

FDA PMA P40024/s051 Executive Summary

Medicis Aesthetics, Inc.
Restylane
April 27, 2011

FDA Executive Summary
April 26, 2011 Panel Meeting of
General and Plastic Surgery Devices Panel

Introduction

This is the Executive Summary for Premarket Approval (PMA) application supplement 51 to PMA P040024 (i.e., P040024/s51) submitted by Medicis Aesthetics, Inc. for the medical device named Restylane, (a transparent, viscous gel composed of hyaluronic acid chemically cross-linked with BDDE and suspended in a buffer at pH = 7 and a concentration of 20 mg/mL). Restylane was previously approved under PMA P040024 (03/25/2005) for “mid-to-deep dermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds.” The current PMA supplement provides clinical data in support of a new Indication for Use (i.e., Lip-Augmentation). Restylane has been reviewed by the Plastic and Reconstructive Surgery Devices Branch of the Division of Surgical, Orthopedic, and Restorative Devices at the Center for Devices and Radiological Health of the Food and Drug Administration.

This Executive Summary provides an overview of the information submitted by Medicis Aesthetics, Inc in P040024/s51. This summary also provides the rationale for bringing P040024/s51 to the Advisory Panel, an identification of the applicant/manufacture, the proposed indications for use, and the FDA review team’s summary of the clinical study information.

Rationale for Bringing P040024/s51 to the General and Plastic Surgery Devices Panel

The FDA review team is presenting the P040024/s51 to the General and Plastic Surgery Devices Panel for deliberation of the safety and effectiveness of Restylane for use in lip augmentation based upon the results from clinical studies. The device is being taken to Panel since dermal filler injection for lip augmentation is a first of the kind indication for use. *FDA may refer the PMA to a Panel on its own initiative, and will do so upon the sponsor’s request of an applicant, unless the FDA determines that the application substantially duplicates information previously reviewed by a Panel.*¹

The FDA review team seeks the Panel’s input to determine whether the current data and/or studies are sufficient to support the risk/benefit of the device’s proposed indications for use. The FDA review team will provide a history of the device application and a summation of the research protocols, and then provide its analysis of the data and remaining issues that will provide the basis for several questions to the Advisory Panel at the Panel Meeting.

¹Code of Federal Regulations Title 21§814.44(a)

Table of Contents

Section	Page Number
Applicant/Manufacturer Information.....	6
Indications for Use.....	7
Device Description.....	8
Principles of Operation.....	9
Manufacturing Information and Preclinical Testing.....	10
I – Summary of Clinical Studies.....	11
II – Protocol MA-1300-15 Clinical Study.....	12
Clinical Study Design.....	12
Primary Aim.....	12
Sample Size.....	12
Inclusion and Exclusion Criteria.....	13
Selection of Patients.....	14
Study Plan.....	14
III – Protocol MA-1300-15 Clinical Study Outcomes	15
Patient Demographics.....	15
Additional information on the Study Population.....	18
Lost to Follow-up Patients.....	18
Injected Volume of Restylane.....	19
Primary Effectiveness Endpoint Results.....	20
FDA Review Team’s Comments on the Primary Effectiveness Outcome.....	20
Secondary Effectiveness Endpoint Outcomes	21
FDA Review Team’s Comments on the Secondary Effectiveness Outcomes	26
Effectiveness Outcomes in Patients with Fitzpatrick IV and V Type Skin	27
FDA’s Comments on the Effectiveness Outcomes in Patients with Fitzpatrick IV and V Type Skin	28
Study MA-1300-15 Safety Outcomes.....	29
Safety Outcomes in patients with Fitzpatrick Skin Types IV and V	34
Additional safety assessments	35
FDA Comments on the Safety Outcomes	39
Post-Approval Study.....	40

IV – FDA Review Team’s Conclusions for Panel Consideration	40
V - Executive Summary Section for Post Approval Studies	41

Table of Figures and Tables

<u>Figure</u>	<u>Page Number</u>
Table 1. Restylane Clinical Studies.....	11
Table 2. Medicis Lip Fullness Scale.....	12
Table 3. Subject Accountability Study MA-1300-15.....	15
Table 4. Patient Demographics for the Entire Study Population	16
Table 5. Demographics for Fitzpatrick IV and V Skin Type Patients.....	17
Table 6. Time and Reasons for Patients Leaving the Study Early.....	18
Table 7. Proportion of MLFS Responders Measured by the Blinded Evaluator....	20
Table 8. Proportion of MLFS Responders from Baseline in Upper and Lower MLFS as Measured by the Blinded Evaluator	22
Table 9. Proportion of Responders from Baseline in the Upper and Lower MLFS as Assessed by the Treating Investigator by Visit	23
Table 10. Proportion of Responders from Baseline in the Upper and Lower MLFS as Assessed by the IPR by Visit	24
Table 11. Treating Investigator GAIS	24
Table 12. Responder Analysis From Different Evaluators: Upper and Lower Lips Combined	26
Table 13. Proportion of Responders Measured by the Blinded Evaluators’ Assessment of MLFS Score for both Upper and Lower Lips at Week 8	28
Table 14. Incidence of Treatment Emergent Adverse Events Reported in 5% or Greater of the Study Population by Severity	29
Table 15. Duration of Treatment Emergent Adverse Events Reported by 5% or Greater of the Study Population by Severity	30
Table 16. Summary of Treatment Emergent Adverse Events in the Lip Area	31
Table 17. Intensity of Adverse Outcomes Reported in the Subject Diary	32
Table 18. Duration of Adverse Outcomes Reported in the Patient Diary	33

Table 19. Incidence of Treatment Emergent Adverse Events Reported by 5% or Greater of the Patients with Fitzpatrick Skin Types IV and V	34
Table 20. Lip Texture Scoring Criteria	35
Table 21. Lip Firmness Scoring Criteria	36
Table 22. Lip Symmetry Scoring Criteria	37

Applicant/Manufacturer Information

Medicis Aesthetics, Inc.
7720 N. Dobson Road
Scottsdale, AZ 85256

Indications for Use

Restylane is currently indicated for mid-to-deep dermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds. Supplement 51 seeks to add a new indication for use, i.e., “lip augmentation.”

Device Description

Restylane is a gel of hyaluronic acid purified from a Streptococcus species of bacteria that is chemically crosslinked and suspended in physiologic buffer at pH = 7 to a concentration of 20mg/ml. The product is approved for Gel fill sizes of 0.4, 0.7, 1.0 and 2.0 ml. The contents of each product syringe are sterile and the syringe is co-packaged with a sterile 29G or 30G needle(s).

