demographics for the study are presented in Table 19.

Table 19. Patient Demographics for the Study Population

Characteristic	Restylane n =20
Age	
N	20
Mean (SD)	52.8 (13.4)
Median	53.5
Range	27 - 80
Gender	
Male	2 (10%)
Female	18 (90%)
Race/Ethnicity	
White	17 (85%)
Hispanic or Latino	2 (10%)
Other (Eurasian)	1 (5%)

Additional information on the Study Population:
Prior medications were taken by 80% of subjects. The most frequently used concomitant medication drug classes were HMG COA reductase inhibitors, other antidepressants, other anti-epileptics, propionic acid derivatives, and thyroid hormones (four subjects each). In addition, concomitant medications in conjunction with treatment administration included topical anesthetics (Betacaine LA) and other antiseptics and disinfectants (alcohol) for all subjects (100%). All subjects received cold compress therapy at the time of injection to prevent post-operative swelling.

Safety Outcomes:

Seven treatment emergent adverse events (TEAEs) were experienced by 4/20 (20%) of the subjects. The majority (5/7) of the TEAEs (i.e., thyroiditis, dysphagia, sinusitis, thyroid neoplasm, and cellulitis) were severe, but not related to treatment. Two subjects had one event each of mild bruising that was related to the injection procedure.

There were two severe adverse events (SAEs) during the study. One death occurred when a patient (with a medical history indicating hypothyroidism) experienced cardiac arrest on Day 29 resulting from a thyroid neoplasm. Another subject (whose medical history included rheumatoid arthritis, peripheral neuropathy, and hyperlipidemia) was hospitalized for severe cellulitis of the left lower extremity that was refractory to antibiotic therapy. The subject recovered approximately 3 months after hospitalization and completed the study. Both SAEs were considered unrelated to the study device.

Daily subject recording of anticipated adverse outcomes was performed for the first two weeks after treatment. The outcomes observed were similar to those reported in the Pivotal Study.

- **Non-IDE Canadian Pilot Study** MA-1300-14, "Open-Label, Pilot Study to Assess the Effectiveness and Safety of Restylane in the Restoration of Soft Tissue Fullness of the Lips"

Clinical Study Design:

Clinical Study MA-1300-14 was an open label study performed in Canada to assess the safety and preliminary effectiveness of Restylane in the restoration of soft tissue lip fullness in 21 patients. The study did not include randomization to a Control.

Inclusion and Exclusion Criteria:

Eligible patients required upper and lower lips with a MLFS score of 1, 2, or 3.

Study Plan:

After screening, subjects had both lips treated with Restylane to optimal lip augmentation.. Follow-up study visits occurred at Hour 72 (by telephone) and Weeks 2, 4, 8, and 12 for safety and effectiveness assessments. Touch-up with Restylane was available at Week 2, if needed.

VI – Study MA-1300-14 Outcomes

19/21 subjects completed Study MA-1300-14. One subject discontinued due to an adverse event (anxiety attack) and another subject discontinued due to non-compliance with the study schedule.

Patient Demographics:

The demographic and baseline characteristics for the study population are presented in Table 20.

Table 20. Patient Demographics Study MA-1300-14

Characteristic	Restylane n =21
Age	
N	21

Mean (SD)	41.1 (11.4)
Median	40.0
Range	26-65
Gender	
Male	3 (14%)
Female	18 (86%)
Race/Ethnicity	
Asian	1 (5%)
White	17 (81%)
Hispanic or Latino	3 (14%)
Blinded Evaluator Baseline MLFS Score	
Mean Upper Lip	1.7
Mean Lower Lip	2.4

Safety Outcomes:

The incidence and severity of adverse experiences- There were 8 TEAEs reported in 6 subjects. This included nasopharyngitis (n=2) and eyelid boil (n=1), influenza (n=1), pyelonephritis (n=1), contusion (n=1), fall (n=1), and anxiety (n=1). Four events were judged severe (i.e., Eyelid Boil, Pyelonephritis, Contusion and Fall), two were judged moderate (i.e., Influenza and Nasopharyngitis) and two were judged mild (i.e., Nasopharyngitis and Anxiety). No TEAE was judged related to study treatment and no SAE was reported.

One TEAE led to subject discontinuation. The Subject (with a history of anxiety) had an anxiety attack relating to the presence of Restylane in the lips. The Investigator considered the event to be mild and unrelated to study treatment.

