

FDA PMA P40024/s051
Addendum
Executive Summary

Medicis Aesthetics, Inc.
Restylane
April 27, 2011

FDA Executive Summary Addendum
April 27, 2011 Panel Meeting of
General and Plastic Surgery Devices Panel

Introduction

This Addendum to the Executive Summary for Premarket Approval (PMA) application supplement 51 to PMA P040024 (i.e., Injection of Restylane for lip augmentation) reflects additional information received from the sponsor subsequent to the previously distributed Executive Summary document.

Restylane is 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.” PMA supplement 51 (P040024/s51) 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 Addendum to the Executive Summary provides an overview of additional clinical information submitted by Medicis Aesthetics, Inc, the FDA review team’s summary of the clinical study information and specific questions to be discussed by the Advisory Panel.

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)

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Applicant/Manufacturer Information

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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., “submucosal implantation for 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).

I – Summary of Clinical Studies

Medicis Aesthetics, Inc. has performed six US 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 addendum to the Executive Summary presents: 1) additional information on the results of Pivotal Study MA-1300-15, 2) summaries of the two Pilot Studies of Restylane injections for lip augmentation, and 3) relevant Post Market Experience with Restylane injections in lip augmentation. 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

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

The following describes additional information submitted subsequent to the preparation of the Executive Summary concerning 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.”

Special Patient Population Issues:

Regarding *patients aged 18-21* (i.e., transitional adolescents) 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 all were initially randomized to Restylane treatment. Three of the four subjects were retreated at Week 24 and one subject declined retreatment for an unspecified reason. (The patient who declined treatment was assessed as achieving at least a one grade MLFS improvement from baseline through Week 24 by the Blinded Evaluator, Treating Investigator, and IPR).

The mean volume of Restylane injected into the lips for initial treatment (including touch ups) for these four patients was 2.575 mL per subject (compared to 2.9 mL for the entire study population). At the Week 24 retreatment, the mean volume of Restylane injected into the lips (including touch up) for these three subjects was 1.75 mL per subject compared to 1.8 mL for the entire study population.

Regarding device safety in subjects aged 18-21 years, 2/4 subjects experienced 12 Treatment Emergent Adverse Events (TEAEs) after the initial Restylane injection and 2/3 subjects experienced 5 TEAEs after the Week 24 Restylane treatment. A summary of TEAEs in this patient population are presented below in Table 2, which may be compared to the Incidence of Treatment Emergent Adverse Events presented in Table 14 and in the initial Executive Summary.

Table 2. Summary of Treatment Emergent Adverse Events for Subjects Less than 22 Years Old

System Organ Class	No Treatment n=0		1 st Treatment n=4		2 nd treatment n= 3	
	Events	Subjects	Events	Subjects	Events	Subjects
Any TEAE	0	0	12	2 (50%)	5	2 (67%)
Gastrointestinal Disorders						
Gastritis	0	0	1	1 (25%)	0	0
Haematochezia	0	0	1	1 (25%)	0	0
General Disorder and Administrative - Site Conditions						
Fatigue	0	0	1	1 (25%)	0	0
Swelling	0	0	4	2 (50%)	5	2 (67%)
Infections and Infestations						
Influenza	0	0	1	1 (25%)	0	0
Injury, Poisoning, and Procedural Complication						
Contusion	0	0	2	2 (50%)	0	0
Metabolism and Nutrition Disorders						
Insulin Resistance	0	0	1	1 (25%)	0	0
Psychiatric Disorders						

Insomnia	0	0	1	1 (25%)	0	0
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Regarding device effectiveness, the Blinded Evaluator judged 4/4 (upper lip), 2/2 (lower lip) and 4/4 (upper and lower lips combined) subjects as Responders at Week 8. All four subjects were also assessed as MLFS Responders for the upper lip, lower lip, and upper and lower lips combined by the Treating Investigator and IPR.

Study MA-1300-15 enrolled 38 *subjects with Fitzpatrick type IV, 3 patients with Fitzpatrick type V and no subjects with Fitzpatrick type VI skin.* In support of the safety of Restylane use for lip augmentation in the general U.S. population, the sponsor cited the results of Study MA-1300-15 as well as previously completed and reviewed clinical studies with Restylane (and Perlane). The most relevant clinical data are from Study MA-1400-01, which was a randomized, comparative evaluator blinded study of the safety and efficacy of Restylane and Perlane injection in the nasolabial folds of 150 subjects with Fitzpatrick Types IV, V, or VI skin. In Study MA-1400-01 Restylane and Perlane were well tolerated and non-immunogenic in subjects with darker skin types and the safety profile for this patient population was similar to other populations studied. Study MA-1400-01 also provided evidence that Restylane and Perlane was effective in correcting facial folds and wrinkles, (such as nasolabial folds and oral commissures) in subjects with darker Fitzpatrick skin types.