Principles of Operation:

Dermal implantation of chemically crosslinked hyaluronic acid provides space-filling volume to the skin and hence correction of moderate to severe facial wrinkles and folds.

Manufacturing Information and Preclinical Testing:

Supplement 51 to PMA P040024 presents clinical data to support approval of a new indication for use, i.e., “lip augmentation.” Because the sponsor has not proposed any change in product manufacture or specification, the supplement does not contain any manufacturing information or preclinical testing. Instead, the data presented previously in PMA P040024 are suggested to be sufficient to support the new proposed indication for use.

I – Summary of Clinical Studies

Medicis Aesthetics, Inc. has performed six studies (in 846 subjects) with Restylane for the treatment of nasolabial folds and lip augmentation. There are three studies concerning lip augmentation (i.e., Pivotal Study MA-1300-15, US Pilot Study MA-1300-13K and Canadian Pilot Study MA-1300-14). This summary presents the results of the pivotal study. An Addendum to the Executive Summary that describes the results of both Pilot Studies and relevant Post Market Experience with Restylane injections in lip augmentation will be forwarded to the Panel shortly. The sponsor also completed Post Approval Study MA-1400-01 to evaluate the safety and effectiveness of Restylane and Perlane nasolabial fold injections in patients with Fitzpatrick skin types IV, V and VI. The results of Study MA-1400-01 were previously reviewed and changes to the product label including this information were approved by FDA. Hence an FDA-approved summary of Study MA-1400-01 may be found in the current product label.

Table 1. Restylane Clinical Studies

Clinical Study	Study No.	Study Design	Objective	No. of Sites	No of Pts.
Pivotal ¹	MA-1300-15	Randomized, Evaluator-Blinded No Treatment Controlled Multicenter Study	Evaluate the safety and effectiveness of Restylane in augmenting the soft tissue fullness of lips	12 sites	180 pts
Pilot ¹	MA-1300-13K ¹	Open-Label, Single Center, Blinded-Evaluator, Pilot Study	Evaluate the safety of Restylane in augmenting the soft tissue fullness of lips	1 site	20 pts
Pilot ¹	Study MA-1300-14 ¹	Open-Label, Pilot Study to Assess the Effectiveness and Safety of Restylane in the Restoration of Soft Tissue Fullness of the Lips	Evaluate the safety of Restylane in augmenting the soft tissue fullness of lips (Canadian Study – Non-IDE)	2 sites	21 pts
Pivotal	MA-1400-01	Randomized, Comparative Evaluator-Blinded Study	Evaluate safety and efficacy of Restylane and Perlane injections in the nasolabial folds in subjects with Fitzpatrick skin types IV, V and VI.	9 sites	150 pts
Pivotal	31GE0003	Randomized, Evaluator-Blinded Multicenter Study	Compare the safety and efficacy of Restylane and Zyplast for correction of nasolabial folds	6 sites	138 pts
Pivotal	MA-1400-02	Prospective, Randomized, Comparative, Multicenter Study	Evaluate sensitization to Restylane and Perlane (and acute safety profile assessment)	17 sites	283 pts
Post Approval	MA-04-003	A Randomized, Evaluator-Blinded, Multicenter Study	Compare efficacy and persistence of correction of nasolabial folds with Restylane using 2 different retreatment schedules	3 sites	75 pts

¹ These studies are the subject of the current Panel Track PMA Supplement.

The following is an in-depth description of the pivotal study supporting the proposed change in the indication for use (i.e., augmentation of soft tissue fullness of the lips).

II – Study MA-1300-15, “Randomized, Evaluator-Blinded No Treatment Controlled Multicenter Study”

Clinical Study Design:

Study MA-1300-15 was a randomized, evaluator-blinded, No Treatment controlled study of the effectiveness and safety of Restylane in the augmentation of soft tissue fullness of the lips.

Primary Aim:

The primary effectiveness endpoint was a test of whether Restylane was more effective than No Treatment (as determined by Blinded Evaluator assessment of lip fullness) at 8 weeks after treatment that was compared to baseline lip fullness assessments performed by the treating investigator. Separate upper and lower lips evaluations were performed (as co-primary endpoints) using the validated 5 grade Medicis Lip Fullness Scales (MLFS). Treatment success was defined as at least a one grade increase in MLFS for both upper and lower lips. The MLFS is presented below in Table 2.

Table 2. Medicis Lip Fullness Scale

1	Very Thin
2	Thin
3	Medium
4	Full
5	Very Full

The primary safety objective was to identify the incidence of all adverse events including subject adverse outcomes reported 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 qualified health care professional other than the treating investigator or blinded evaluator included lip assessments for texture, firmness, symmetry, product palpability, mass formation, lip movement, function, and sensation.

Sample Size

For the primary effectiveness assessment of the superiority of Restylane compared to No Treatment, a sample size of at least 120 treated-subjects and 40 No Treatment-subjects for each lip (accounting for a 10% drop-out rate) yielded 99% power to detect a difference in response at Week 8 of 25% in No Treatment-subjects versus 70% in the Restylane-subjects (based on a one-sided Fisher’s Exact test with $\alpha=0.05$).

An adverse event that occurred in 1% of the population had a 74% probability of being observed in at least one subject in the clinical study of 135 Restylane subjects (based on

binomial probability). Blinded Evaluators were masked to treatment assignment. Per FDA's suggestion, the Blinded Evaluators were not to make any live assessments until Week 8, to ensure blinding.

Inclusion and Exclusion Criteria:

The Inclusion Criteria in this study were males and non-pregnant or non-breast feeding females who were: 1) 18-65 years old, 2) seeking augmentation therapy for the lips, 3) willing to comply with the requirements of the study, (including sequential photography or imaging), 4) willing to abstain from any other facial plastic surgical or cosmetic procedure for 9 months (e.g., laser or chemical resurfacing, facelift, etc), and 5) willing to give written informed consent to participate in the study. All female subjects agreed to: 6) use an acceptable form of birth control during the study period and 7) 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 as assessed at baseline by the Treating Investigator 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 as assessed at baseline by the Treating Investigator 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.