Daily subject recording of anticipated adverse outcomes was performed for the first two weeks after treatment. The outcomes observed were similar to those reported in the Pivotal Study.

- **Relevant Post Market Experience**

Review of the sponsor's global postmarketing safety database and the FDA Manufacturer and User Facility Device Experience database (MAUDE) were performed to identify additional safety information about the previous off-label use of Restylane for lip augmentation.

The *Medicis Global Postmarketing Safety Database* was reviewed for lip area-adverse events from January 01, 2007 to September 30, 2010. The most commonly reported events were: General disorders and administration site conditions (i.e., Implant site swelling, pain, bruising, mass (lumps, bumps), erythema, and Lack of effect) and 2) Infections and infestations (i.e., Herpes). The events generally occurred immediately after treatment and the majority were mild or moderate in severity. These events appeared similar to the adverse events observed in the US pivotal study. Table 21 compares the incidence of Restylane adverse events from January 1, 2007 to September 30, 2010 after nasolabial fold and lips injections.

Table 21. Restylane Adverse Events Related to NLF and Lip Injections from 01/01/2007 to 09/30/2010

	Nasolabial Fold		Lip	
Adverse Event	**No.**	**%**	**No.**	**%**
Mass/Induration	73	11.5%	79	10.4%

Swelling	63	9.9%	123	16.2%
Non Dermatological Events	58	9.1%	71	9.4%
Device Ineffective	57	9.0%	98	12.9%
Erythema	48	7.6%	30	4.0%
Bruising/Bleeding	44	6.9%	47	6.2%
Medical Device Implantation	36	5.7%	60	7.9%
Discolouration	32	5.0%	18	2.4%
Pain/Tenderness	29	4.6%	51	6.7%
Extrusion Of Device	29	4.6%	14	1.8%
Ischemia/Necrosis	23	3.6%	17	2.2%
Infection/Abscess	17	2.7%	15	2.0%
Papules/Nodules	17	2.7%	17	2.2%
Injection Site Reactions	13	2.1%	14	1.8%
Capillary Disorder	10	1.6%	1	0.1%
Rash	8	1.3%	3	0.4%
Product Quality Issue	8	1.3%	6	0.8%
Hypersensitivity	7	1.1%	20	2.6%
Inflammation	7	1.1%	4	0.5%
Pruritus	7	1.1%	7	0.9%
Device Dislocation	6	0.9%	4	0.5%
Acne	6	0.9%	2	0.3%
Herpes	5	0.8%	14	1.8%
Other Dermatological Event	5	0.8%	14	1.8%
Granuloma/Foreign Body Reaction	4	0.6%	3	0.4%
Scar/Scab/Skin Atrophy	4	0.6%	6	0.8%
Eye Disorders	3	0.5%	2	0.3%
Urticaria	3	0.5%	1	0.1%
Accidental Exposure	3	0.5%	0	0.0%
Swelling Face	2	0.3%	2	0.3%
Dermatitis	2	0.3%	1	0.1%
Investigations	2	0.3%	0	0.0%
Muscle Disorders	1	0.2%	1	0.1%
Device Misuse	1	0.2%	5	0.7%
Fistula/Leakage	1	0.2%	1	0.1%
Blisters/Vesicles	0	0.0%	6	0.8%
Dermatofytos	0	0.0%	0	0.0%
Swollen Tongue	0	0.0%	1	0.1%
Unevaluable Event	0	0.0%	0	0.0%

In a review of the MAUDE database for Medical Device Reports (MDRs), 37 MDRs identified the site of Restylane injection as "lips", "upper lip" or "lower lip", and "vermilion border". These adverse events are presented below in two categories based on time-to-event; 1) within the first 24 hours post-injection and 2) after 24 hours post-injection.

Post-injection adverse events during the first 24 hours – The following adverse events were reported as occurred immediately after injections or within the first 24 hours: Allergic reaction and anaphylactic shock; skin discoloration, bruising, blanching, lesions resulting in necrosis, scarring or dark spots; hard bumps; infection (including grape- size lumps that were incised and drained); and Angioedema.

Adverse events that occurred beyond 24 hours up to months after injection included: mass/lesions under the skin; hyperpigmentation; dry lips; desquamation/peeling, broken capillaries; delayed hypersensitivity; Numbness; Hypertrophic scar tissue; and Herpes.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

A. Panel Meeting Recommendation

At the April 27, 2011 meeting of the General and Plastic Surgery Devices Advisory Panel the PMA supplement was recommended for approval. Background information on this Panel meeting is available at http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/GeneralandPlasticSurgeryDevicesPanel/ucm252477.htm.