In support of the limited number of patients with Fitzpatrick type V and VI skin that were enrolled in Study MA-1300-15, the sponsor also consulted with leaders in the field of aesthetic treatment regarding lip augmentation in persons of color. These experts repeatedly emphasized that it is very difficult, if not impossible, to recruit person of color with very thin or thin lips. Also patients with darker skin types generally do not have a desire to have fuller lips. Consequently, the sponsor believes that Study MA-1300-15 collected a reasonable amount of clinical data in persons of color to support approval of Restylane injections for lip augmentation for the general U.S. population.

FDA comments on Special Patient Populations:

- Regarding *patients aged 18-21* enrolled in Study MA-1300-15, the PMA provides volume, effectiveness and adverse event data for the four patients under 22. No differences were found for this age group. While the data do not raise any new concerns, FDA does not believe that data from 4 patients is sufficient to infer clinical outcomes for a patient population who may receive many treatments over their lifetime. The Advisory Panel will be asked to discuss the safety and effectiveness of Restylane for lip augmentation in patients under the age of 22.
- Regarding patients with Fitzpatrick type IV and V skin the enrolled in Study MA-1300-15: For additional information on Study MA-1400-01 (i.e., Randomized, Comparative Evaluator-Blinded Study to Evaluate safety and efficacy of Restylane and Perlane injections in the nasolabial folds in subjects with Fitzpatrick skin types IV, V and VI), FDA recommends review of the current Restylane label in which pages 3-12 describe the Restylane safety profile and pages 19-20 describe Restylane effectiveness.

- Given the enrollment of 3 subjects with type V and no patients with type VI skin in Study MA-1300-15, FDA has concern as to whether the safety and effectiveness of Restylane injections for lip augmentation have been adequately evaluated in persons of color. Because previous studies with Restylane injections in the nasolabial folds did not indicate a difference in adverse event profiles compared to patients with Fitzpatrick Type I, II and III skin, FDA will ask for Panel comment on: 1) whether clinical data collected in studies of nasolabial fold injections is predictive for outcomes after lip injection in persons of color, 2) the frequency that persons of color might seek lip augmentation with Restylane and 3) whether sufficient Pre-Market data have been collected to support use of Restylane for lip augmentation in the general U.S. population.

Device safety issues:

The total number of subjects that reported moderate and severe abnormality of lip texture, firmness or symmetry is presented below in Table 3. While a qualified health care professional made these assessments, the subjects generally rated themselves as very satisfied with their appearance on the GAIS scale.

Table 3. Subjects with Moderate to Severe Abnormality of Lip Texture, Firmness or Symmetry

Lip Assessment	First Treatment with Restylane (N=172)		Second Treatment with Restylane (N=93)	
	Moderate	Severe	Moderate	Severe
Firmness	1 (1%)	0	0	0
Symmetry	6 (3%)	5 (3%)	6 (6%)	4 (4%)
Texture	10 (6%)	1 (1%)	1 (1%)	0

The total number of subjects that reported adverse outcomes affecting daily activity (or worse) is presented in Table 4. After the first Restylane treatment, 67 patients reported symptoms that “affected daily activity” and 17 subjects reported “disabling” symptoms. 26 subjects reported symptoms that “affected daily activity” and 4 subjects reported “disabling” symptoms after their second Restylane treatment series. Of the Restylane patients who reported a diary symptom severity of “affects daily activity,” 85% of the subjects chose to receive retreatment at Week 24. For subjects in the Restylane treatment group who had a maximum diary symptom severity of “disabling,” 54% of the subjects chose to receive retreatment at Week 24.

Table 4. Total Number of Subjects Reporting Adverse Outcomes

	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%
Total	--	--	--	38 95%	2 5%	0	0	7 4%	104 53%	67 34%	17 9%	11 11%	63 61%	26 25%	4 4%