The Exclusion Criteria in this study were: 1) a history of allergy or hypersensitivity to injectable hyaluronic acid gel, 2) a history or the 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, such as inflammation, infection, facial psoriasis, herpes zoster, acanthosis, cancer, precancer, actinic keratosis, etc., 3) a history of the use of any biodegradable or non-biodegradable tissue augmentation therapy or aesthetic facial surgical therapy below the level of the lower orbital rim, (e.g., injection or other form of implantation of tissue augmenting substances, fillers, fat augmentation, Botox injections, facelift, or dental work in the preceding eight months, or plans to use these substances or have these procedures during the study), 4) the presence of any contraindication to the implant procedures, including use of platelet inhibiting agents (e.g., aspirin) or other anticoagulant, in a relevant period before study entry, 5) 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, 6) the presence of any condition, (which in the opinion of the investigator) made the subject unable to complete the study per protocol (e.g., subjects not likely to avoid other facial cosmetic treatments; subjects not likely to stay in the study for up to nine months because of other commitments, concomitant conditions, or past history; subjects anticipated to be unreliable; or subjects who have a concomitant condition that might confuse or confound study treatments or

assessments), 7) the presence of known allergies or hypersensitivity reactions to local topical anesthetics or nerve blocking agents (if such products were intended to be used for that subject), 8) the presence of cancerous or precancerous lesions in the area to be treated, 9) a history of prior surgery to the upper or lower lip, 10) a history of prior significant trauma, (such as dog bite or laceration, to the upper or lower lip resulting in formation of a scar), 11) the presence of facial hair that could interfere with MLFS evaluation, 12) a history of herpes labialis and an outbreak within four weeks of study entry or with four or more outbreaks in the 12 months prior to study entry, 13) the presence of mild, moderate, or severe abnormal rating for texture or firmness or detection of any abnormal lip structure, such as a scar or lump, 14) the presence of moderate or severe abnormal rating for lip symmetry, 15) the presence of abnormal rating in lip movement, with inability to pronounce three or more of the preselected words, 16) the presence of abnormal rating in lip function, with inability to effectively suck water through a straw, 17) the presence of abnormal rating in lip sensation, with inability to feel a 0.4G monofilament or a cotton wisp at any site on the lip, 18) the presence of any mass formation at screening, 19) current use of immunosuppressive therapy, 20) a history of connective tissue diseases such as rheumatoid arthritis, systemic lupus erythematosus, polymyositis (PM), dermatomyositis (DM) or scleroderma, or 21) participation in any interventional clinical research study within 30 days prior to randomization.

Selected Patients:

Patients who met the entry criteria were enrolled and randomized in a 3:1 ratio to immediate Restylane treatment (n=135) or a No Treatment Control (n=45), because there is no FDA-approved product for lip augmentation. The study was also designed to enroll a minimum of 30 subjects with darker skin types (i.e., Fitzpatrick IV, V or VI). Randomization was stratified by Fitzpatrick skin type, (i.e., stratum #1 - Skin Types I-III and stratum #2 - Skin Types IV-VI). To maintain masking, Control subjects did not receive Restylane injections until Week 24.

Study Plan:

Subjects were enrolled at 12 investigational centers. To assist in maintaining Blinded Evaluator masking, all baseline assessments (including MLFS scoring) were performed by the Treating Investigator (including MLFS scoring) and a qualified health care professional (including lip safety assessments). Patients were evaluated at 72 hours and 2, 4, 8, 12, 16, 20, 24, weeks after the last treatment (or No Treatment). Touch-up treatments with the products assigned by randomization were provided at 2 weeks post-treatment, if required to achieve optimal correction.

Subjects completed a 14 day post treatment diary after each injection. The Treating Investigator assessed safety outcomes at each visit and a study staff member evaluated patients for abnormal lip texture, lip firmness, and lip symmetry, as well as abnormal lip movement, function, sensation (i.e., Monofilament test and Cotton Wisp test), and mass formation at each study visit. Laboratory values and vital signs were not collected in this study

The Treating Investigator performed MLFS and Global Aesthetic Improvement Scale (GAIS) evaluations after each visit. The Blinded Evaluator determined MLFS scores at Weeks 8, 12, 16, 20, and 24 after the last treatment. Subjects performed a GAIS evaluation after each visit. Photographic records were collected after each visit.

All subjects (i.e., Treatment and Control) were offered Restylane injections at the Week 24 visit. Clinical visits after this injection (i.e., the initial treatment for Control subjects or re-treatment for initial Restylane subjects) included monitoring safety outcomes at 72 hours, as well as Weeks 2 and 4 after the last treatment in a manner consistent with the initial treatment protocol. Touch-up treatments were provided at 2 weeks post-treatment, if required to achieve optimal correction.

III – Study MA-1300-15 Outcomes

This was a multicenter (12 sites), prospective, blinded study involving 180 enrolled patients. Of the enrolled patients, 116/135 (86%) Restylane and 39/45 (87%) Control subjects completed the study. No subject discontinued the trial due to an adverse event. Subject accountability is displayed below in Table 3.

Table 3. 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

Patient Demographics:

Demographic characteristics were similar for the No Treatment and Restylane groups at baseline. Overall, the mean age for study subjects was 47.6 years, most subjects were female and White (99% and 94%, respectively), and the majority were identified as not being of Hispanic or Latino descent (89%). The mean height for subjects at entry was 163.53 cm and the mean weight was 67.87 kg.

The study included 139 subjects (77%) with Fitzpatrick I, II, or III skin types and 41 subjects (23%) with Fitzpatrick skin types IV and V. No patient with Fitzpatrick skin type VI was enrolled. Subjects with lighter skin types (i.e., Fitzpatrick skin types I, II, or III) required both the upper and lower lips to be assessed as either very thin (1) or thin (2) at screening. Subjects with darker skin (i.e., Fitzpatrick Types IV, V, or VI) needed only one lip (i.e., upper or lower) to be assessed as very thin (1) or thin (2) by the Treating Investigator at screening; however, for subjects that had only one qualifying lip, the other lip could have been treated with Restylane for symmetry purposes, (but effectiveness assessments were not completed for the non-qualifying lip). The demographics of the

entire study population are presented in Table 4. Table 5 presents the demographics for patients with Fitzpatrick Skin Types IV and V.

Table 4. 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 / Alaskan Native	1 (2%)	1 (<1%)	2 (1%)
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 5. Demographics for Fitzpatrick IV and V Skin Type Patients

Characteristic	No Treatment	Restylane	Total
----------------	--------------	-----------	-------

	N=10	N=31	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 both 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 between 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 acetylsalicylic 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%.