B. FDA's Post-Panel Action

After the Panel meeting, FDA completed review of the product labeling and additional clinical data. In specific, the limited clinical data available for Restylane use in persons between the ages of 18-21 was considered. Through literature review and re-evaluation of previously submitted data from all Restylane premarket studies, it was determined that there were insufficient safety data to support Restylane use for lip augmentation in patients under the age of 21. Consequently, the product should be indicated for submucosal implantation for lip augmentation in patients over the age of 21.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Safety Conclusions

The adverse effects of the device are based on data collected in three clinical studies conducted to support PMA approval as described above as well as evaluation of off-label device use in the Post Market setting. The submitted data provided a reasonable assurance that the device is safe for use in lip augmentation in patients over the age of 21. The specific conclusions are:

- The majority of TEAEs observed in Study MA-1300-15 were mild in intensity (i.e., 672/795 (85%) and 264/267 (99%)), after the first and second treatments, respectively. For receiving their first Restylane treatment series a mean TEAE duration of 15.6 days was observed and for subjects receiving their second Restylane treatment series at Week 24 a mean duration of 10.4 days was observed.

- In Study MA-1300-15, four serious adverse events were reported in the Restylane treatment group, i.e., diverticulitis (n=1), pneumonia and pneumococcal infection (n=1), lumbar spinal stenosis (n=1) and transient ischemic attack (n=1).

- In Study MA-1300-15, the frequency of adverse outcomes reported in the 14 day patient diary was 97.1% (upper lip) and 94% (lower lip) for subjects receiving their first Restylane treatment. The commonly reported adverse outcomes (e.g., pain, swelling, tenderness, contusion (bruising/ecchymosis), and erythema) were anticipated and attributed to the procedure or Restylane. Onset was typically within a day of treatment and resolution usually

occurred within 15 days or less. 15% of the patients experienced adverse outcomes (typically swelling and tenderness) that lasted longer then 15 days.

- There were a few occurrences of abnormal lip texture, lip firmness, lip asymmetry, lip movement lip sensation and mass formation. In general none of the lip assessments were remarkable or presented any safety concerns.

- The majority of Restylane patients experienced a palpable implant through the Week 24 visit with device palpability decreasing over time (e.g., at Week 8 the device was palpable (with an expected feel) in 92% of treated upper lips and 89% of treated lower lips. By Week 24, device palpability was reported in 61% and 62% of the treated upper and lower lips, respectively). An unexpected feel was reported for 3% of the Restylane patients.

- The safety information on Restylane lip augmentation in persons of color was derived from a sample size of 38 persons with Fitzpatrick Type IV and 3 patients with Fitzpatrick Type V skin. The incidence of TEAEs reported were similar to the overall study population, with the exception of swelling which was reported more frequently in persons of color.

B. Effectiveness Conclusions

Assessment of product effectiveness is based on the results of Pivotal Study MA-1300-15. These submitted data provided a reasonable assurance that the device is effective for use in lip augmentation in patients over the age of 21. The specific conclusions are:

- The study met the pre-specified primary effectiveness criterion in that the difference in the proportion of Responders for upper and lower lips, separately and combined, for Restylane and No Treatment cohorts was statistically significant ($p<0.001$) in favor of Restylane. In the Restylane group at Week 8, 94.8% (127 /134) of the subjects were upper lip Responders and 94.3% (115/122) of the subjects were lower lip Responders. For upper and lower lips combined, 92.6% (125/135) of the subjects responded to Restylane at Week 8. In the No Treatment group, 36.4% (upper lips) and 38.5% (lower lips) of the subjects had Blinded Evaluator MLFS ratings that were at least one grade higher than baseline and 28.9% of the No Treatment subjects were Responders for both upper and lower lips combined.

- The study met the prespecified secondary effectiveness endpoints for the proportion of Responders when comparing Restylane to No Treatment cohorts based on: 1) the Blinded Evaluators' MLFS ratings from Weeks 12 – 24; 2) the Treating Investigators' MLFS ratings from Weeks 2-24; 3) the IPRs' MLFS ratings from Weeks 4-24; 4) the Treating Investigators' GAIS scores; and 5) the Subjects' GAIS scores.

C. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

XIV. CDRH DECISION

CDRH issued an approval order on October 11, 2011.

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling. *(See General hints)*

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

Post-approval Requirements and Restrictions: See approval order.