No treat pts = Patients initially randomized to No Treatment

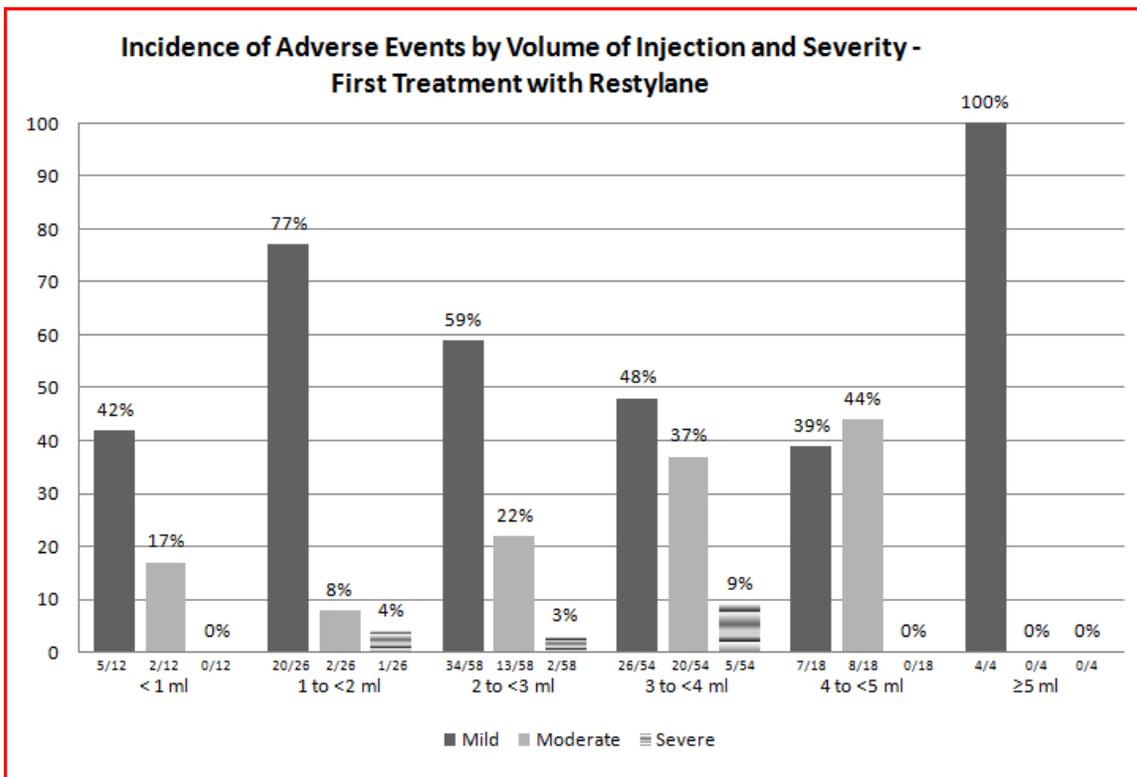
1st treat pts = Patients initially randomized to Restylane Treatment or No Treatment patients receiving their first injection at Week 24

2nd treat pts = Patients initially randomized to Restylane Treatment receiving their second Restylane injections at Week 24

N = None, T = Tolerable, A=Affects daily Activity, D = Disabling

Regarding *the relationship between volume injected and adverse event occurrence*, the sponsor reported that injection of higher volumes did not appear to be a predictor for a higher incidence or more severe adverse events. These data are presented below in Table 5.

Table 5. Relationship Between Injected Dose and Adverse Event Occurrence



With regards to the *feel of Restylane-treated lips* in Study MA-1300-15, the previous Executive Summary indicated that: 1) the lip texture assessments recorded the development of any papules during the study, 2) the majority (i.e., 61% - 100%) of Restylane subjects experienced a palpable implant through Week 24 (that decreased over time), 3) an unexpected feel of the product was observed in 3% of the Restylane patients and 4) Lip mass formation was judged as normal for all subjects at all time points with the exception of one Restylane patient that 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).

To further clarify the feel of treated lips, the sponsor provided information indicating that 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. This event started two months after the initial injection, and resolved approximately 5 weeks later. There were also five subjects that reported eight events of lump/lumps during the study, (assessed by the health care professional). These events were also captured as part of the lip safety device palpability assessment as an “unexpected feel” of the product. Typical treatment for this type of event included massaging the lump/lumps. All of these events were considered to be caused by the injection procedure and not related to the device. The events occurred within 15 days or less from the time of an injection (i.e., initial treatment, touch up, or retreatment at Week 24), and all events resolved before the end of the study.

Because incidences of *lip swelling* were initially presented in Tables under the categories of both GI Disorder and General Disorders and Administrative Site Conditions, the sponsor clarified that the seven events of lip swelling listed under GI Disorders should be classified as a General Disorders and Administrative Site Conditions which included 221 events. Thus, combining lip swelling, swelling and edema which were presented under both GI Disorders or General Disorders and Administrative Site Conditions yielded a total of 113 (66%) subjects with swelling of the lips after the first Restylane treatment and 52 (56%) subjects with swelling in the lips after Restylane retreatment.