Lost to follow-up patients

Table 6 identifies the reasons that patients left the study before completion.

Table 6. Time and Reasons for Patients Leaving the Study Early

No.	PID	Time after treatment
Withdrew Consent		
1		3 days after first treatment
2		4 months after first treatment
3		7 months after first treatment
4		1 month after first treatment
5		9 days after first treatment
6		6 months after first treatment
7		5 months after first touch up treatment
8		2 months after first treatment
Lost to Follow-Up		
1		4 months after first touch-up treatment
2		7 months after first treatment
3		6 months after first treatment
4		4 months after first treatment
5		2 months after first treatment
6		2.5 months after first treatment
7		4 months after first touch up treatment
8		7 months after first touch up treatment
9		3 months after first touch up treatment
10		6 months after first touch up treatment
Investigator Decision		
1		5 months after first touch up treatment

Injected Volume of Restylane:

The mean volume of Restylane injected into the lips for initial treatment (including touch-ups) was 2.9 mL. (A dose not exceeding 1.5 ml per upper lip and 1.5 ml per lower lip was recommended per treatment session.) Device implantation was achieved by submucosal injection to the upper and lower lips of all subjects. The majority of subjects received 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).

At the Week 24 treatment (including touch up), the mean volume of Restylane injected was 1.8 mL for retreatment subjects. No Treatment patients who received their first Restylane treatment were injected with a mean volume of 2.4 mL. The submucosal injection was the most common implantation depth for upper and lower lips of both treatment groups and the primary method of injection for most subjects was linear retrograde to enhance the vermilion border. For subject receiving retreatment at Week 24, the mean length of time needed to perform the injections was 9.5 minutes for both lips and 4.3 minutes was required for the touch up visit. For subjects in the No Treatment group, the median length of time needed to initially treat both lips (at Week 24) was 12.9 minutes and 7.7 minutes were required for the touch up visit.

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. Submucosal injection was used for all Restylane implants. Patients with Fitzpatrick Skin Types IV and V also were injected by a combination of methods, however, the linear retrograde method was the primary technique used by most of the Treating Investigators for enhancing the vermilion border for subjects of darker skin types (compared to linear antegrade or serial puncture).

For patients with Fitzpatrick Skin Types IV and V, the mean volume for retreatment and touch-ups at Week 24 was 1.4 mL. The mean length of time to perform the injection was 10.9 minutes (retreatment) and 4.9 minutes (touch up visit). For patients with Fitzpatrick Skin Types IV and V in the No Treatment group, the mean volume injected at Week 24 was 2.1 mL. The mean length of time to perform the injection for these patients was 16.8 minutes (initial treatment), and 7.9 minutes (touch up). The depth of injection for all subjects in both treatment groups was submucosal, and the linear retrograde technique was the most commonly used method of injection.

The Treating Investigator determined that *the second treatment session* was not more difficult than the initial treatment session in 98% of the subjects. In two patients the second injection was more difficult, because previous dermal filler remained at the injection site (in both cases). Neither of these subjects reported pain as an adverse event during re-treatment, and both assessed their upper and lower lips as improved or better on the GAIS scale at the following visit.

Primary Effectiveness Endpoint Results:

The sponsor's 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 Primary Effectiveness endpoint compared the differences in the Blinded Evaluators' MFLS assessments at Week 8 post treatment with the Treating Investigators' baseline MLFS score for the Restylane and No Treatment cohorts. (The study was designed in this manner to avoid unmasking the Blinded Evaluator to treatment assignment.) 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. (MLFS scoring was assisted by separate photo-guides for the upper and lower lips). The results of the primary effectiveness endpoint are presented in Table 7.

Table 7. 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 assessment 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.

FDA Review Team's Comments on the Primary Effectiveness Outcome:

- 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.

Based on the study results at Week 8, the FDA statistician calculated that if 100 patients were injected, a little over 50 patients would be Responders. FDA will request Panel Comment on the potential effectiveness of Restylane use for lip augmentation.

- Subjects who did not have a Week 8 assessment had their data imputed using a hot deck procedure. When the missing data was imputed using the subject's baseline MLFS value, then the proportion of MLFS responders from baseline for upper and lower lip combined was 113/135 (83.7%) of the subjects, [115/134 (85.8%) of the subjects for the upper lip, and 104/122 (85.2%) of the subjects for the lower lip]. In the No Treatment group, the Responders for upper and lower lips combined were 12/45 (26.7%) of the subjects, [14/44 (31.8%) of the subjects for upper lips and 13/39 (33.3%) of the lower lip subjects.] The between group differences in proportion of MLFS responders were statistically significant (p-value <0.001) for all comparisons. Other missing data analyses could be performed, but because the difference between Restylane and No Treatment cohorts was so large, the results do not change with different sensitivity analyses.
- The primary population for the effectiveness analysis was the Intent-to Treat (ITT) population. The Protocol stated that if there was more than a 10% difference in the sample size of the ITT and Per Protocol (PP) populations, a supportive analysis of the primary endpoint was to be conducted based on the PP population. Because there was less than a 10% difference in the sample size of the ITT and PP populations, (5.5%); the PP analyses were not performed.

Secondary Effectiveness Endpoints Outcomes:

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

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. Over time, the proportion of Responders in the Restylane group became smaller, while the proportion of Responders in the No Treatment group remained the same. Missing data were not imputed for the secondary effectiveness endpoints. Table 8 presents the Blinded Evaluators' MLFS scores from Weeks 12- 24 when upper and lower lip outcome measures were combined.

Table 8. 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).

Treating Investigators' determination of MLFS scores were performed at each time point after treatment and compared to baseline condition. Success was defined as at least one grade increase from Baseline in the upper and lower lips. Table 9 presents the proportion of Responders for upper and lower lips based on the Treating Investigators' MLFS rating.

Table 9. Proportion of Responders from Baseline in the Upper and Lower MLFS as Assessed by the Treating Investigator by Visit

Assessment Time point	Treatment Group	No. of Subjects	# pts w/ non-missing data	# (%) responders*	p-value
Upper and Lower Lip Combined					
Week 2	Restylane	135	129	127 98.4%	
	No Treatment	45	38	0 0%	
	Difference	--		98.4%	< 0.001*
Week 4	Restylane	135	126	125 99.2%	
	No Treatment	45	38	0 0%	
	Difference	--		99.2%	< 0.001*
Week 8	Restylane	135	122	109	

	No Treatment	45	40	2 5%	89.3%
	Difference	--			84.3%
Week 12	Restylane	135	121	107 88.4%	< 0.001*
	No Treatment	45	39	2 5.1%	
	Difference	--			83.3%
Week 16	Restylane	135	121	91 75.2%	< 0.001*
	No Treatment	45	39	2 5.1%	
	Difference	--			70.1%
Week 20	Restylane	135	117	79 67.5%	< 0.001*
	No Treatment	45	39	3 7.7%	
	Difference	--			59.8%
Week 24	Restylane	135	115	55 47.8%	
	No Treatment	45	38	1 2.6%	
	Difference	--			45.2%

Independent photographic reviewers' (IPR) assessment of MLFS score was performed after study completion using photographic images collected during the study. The IPR was performed by three off-site reviewers who determined the percent Responders by comparing patients' photos from Baseline and Weeks 4 - 24. No Treatment cohort photos were also evaluated. A Responder was defined as at least one grade increase from Baseline on the MLFS scale. Table 10 summarizes the results of the IPRs' MLFS scores.

Table 10. Proportion of Responders from Baseline in the Upper and Lower MLFS as Assessed by the IPR by Visit

Assessment/ Time point	Treatment Group	# Subjects in ITT	# pts w/ non- missing data	# (%) responders*	p-value
Upper and Lower Lip Combined					
Week 4	Restylane	135	124	94 75.8%	
	No Treatment	45	38	2 5.3%	
	Difference	--			70.5%
Week 8	Restylane	135	120	70 58.3%	< 0.001*
	No Treatment	45	40	4 10%	
	Difference	--			48.3%
Week 12	Restylane	135	119	57 47.9%	< 0.001*
	No Treatment	45	38	3 7.9%	
	Difference	--			40.0%
Week 16	Restylane	135	120	51	

	No Treatment	45	39	42.5%	
	Difference	--		37.4%	< 0.001*
Week 20	Restylane	135	117	46 39.3%	
	No Treatment	45	39	3 7.7%	
	Difference			31.6%	< 0.001*
Week 24	Restylane	135	112	41 36.6%	
	No Treatment	45	39	3 7.7%	
	Difference			28.9%	< 0.001*

Treating Investigators' assessment of improvement using the GAIS at each time point after treatment with Restylane compared to No Treatment. Improvement was defined as a score of improved or better using the GAIS and the statistical difference in the proportion of Restylane and No Treatment Responders (based on GAIS scores) was evaluated using Fisher's Exact Test. The Treating Investigator GAIS is presented in Table 11.

Table 11. Treating Investigator (GAIS)

3	Very much improved	Optimal cosmetic result for the implant in this subject
2	Much improved	Marked improvement in appearance from the initial condition, but not completely optimal for this subject
1	Improved	Obvious improvement in appearance from the initial condition
0	No change	The appearance is essentially the same as baseline
-1	Worse	The appearance is worse than the original condition
-2	Much Worse	Marked worsening in appearance from the initial condition
-3	Very much worse	Obvious worsening in appearance from the initial condition

When the scores for upper and lower lips were combined, Treating Investigators judged 100% of the Restylane subjects as improved or better at Weeks 2 and 4. At Weeks 8, 12, 16, 20 and 24, the proportion of subjects from Baseline assessed as improved or better was 97.5%, 90.1%, 78.5%, 70.9%, and 60.9%, respectively. In the No Treatment group, no subjects (0%) were assessed as improved or better from Baseline to Weeks 2, 8, 16, and 24. At Weeks 4 and 20, one subject was judged improved or better from baseline. The differences in GAIS were statistically significant at all time points.

Subject assessment of improvement at each time point after treatment based on a GAIS score and comparing Restylane with No Treatment. A Responder was defined as a score of improved or better from Baseline on the 7-point GAIS for the upper and lower lips,

separately. The Subject GAIS scale was the same as that displayed in Table 11, however the narrative component was removed.

When the upper and lower lip outcomes were combined, the proportions of subjects that assessed themselves as improved or better from Baseline in the Restylane group were 97.7% (Week 2), 99.2% (Week 4), 96.7% (Week 8), 91.7% (Week 12), 85.0% (Week 16), 76.1% (Week 20), and 74.1% (Week 24). In the No Treatment group, none (0%) of the patients assessed themselves as improved from Baseline at any visit. The differences in proportion of Restylane and No Treatment group Responders were statistically significant at all time points.

Extent of correlation between the MLFS and GAIS scores rated by Treating Investigators, was determined to assess trends between the two scales. The correlation among the degree of response per the MLFS and the GAIS scores for the Treating Investigator was determined at each time point using Spearman's rank correlation coefficients, (separately for the upper and lower lips). The correlation in ratings by Treating Investigator for upper and lower lips between week 2 and week 24 ranged from 0.698 to 0.819. These results were statistically significant.

Extent of correlation between the MLFS score by the Treating Investigator and the Subject GAIS scores was determined (separately for the upper and lower lips), to assess trends between the two scales. The correlation among the degree of response per the MLFS and the GAIS scores for the Treating Investigators and Subjects was determined at each time point using Spearman's rank correlation coefficients. The correlation coefficients for the upper lip ranged from 0.458 (Week 24) to 0.626 between Weeks 2-20. Correlations for the lower lip ranged from 0.542 – 0.654 between Weeks 2-24. A statistically significant result was observed at each time point.

Agreement among the proportion of Responders determined by the MLFS and GAIS scales as judged by the Treating Investigators was evaluated for each lip separately. Agreement among the proportion of Responders via the MLFS (i.e., at least a one grade increase) and the GAIS (i.e., a score of one or greater) was determined using weighted kappa statistics, for the Treating Investigators' assessments. The weighted kappa coefficients (95% CI) for the agreement between MLFS lip fullness ratings and GAIS aesthetic satisfaction ratings by the Treating Investigators for both upper and lower lips by visit were 0.942 (0.878, 1.000) at Week 2 and 0.88 (0.793, 0.967) at Week 12, suggesting agreement between the MLFS and GAIS ratings. From Weeks 16 to 24, there was agreement between the MLFS and GAIS ratings for the lower lip (i.e., 0.734 [0.616, 0.852] and 0.681[0.559, 0.803], respectively). The exact agreement ranged between 85-99%. These correlations were statically significant.