Regarding the *relation between injection technique and adverse event onset*, the sponsor performed an analysis of subjects that received only one particular method (e.g. linear retrograde only) as well as those subjects that received any combination of injection methods such as linear retrograde and linear antegrade. The data show that the number and types of adverse events reported by a particular injection method, or any combination, was fairly similar to most of the commonly reported TEAEs overall and there were no specific safety concerns for any of the injection methods. As discussed in the initial Executive Summary the majority of subjects were treated with a combination of injections methods.

Regarding subjects who chose not to get a second treatment at Week 24, the sponsor clarified that there were 23 subjects who did not receive retreatment at 6 months. Seven patients cited continued efficacy of the first treatment as the reason, four subjects cited a previous side effect, two patients claimed other reasons, and the reasons for 10 other patients were unknown. For the four subjects who declined retreatment, the adverse events 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 adverse events 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 adverse events that affected daily activity or were disabling.

Regarding the incidence of *herpes infections* in Study MA-1300-15, the number of events and subjects reported are presented below in Table 6. 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 6. Summary of Herpes Infections – Safety Population

System Organ Class/ Preferred Term	Treatment Group					
	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%)

FDA comments the additional safety information:

- Five subjects reported eight events of lump/lumps assessed as an “unexpected feel,” during the study and one patient had a mass reported as a cyst which required drainage. There were no events captured as nodules, however, lumps with an unexpected feel are probably not discernible from nodules. All of these events resolved by the end of the study. The duration of the lumps was not clarified. The approved Restylane label currently lists the incidence of hardness/nodules as 3% (2/75 in study MA-004-03). If 5/180 patients are assumed to have similar lumps, this is a similar profile to that observed at nasolabial fold injection.
- Regarding the relationship between injected dose and adverse event onset, the submitted data do not show a linear relationship between adverse events of mild severity however, there is a difference between very small (<1cc) and very large (>5cc) volumes in both adverse events (primarily contusion) after first treatment. There is also an increase in moderate and severe adverse events related to injection volume. There is no appearance relationship between injected dose and adverse events after retreatment at Week 24.
- Regarding the relationship between injection method and adverse event onset, the submitted data show the highest AEs for linear retrograde alone (98-100%). The combination of different methods seems to show a lower incidence of AEs (60-80%) with the largest difference apparent in swelling (100% vs 60%). Interpretation of these events is complicated by the large number of subjects who received Restylane injections by a combination of techniques.
- The subjects appear to have received antivirals as treatment for an episode of oral herpes simplex. Presumably, since they all had associated herpes, none of the

patients received prophylactic treatment. The rates are similar between No Treatment and Restylane groups; however it is not clear that the No Treatment patients had their outbreak before receiving treatment.

Device Effectiveness Issues

Regarding the definition of *Treatment Responder* (i.e., a patient with a one point or greater improvement from the Treating Investigators' Baseline assessment to the Blinded Evaluators' Week 8 assessment), additional information was submitted concerning the absolute magnitudes of patients' MLFS improvement. Such information assists in evaluating the impact of a one grade variance in MLFS judgements by the Treating Investigator and Blinded Evaluator on the frequency of Treatment Responder decisions. This concern was based on the observation that 28% of the patients in the No Treatment Group were judged Responders by Blinded Evaluators at Week 8, when the results of upper and lower lip assessments were combined.

Table 7 presents a summary of the *absolute change in MLFS from Baseline for Upper and Lower Lips at Week 8*. For subjects randomized to Restylane at Baseline the mean upper lip MLFS change was 2.1 points and the mean lower lip MLFS change was 1.8 units. For subjects randomized to the No Treatment group at Baseline, the mean MLFS change from Baseline to Week 8 was 0.5 points for the upper and 0.4 points for the lower lips. The difference in the magnitude of absolute change from Baseline to Week 8 for the two treatment cohorts was statistically significant.

Table 7. 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

Because the magnitude of change may also reflect patients' initial MLFS score, summaries of the changes from Baseline to Week 8 for upper and lower lips are presented below in Table 8 (very thin lips at Baseline) and Table 9 (thin lips at Baseline).

Table 8. Summary of MLFS Change from Baseline (Blinded Evaluators' Assessment) for Very Thin Lips at Week 8 – ITT Population^{1,2}

Assessment/ Time Point	Statistic	No Treatment (N=45)		Restylane (N=135)	
		Observed	Change from Baseline	Observed	Change from Baseline
Treating Investigator Baseline Assessment: Upper or Lower Lip = Very Thin=1					
Upper Lip					
Week 8	n	25	25	76	76
	Mean (S.D.)	1.5 (0.9)	0.5 (0.9)	3.3 (1.1)	2.3 (1.1)
	Median	1.0	0.0	3.0	2.0
	Min, Max	1,4	0, 3	1, 5	0,4
Lower Lip					
Week 8	n	18	18	40	40
	Mean (S.D.)	1.3 (0.6)	0.3 (0.6)	3.1 (0.9)	2.1 (0.9)
	Median	1.0	0.0	3.0	2.0
	Min, Max	1, 3	0, 2	1, 5	0, 4

¹Lip Fullness (MLFS) values: 1=Very Thin, 2=Thin, 3=Medium, 4=Full, 5=Very Full.

²Only lips with a baseline MLFS assessment of 1 (Very Thin) or 2 (Thin) are included in the analysis.

Table 9. Summary of MLFS Change from Baseline (Blinded Evaluators' Assessment) for Thin Lips at Week 8 – ITT Population^{1,2}

Assessment/ Time Point	Statistic	No Treatment (N=45)		Restylane (N=135)	
		Observed	Change from Baseline	Observed	Change from Baseline
Treating Investigator Baseline Assessment: Upper or Lower Lip = Thin=2					
Upper Lip					
Week 8	n	14	14	45	45
	Mean (S.D.)	2.5 (0.7)	0.5 (0.7)	3.7 (0.9)	1.7 (0.9)
	Median	2.0	0.0	4.0	2.0
	Min, Max	2,4	0, 2	1, 5	-1, 3
Lower Lip					
Week 8	n	17	17	71	71
	Mean (S.D.)	2.5 (0.5)	0.5 (0.5)	3.6 (0.9)	1.6 (0.9)
	Median	2.0	0.0	4.0	2.0
	Min, Max	2,3	0,1	1,5	-1,3

¹Lip Fullness (MLFS) values: 1=Very Thin, 2=Thin, 3=Medium, 4=Full, 5=Very Full.

²Only lips with a baseline MLFS assessment of 1 (Very Thin) or 2 (Thin) are included in the analysis.

Regarding differences in numbers of patients in the ITT effectiveness analyses, the sponsor clarified that per the MA-1300-15 study criteria, subjects with Fitzpatrick skin types IV, V, or VI were only required to have a MLFS score of very thin [1] or thin [2] for at least one lip (either upper or lower) as assessed at Baseline by the Treating Investigator for enrollment. For individual lip assessment (upper lip or lower lip), only the qualified lip for subjects with Fitzpatrick skin type IV and V were included in the effectiveness analysis of individual lips, however, all subjects are included in the effectiveness for upper lip and lower lip combined and safety assessments.

Regarding the imputation of missing data in the Primary Effectiveness analysis, the sponsor clarified that upper lip data from 13 Restylane and 5 No Treatment subjects were imputed using the hot deck method. For the lower lip summaries, data from 11 Restylane and 4 No Treatment subjects were imputed using the hot deck method. For the upper and

lower lip combined summaries, data from 13 Restylane and 5 No Treatment subjects were imputed using the hot deck method.

Regarding logistic regression modeling to evaluate the impact of covariates such as study site, age, gender, race, need for touch up, method of injection, depth of injection, and volume of injection on the co-primary efficacy endpoints, the sponsor stated that due to the large proportion of Restylane subject Responders, the logistic regression models were unable to generate valid maximum likelihood estimates, therefore these analyses could not be performed to provide meaningful results. Therefore, exploratory analyses for each parameter was evaluated using the Fisher's Exact, Chi-Square, or t-tests. The only parameters that could potentially impact the Responder rate were: 1) investigational site for the lower lips only and 2) the use of optional touch-up for the upper lips. To account for the potential site effect, the primary effectiveness analyses were repeated using a Cochran-Mantel-Haenzel (CMH) test, stratified by investigational site. Differences between Restylane and No Treatment were still highly significant for the upper, lower, and upper / lower lips combined ($p < 0.001$), and the Breslow-Day Tests for Homogeneity of the Odds Ratios across investigational sites were all non-significant ($p=0.3016, 0.2308, 0.1073$) for upper, lower, and upper / lower lips combined, respectively).

Regarding a weighted kappa analysis for the degree of agreement in MLFS scoring between Blinded Evaluator, Treating Investigator, and IPR assessments, the sponsor believes that the Week 8 data suggest a 'fair' agreement between the three Raters (see Table 10). The sponsor also suggested that the statistically significant differences in the proportion of Responders for Restylane and No Treatment cohorts determined by each assessor is a more important predictor of device effectiveness. Table 11 presents the proportion Composite Responders for the upper and lower lips combined at Week 8, (where a Composite Responder is defined as a subject with an improvement of at least one point on the MLFS from Baseline (Treating Investigator) to the Week 8 as judged by the Blinded Evaluator , Treating Investigator and IPR assessment).