Agreement among the MLFS between the Treating Investigator, Blinded Evaluator, and IPR assessments was determined using weighted kappa statistics, separately for the upper and lower lips. The results for Upper and Lower Lips Combined are presented below in Table 12.

**Table 12. Responder Analysis From Different Evaluators:
Upper and Lower Lips Combined**

Assessment/ Time Point	Treatment Group	Blinded Live Evaluator	Treating Investigator	IPR
Week 8	Restylane	0.93	0.89	0.58
	No Treatment	0.29	0.05	0.10
	Difference	0.64	0.84	0.48
Week 24	Restylane	0.70	0.48	0.37
	No Treatment	0.37	0.03	0.08
	Difference	0.33	0.45	0.29

The weighted kappa coefficients (95% CI) for the agreement in MLFS ratings of Responders for upper and lower lips as rated by the Blinded Evaluators, Treating Investigators, and IPRs in the Restylane and No Treatment groups at Week 8 were presented. For the upper lips at Week 8, the agreement between the Blinded Evaluators and Treating Investigators was kappa =0.638; the agreement between the Blinded Evaluators and IPRs at this time point was kappa =0.366; and the agreement between the IPRs and the Treating Investigators was kappa=0.407. For the lower lips at Week 8, the agreement between the Blinded Evaluators and Treating Investigators was kappa =0.665; the agreement between the Blinded Evaluators and IPRs was kappa =0.297; and the agreement between the IPRs and the Treating Investigators was kappa=0.502.

FDA Review Team’s Comments Secondary Effectiveness Outcomes:

- 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.
- Differences in the proportion of MLFS Responders (i.e., comparing Restylane and No Treatment cohorts) were statistically significant at all visits ($p < 0.001$ to p -value 0.018) for both Treating Investigators and IPRs. Interestingly, while evaluations showed a significant difference, the estimated proportion of Responders was very different in Blinded Evaluators, Treating Investigators and IPRs. The unblinded Treating Investigators reported the largest difference. The IPRs scored the smallest improvement in the Restylane group and the smallest differences overall. This may reflect in part, differences in the incidence of Responders in the No Treatment cohort.
- The sponsor-calculated weighted kappa values (based on the categorization of MLFS Responders), were 0.64 between the Blinded Evaluators and the Treating Investigators, 0.37 between the Blinded Evaluators and the IPRs, and 0.41 between the Treating Investigators and the IPRs. FDA calculated a weighted kappa value using the MLFS values alone (rather than MLFS-Responders) of 0.58 between the Blinded Evaluators and the Treating Investigators. FDA believes that a fair (not great) amount of agreement exists between the Blinded Evaluators and Treating Investigators. The difference between the Blinded Evaluator and IPRs appears to be poor.

Effectiveness Outcomes in Patients with Fitzpatrick IV and V Type Skin:

The effectiveness of Restylane for lip augmentation in patients with Fitzpatrick Types IV and V skin types was suggested by the statistically significant differences between Restylane and No Treatment groups in the Primary Effectiveness endpoint (i.e., see Table 13 below) and the following secondary endpoints:

- 1) the proportion of Responders as determined by the Blinded Evaluators' MLFS scores for Weeks 12-16;
- 2) the proportion of Responders from Baseline as determined by the Treating Investigators' MLFS assessment;
- 3) the proportion of Responders as determined by the IPRs' MLFS assessment at Week 4;
- 4) the proportion of patients with improvement or better from Baseline as determined by the Subjects' GAIS scores from Weeks 2-24; and
- 5) the proportion of subjects with improvement or better from Baseline as determined by the Treating Investigators' GAIS score from Weeks 2-24.

The proportion of Responders determined from the Blinded Evaluators' MLFS scores at Weeks 20 and 24 were not statistically significant. (For example at week 20, 18/27 (66.7%) Restylane and 3/9 (33.3%) No Treatment patients were Responders ($p=0.122$). At Week 24, 17/27 (63.0%) Restylane and 3/9 (33.3%) No Treatment patients were Responders ($p=0.146$.) Similarly the differences in treatment group outcomes as judged by the IPRs' MLFS scores were not statistically significant at Weeks 8-24 at the 0.05 level.

Table 13. Proportion of Responders Measured by the Blinded Evaluator's Assessment of MLFS score for both Upper and Lower Lips at Week 8.

Assessment Time Point	Treatment Group	No of Subjects	No of Responders	Proportion of Responders	p-value
Upper Lip					
Week 8	Restylane	30	28	0.933	
	No Treatment	9	5	0.556	
	Difference	--	--	0.378	0.018
Lower Lip					
Week 8	Restylane	18	17	0.944	
	No Treatment	4	0	0.000	
	Difference	--	--	0.944	< 0.001
Upper and Lower Lip Combined					
Week 8	Restylane	31	29	0.935	
	No Treatment	10	3	0.300	
	Difference	--	--	0.635	< 0.001

FDA's Comments on the Effectiveness Outcomes in Patients with Fitzpatrick IV and V Type Skin:

- The results of the effectiveness analysis for subjects with Fitzpatrick skin types IV and V show a statistically significant difference between the treatment groups in favor of Restylane at Week 8 as assessed by the Blinded Evaluator with an upper lip p-value of 0.018 and a lower lip p-value <0.001. The upper and lower lips combined yield a p-value <0.001. However, the study enrolled 38 persons with Fitzpatrick Type IV, 3 patients with Fitzpatrick Type V and no patients with Fitzpatrick Type VI skin. Assessments of product effectiveness in this subgroup are based on 31 Restylane and 10 No Treatment patients with Fitzpatrick skin types IV and V. It is unclear whether meaningful analyses of product effectiveness in this patient population are possible given the small number of patients studied and the absence of persons with Fitzpatrick Type VI skin. It is also unclear whether persons with Fitzpatrick Type V and VI skin will seek Restylane use for lip augmentation. Hence, FDA will request comment from the Advisory Panel on the adequacy of the data for this patient population.
- While non-significant differences in effectiveness outcomes were observed for patients with Fitzpatrick Type IV and V skin in the: 1) the Blinded Evaluators' MLFS scores at Weeks 20 and 24 and 2) IPRs' MLFS scores at Weeks 8-24, FDA recognizes that the study was not powered to detect these differences and the sample size in each analysis was most likely too small to provide meaningful results.

Study Safety Outcomes:

Safety endpoints were:

- 1) specific anticipated events (i.e., bruising, redness, swelling, pain, tenderness, itching, and other) were reported during the first 14 days after each treatment in a subject diary;
- 2) lip safety assessments and treatment emergent adverse events (TEAE) evaluated by Treating Investigators at each scheduled visit; and
- 3) lip texture, firmness, symmetry, product palpability, mass formation, lip movement, function, and sensation evaluated by a designated study staff member.

Of the 180 subjects enrolled in the study, 172 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 14.

Table 14. 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

Subjects receiving their first Restylane treatment series had the longest mean duration for reported TEAEs (15.6 days). Subjects receiving a second Restylane treatment series (i.e., Week 24) had a mean duration of 10.4 days for any TEAEs. The mean duration of TEAEs for subjects in the No Treatment group was 12.4 days. The mean duration for TEAEs are presented in Table 15.

Table 15. 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	-	1	3
	Range	-	1-16	3-19

The number of events and subjects reporting TEAEs in the lip area are presented in Table 16. The median time to onset for commonly reported TEAEs was largely within one day of treatment. The median time to onset was similar for subjects receiving their first (Baseline) and second (Week 24) Restylane treatment series, with the exception of nasopharyngitis and headache. This discrepancy may be due to the number of days in the reporting period (~180 days for the first treatment compared with ~28 days for the second treatment).

Table 16. Summary of Treatment Emergent Adverse Events in the Lip Area

System Organ Class	No Treatment n=45		1 st Treatment n=172		2 nd 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%)
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 17) and duration (Table 18) of adverse outcomes reported in the *Patient Diaries* are presented below.

Table 17. Intensity* of Adverse Outcomes Reported in the Subject Diary

	No treat pts (=45)	1 st treat pts (n=172)	2 nd treat pts (n=93)	No Treatment				1 st Restylane treatment				2 nd 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	166 96.5%	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 18. 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%)	95 (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%)	43 (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

Safety Outcomes in 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 19 summarizes the TEAEs experienced in 5% or greater of patients with Fitzpatrick Skin Types IV and V. The incidence of subjects with TEAEs after the first and second Restylane treatment series was 87% and 86%, respectively. These event rates are similar to the overall study population with the exception of swelling which was higher in patients with Fitzpatrick Type IV and V skin. After the first Restylane treatment series the incidence of swelling was 58% in the total population and 67% in patients with Fitzpatrick type IV and V skin. After the second Restylane treatment series (at the Week 24 visit), the incidence of swelling was 55% in the total population and 77% in patients with Fitzpatrick skin types IV and V.

Table 19. 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		1 st Treatment n=39		2 nd 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

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 20.

Table 20. 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 21.

Table 21. 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	Lip was slightly firm with lateral compression or required slightly greater than normal	Lip was firm with lateral compression or required distinctly greater than normal pressure to distort the surface or pressure	Lip was very firm with lateral compression or requires significantly greater than normal pressure to distort the

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.	pressure to distort the surface. Upon palpation, an abnormal structure such as a scar or lump was felt, but was not visible.	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.	surface. Upon palpation, an abnormal structure such as a scar or lump was felt and was visually distracting.
---	--	---	--

About 23% of subjects exhibited mild abnormal lip firmness at some point during the study. One subject exhibited moderate lip firmness, and this case resolved in less than 2 weeks. No subjects experienced severe abnormal upper or lower lip firmness at any time point. The one Restylane subject with moderate abnormal lower lip firmness at the 72 hour visit was rated mild at Week 2 and normal by Week 4. Lip swelling was commonly reported after Restylane injection, which may have contributed to the incidence of abnormal upper and lower lip firmness scores that resolved over time.

Lip symmetry was judged with the criteria presented in Table 22.

Table 22. 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.

Nine Restylane subjects experienced mild upper lip asymmetry and one subject experienced mild lower lip asymmetry at Baseline. After treatment, most subjects had normal upper and lower lip symmetry throughout the course of the study.

Severe lip asymmetry occurred in 16/180 (8.9%) of the patients at some time 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. The majority of the subjects with abnormal upper or lower lip symmetry were judged as “mild.” The frequent occurrence of lip swelling may have contributed to the incidence of lip asymmetry.

Lip movement was tested by assessing the ability of a subject to pronounce a preselected series of words (e.g., spear, verse, liver, peep, fire, staff, member, simmering, drab, and babble.) 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 time points during the study.

Lip sensation was tested via two methods: 1) the monofilament test which evaluated 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 which evaluated 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. The three different points on the upper and lower lips were tested randomly. Subjects were blindfolded and asked to acknowledge sensation or lack of sensation at each point. Subjects were given two attempts if unable to detect the stimulus the first time.

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 by a qualified staff member. Assessment included asking the evaluator "Is the product palpable? If yes, is this the expected feel or unexpected feel (i.e., non-uniform density or unexpected lumpiness) for the product?" 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). Implant massage appeared to help create a more uniform product density.

Lip mass formation was judged as normal for all subjects at all time points with one exception. One Restylane patient had a negative upper lip response at Week 2 after re-treatment at Week 24. At the following Week 4 visit, the lip mass was judged as normal. (This subject had an upper lip cyst that was drained during an in-office procedure). At both the Week 2 and 4 visits after the Week 24 re-treatment, the Treating Investigator and the Subject assessed the upper lip as much improved or greater on the GAIS scale.

TEAEs were also evaluated based on the *method and depth of injection*. The most common injection method was linear retrograde, compared to linear antegrade and serial puncture. It was also the primary method of injection chosen by the majority of Treating Investigators for enhancing the vermilion border and improving Subject satisfaction.

The incidence of all TEAEs after linear retrograde injection was 86%, 65% and 41% for subjects at the initial Restylane series, the Restylane re-treatment series and No Treatment at Baseline cohort, respectively. The incidence of TEAEs after linear antegrade injection of Restylane was 81% (first treatment), 58% (second treatment) and 47% (No Treatment at Baseline cohort). The incidence of TEAEs after serial puncture

injection of Restylane was 79% (first treatment), 24% (re-treatment) and 50% (No Treatment at Baseline). Because the majority of subjects had a combination of injection methods at each treatment session, it is difficult to interpret safety outcomes reported as a function of injection method.

Assessing of Repeat Injections - The Treating Investigator evaluated if the second treatment was more difficult to perform than initial treatment, and, if so, why? For 98% of the subjects, treatment at Week 24 was no more difficult than 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.