Table 10. Degree of Agreement in MLFS Scores for Blinded Evaluators, Treating Investigators and Independent Photographic Reviewers (IPR) at Week 8

Assessors	Exact Agreement	Weighted Kappa	95% C.I.
Upper Lip			
Blinded Evaluator & Treating Investigator	50.6%	0.367	0.267 - 0.467
Blinded Evaluator & IPR	41.1%	0.255	0.155-0.354
Treating Investigator & IPR	38.6%	0.214	0.117-0.312
Lower Lip			
Blinded Evaluator & Treating Investigator	56.8%	0.422	0.313-0.531
Blinded Evaluator & IPR	43.8%	0.251	0.146-0.355
Treating Investigator & IPR	36.1%	0.160	0.060-0.260

Table 11. Proportion of Composite MLFS Responders for Upper and Lower Lips Combined at Week 8 - ITT Population

Treatment Group	No. of Subjects in ITT	No. of Subjects with Non-Missing Assessments	Composite Responders
Restylane	135	109	0.532
No Treatment	45	35	0
Difference*			0.532

* Statistically significant at the $p < 0.001$ level.

Regarding the *use of topical and injected anesthetics*, Table 12 provides a summary of Anesthetic Use during the study.

Table 12. Summary of Anesthetic Use by Treatment Session^{1, 2, 3, 4}

Route of Administration	1st Treatment with Restylane (N =172)	Touch up After 1 st Treatment with Restylane (N=100)	2nd Treatment with Restylane (N =93)	Touch up After 2 nd Treatment with Restylane (N = 34)
Any Anesthetic Use on Treatment Day	165 (96%)	79 (79%)	74 (80%)	21 (62%)
Topical Anesthetic Only	42 (24%)	24 (24%)	21 (23%)	8 (24%)
Injected Anesthetic Only	91 (53%)	38 (38%)	51 (55%)	13 (38%)
Both Topical and Injected Anesthetic	32 (19%)	17 (17%)	2 (2%)	0

¹Only anesthetics that were taken on the day of Restylane injection are included in this summary.

²Subjects are only counted once for each anesthetic category.

³Anesthetics were determined by medical review of the concomitant medication preferred terms.

⁴Percentages are based on the total number of subjects who received a Restylane injection at the specified time period.

FDA comments on additional effectiveness information:

- The exact agreement between: 1) IPR and Treating Investigator, 2) IPR and Blinded Evaluator, and 3) Treating Investigator and Blinded Evaluator vary between 31% and 61%. This may reflect the subjectivity involved despite the use of a validated scale. The exact agreement between Treating Investigator and Blinded Evaluator varied between 51% and 61%. The sponsor points out that the difference in the proportion of Responders between the Restylane and the No Treatment groups is significant for all Raters. So although they may not agree on the degree of change, each Rater agrees there is a significant change.
- While the study was a Control Investigation, a potential bias does exist because subjects were not blinded to treatment. FDA has few approaches for evaluating whether subject bias may have impacted the Blinded Evaluator, Treating Investigator and Independent Photographic reviewer assessments. For example, might patients knowledge of treatment assignment affected the way they presented themselves for lip assessment (e.g., sticking lips more or less depending on treatment assignment)?

- **The following is an in-depth description of a Pilot study performed under IDE as the initial Restylane investigation for augmentation of soft tissue fullness of the lips).**

III - Clinical 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, prospectively-designed trial conducted at one center with up to 20 subjects that was designed to collect safety information on the use of Restylane for lip augmentation.

Study Objectives:

The primary safety objective was to identify the incidence of adverse experiences, including: 1) concerns about pain, tenderness, erythema, edema, ecchymosis, pruritus, and mass formation (nodule, cyst and abscess) reported in a Subject Diary during the first 14 days after treatment), 2) Investigator assessments at 72 hours and 2, 6, 12 and 24 weeks after treatment, and 3) all observed systemic adverse experiences.

The primary effectiveness objective was to determine Restylane’s value in lip augmentation via a live blinded assessment of lip fullness at Week 12 after treatment as compared to Baseline condition (based on recall of a live blinded assessment of Baseline condition refreshed by pretreatment full-face photography). The Blinded Evaluator scored lip fullness on a three grade global aesthetic improvement scale (GAIS) (i.e., more volume, same volume, lower volume). The co-primary efficacy objective also included a subject satisfaction assessment performed at 12 weeks after lip volume restoration.

Sample Size

This initial evaluation of the safety of Restylane use for lip augmentation was designed to enroll 20 patients. The study did not include randomization of patients to a Control cohort.