FDA Comments on the Safety Outcomes:

- The commonly reported TEAEs (e.g., pain, swelling, tenderness, contusion (bruising/ecchymosis), and erythema) were anticipated and reasonable to attribute to the procedure or Restylane. The onset of these commonly reported TEAEs typically began within a day of being treated and were transient in nature, (i.e., typically resolving in about 15 days or less). 15% of the patients experienced adverse events (typically swelling and tenderness) that lasted longer than 15 days. None the less, over 40% of subjects had adverse events that they felt affected their daily activity or were disabling. FDA will request comment from the Panel regarding the potential safety of Restylane use in lip augmentation
- The similarity in the mean time to onset for subjects receiving first or second Restylane treatments suggests that commonly reported TEAEs occur within a consistent time frame independent of repeat treatment. The incidence of the commonly reported TEAEs generally decreased for subjects receiving their second treatment series which suggests that repeat treatment with Restylane in the lips does not pose any additional safety risk. A decrease in incidence of TEAEs between the first and second treatments may also partially reflect patients who suffered a TEAE after the first treatment not volunteering for retreatment.
- Specific anticipated events were collected in patient diaries during the first 14 days after each treatment session. Overall, a majority of symptoms in all categories at each diary time point were considered tolerable.
- 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. For example, 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. In addition, an unexpected feel was

reported for 3% of the Restylane patients. Given the common occurrence of device palpability in the lips, the Panel will be asked to comment on the significance of this finding and how it might be communicated to physicians and patients should product approval be granted.

- The safety information on Restylane lip augmentation in persons of color is derived from a sample size of 38 persons with Fitzpatrick Type IV and 3 patients with Fitzpatrick Type V skin. No subjects with Fitzpatrick type VI skin were enrolled in the pivotal study. For subjects with Fitzpatrick types IV and 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. Given the number of subjects with Fitzpatrick type IV and V skin, and the absence of patients with Fitzpatrick type VI skin, the Panel will be asked to comment on the use of Restylane for lip augmentation in persons of color and whether data from the previously a reviewed study of 150 patients implanted in nasolabial folds (i.e., see the product label for outcomes reported in “Study MA-1400-01, Evaluate safety and efficacy of Restylane and Perlane in subjects with Fitzpatrick skin types IV, V and VI”) are sufficient to address this concern.
- The study enrolled four subjects under the age of 22 years. Panel comment on device use in patients aged 21 or younger will be requested.

IV – FDA Review Team’s Conclusions for Panel Consideration:

The data from Study MA-1300-15, “Randomized, Evaluator-Blinded No Treatment Controlled Multicenter Study” indicate that the device meet the prespecified Primary and Secondary Endpoints for Effectiveness. Safety information was collected after a single series of Restylane injections in 172 patients and after Restylane re-treatments in 93 patients. Based on these data FDA believes that several issues should considered and Panel comment requested on the following issues.

- Based on the study results at Week 8, the FDA statistician calculated that if 100 patients were injected, approximately 50 would display improvement of at least 1 point on the MLFS compared to No Treatment. By Week 24, about one-third of treated-subjects could expect to be better than pre-treatment. FDA will request Panel comment on the potential effectiveness of Restylane when injected for lip augmentation.
- The study enrolled 38 persons with Fitzpatrick Type IV and 3 patients with Fitzpatrick Type V skin. No patients were treated with Fitzpatrick Type VI skin. Assessments of product effectiveness in this subgroup are based on 31 Restylane and 10 No Treatment patients with Fitzpatrick skin types IV and V. The Panel will be asked to comment on the adequacy of the data for this patient population with regard to device safety and effectiveness.

- Over 40% of subjects had adverse events that they felt affected their daily activity or were disabling. FDA will request comment from the Panel regarding the potential safety of Restylane use in lip augmentation
- While there were few occurrences of abnormal lip texture, lip firmness, lip asymmetry, lip movement lip sensation and mass formation, the majority of Restylane patients experienced a palpable implant through the Week 24 visit with device palpability decreasing over time. Given the common occurrence of device palpability in the lips, the Panel will be asked to comment on the significance of this finding and how it might be communicated to physicians and patients should product approval be granted.
- The study enrolled 4 subjects under the age of 22 years. Panel comment on device use in patients aged 21 or younger will be requested.

Finally, FDA also received additional information concern the safety and effectiveness of Restylane in lip augmentation after this Executive Summary was completed. FDA review of these data is underway and an addendum to the Executive Summary will be distributed to all Panel Members shortly.

V. Executive Summary Section for Post Approval Studies

NOTE TO PANELISTS: FDA's inclusion of a section/discussion on a Post-Approval study (PAS) in this executive summary should not be interpreted to mean that FDA has made a decision on the approvability of this PMA. The presence of post-approval study plans or commitments does not in any way alter the requirements for premarket approval. A recommendation from the Panel on whether the data demonstrates reasonable assurance on device safety and effectiveness must be based solely on the premarket data. The issues noted below are FDA's comments regarding potential post-approval studies.

Overview of Proposed Post-Approval Study

The applicant did not submit a post-approval study plan.

FDA Assessment of PAS Proposal

Should FDA determine the premarket data demonstrate product safety, effectiveness, and risk/benefit profile, there are some potential postmarket questions that may need to be addressed. The Panel will be asked to discuss and comment on the appropriateness of the following possible Post-Approval Study questions:

Questions to Panel

1. The safety data from Study MA-1300-15, "Randomized, Evaluator-Blinded No Treatment Controlled Multicenter Study," reflect single Restylane treatment sessions in 172 patients and a repeat Restylane treatment (i.e., at Week 24) in 93 patients and experience from 21 other patients in two Pilot Studies. Please discuss whether a Post Approval Study is recommended to evaluate the long-term safety of Restylane injections for lip augmentation.
2. The pivotal study enrolled 38 persons with Fitzpatrick Type IV and 3 patients with Fitzpatrick Type V skin. No patients were enrolled with Fitzpatrick Type VI skin. Assessments of product effectiveness in this subgroup were based on 31 Restylane and 10 No-Treatment patients with Fitzpatrick skin Types IV and V. Please discuss the appropriateness of an additional Post Approval Study to further evaluate the safety and effectiveness of Restylane injections for lip augmentation in patients with Fitzpatrick Type IV, V and/or VI skin.
3. The pivotal study enrolled four pediatric subjects under the age of 22 years (range 18-21 years). Please discuss the appropriateness of a Post Approval Study in patients of ages 21 or younger.