Inclusion and Exclusion Criteria:

Subjects included in the study: 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) had decided to seek lip augmentation with Restylane, 3) were willing to comply with procedures, including sequential photography, 4) willing to abstain from any other facial plastic surgical or cosmetic procedures for the first 12 weeks of the study (e.g., laser or chemical resurfacing, facelift, etc), and 5) may have had facial cosmetic procedures outside the area of assessment (e.g., botulinum toxin above the orbital rim, etc.) 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, (e.g., inflammation, infection, facial psoriasis, herpes zoster, acanthosis, cancer, precancer, actinic keratosis, etc.), 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, (including dental work or prior dermal filler augmentation, that could have resulted in volume changes in the face during the course of the study, including use of dermal fillers within the prior eight months or facial procedures below the orbital rim within 6 months of entry), 3) had the presence of any contraindication to the operative procedures including use of platelet inhibiting agents (e.g., aspirin) 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, (e.g., injection or other form of implantation of tissue augmenting substances (but not including Restylane®), Botox injections, or facelift), 6) had 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 24 weeks 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) 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 (i.e., the lip volume enhancement identified pre-operatively by the subject as cosmetically desirable) 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.

Preliminary effectiveness outcomes were determination of the proportion of study subjects with identifiable lip augmentation at Week 12 after Restylane augmentation as measured by: 1) a Blinded Live Evaluator and 2) Subject satisfaction. The proportion of subjects with success was a primary efficacy endpoint. The scoring procedure for the live and 3D image reviews is presented in Table 13.

Table 13. Global Aesthetic Improvement Scale (GAIS) Scoring

Definition	GAIS Score
Lips appear to be same size	Failure
Baseline photograph shows augmentation	Failure
12 week photograph shows augmentation	Success
Poor quality or unable to make judgment	Failure

The co-primary effectiveness endpoint of *subject satisfaction* was scored on a GAIS (worse, same, improved) at Week 12.

Other effectiveness evaluations included the *Treating Investigator* determination of a Wrinkle Severity Rating Score (WSRS) for each subject at baseline. The *Treating Investigator* also assessed satisfaction compared to the intended result on a GAIS of improved, same/no change, or worse at Weeks 2, 6, 12, and 24. *Subjects* also assessed their satisfaction with Restylane on a GAIS at Weeks 2, 6, and 24. (Subjects may have viewed their Baseline photograph to refresh their recollection.) The *Blinded Evaluator* also evaluated paired (Baseline and each interval) 3D images to provide a GAIS assessment of lip augmentation. Assessments were performed for Weeks 2, 6, and 12 week and compared to Baseline using the scores in Table 14.

Table 14. Blinded Evaluator Photographic Evaluation

Definition	Volume Validation	GAIS Score
Lips appear to be same size (Baseline v. interval photographic image)	Neutral volume	Failure
Baseline photograph shows augmentation v. interval photographic image	Negative volume	Failure
Photographic interval image shows augmentation v. Baseline image	Positive volume	Success
Poor quality or unable to make judgment	Indeterminate	Failure

IV – Study MA-1300-13k Outcomes

The study enrolled 20 patients and 19 completed the study. Patient disposition is presented in Table 15.

Table 15. Subject Accountability

	Restylane n=20
Subjects Completing Study	19 (95%)
Withdrew Consent	0
Lost to Follow-up	0
Protocol Violation	0
Medical Reason	0
Death	1 (5%)

Patient Demographics:

The patient demographics for the study are presented in Table 16. The mean height of subjects was 65.8 inches with a range of 61-71 inches. The mean weight of patients was 154.2 pounds with a range of 110-212 lbs.

Table 16. 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:

Safety outcomes included: 1) the incidence and severity of adverse experiences from Restylane when injected in the lips, 2) 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 in a subject diary, 3) identification of the duration of intended palpability of the Restylane in the lip both by subject examination during the initial two week period at 72 hours and 2 weeks and by the Investigator at 72 hours, and 2, 6, 12, and 24 weeks.

The incidence and severity of adverse experiences from Restylane when injected in the lips - Seven treatment emergent adverse events (TEAEs) were experienced by 4/20 (20%) of the Restylane subjects. The majority (5/7) of the TEAEs (i.e., thyroiditis, dysphagia, sinusitis, thyroid neoplasm, and cellulitis) were severe, but not considered to be related to treatment. Two subjects had one event each of mild bruising that was considered to be caused by 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 (i.e., pain, tenderness, erythema, edema, ecchymosis, pruritus, and mass formation (nodule, cyst and abscess) was performed for the first two weeks after treatment. Data on the incidence and duration of events are presented below in Tables 17 and 18, respectively.

Table 17. Maximum Intensity of Symptoms after Treatment, Subject Diary

AER	Total	None	Tolerable	Affected Daily Activity	Disabling
Bruising	17 (85%)	3 (15%)	13 (65%)	4 (20%)	0
Redness	14 (70%)	6 (30%)	12 (60%)	2 (10%)	0
Swelling	19 (95%)	1 (5%)	12 (60%)	7 (35%)	0
Pain	17 (85%)	3 (15%)	17 (85%)	0	0
Tenderness	19 (95%)	1 (5%)	18 (90%)	1 (5%)	0
Itching	2 (10%)	18 (90%)	2 (10%)	0	0
Mass Formation	18 (90%)	2 (10%)	17 (85%)	1 (5%)	0

Table 18. Duration of Adverse Outcomes Reported in the Patient Diary

Location/AER	Total	1 day	2-7 day	8-13 day	> 14 days
Bruising	17 (85%)	0 (0%)	10 (50%)	7 (35%)	0 (0%)
Redness	14 (70%)	2 (10%)	11 (55%)	0 (0%)	1 (5%)
Swelling	19 (95%)	0 (0%)	15 (75%)	3 (15%)	1 (5%)
Pain	17 (85%)	4 (20%)	12 (60%)	1 (5%)	0 (0%)
Tenderness	19 (95%)	3 (15%)	11 (55%)	4 (20%)	1 (5%)
Itching	2 (10%)	1 (5%)	1 (5%)	0 (0%)	0 (0%)
Mass Formation	18 (90%)	3 (15%)	4 (20%)	4 (20%)	7 (35%)

Four subjects also reported seven adverse events in their diaries. One subject reported a mild cold 11 days after injection, one subject reported a severe headache and mild vomiting 6 days after injection, one subject reported severe herpes the day after injection, and one subject reported severe dysphagia, severe swollen thyroid, and moderate sinusitis 6 days after injection. Duration and relationship to study treatment were not determined for the adverse outcomes reported in subject diaries.

The intended palpability of Restylane in the lip was evaluated both by subject examination during the initial two week period at 72 hours and 2 weeks and by the Investigator at 72 hours, and 2, 6, 12, and 24 weeks.

Restylane was palpable in at least one lip for 17/20 (85%) subjects at 72 hours after injection and 7/20 (35%) patients at Week 2. Restylane was not palpable to the Investigator at any time after two weeks following injection. All instances were determined by the Investigator to be the intended feel of the product. Mass formation was reported in 90% of the subject diaries. Most subjects (85%) found this symptom to be tolerable.

Regarding *Restylane palpability and mass formation in the lips*, mass formation was reported in 90% of subject diaries. Most subjects assessed mass formation to be tolerable and indicated a duration of less than two weeks. This led the Treating Investigator to comment “we were advised to instruct patients to record any palpable hyaluronic acid product in the lips as mass formation. Frequently, when injecting hyaluronic acid into the lips, product palpability is commonplace, particularly on the mucosal side; this typically resolves with a few days. Almost always this is totally resolved in less than one week. Therefore filler palpability is not unexpected when injecting hyaluronic acid in the lips. We feel that recording Restylane palpability in the lips as mass formation within the first few days following treatment could make this appear to be an adverse event, when in fact this is not at all a complication associated with the use of Restylane in lip augmentation.”

FDA Comments on the Safety Outcomes:

- The safety outcomes in this study do not appear to be significantly different from those observed in the pivotal study.
- The volume of Restylane injected into the upper lip ranged from 0.08 mL to 1.40 mL. The volume of Restylane injected into the lower lip ranged from 0.05 mL to 1.80 mL. These volumes are smaller than those used in the pivotal study (0.6cc-5.6cc).

Study Effectiveness Endpoint Results:

The co-primary effectiveness variables for this preliminary assessment of Restylane performance were the proportion of subjects with satisfactory lip augmentation at Week 12, based on: 1) Blinded Evaluator’s assessment and 2) Subject satisfaction on the GAIS. Subjects were classified as a success or failure. To be a success, the subject must have had both evident augmentations on Blinded Evaluation and personally believe that the lip had “improved” appearance.

The *Blinded Evaluator’s GAIS* score was 18/18 (100%) percent of subjects improved at Week 2, 16/18 (89%) at Week 6, 7/19 (37%) at Week 12, and 5/17 (29%) at Week 24.

The percent of improved patients via the *Subjects’ GAIS score* (i.e., improved, same, worse) was: 100% at Week 2 (20/20), 100% at Week 6 (18/18), and 100% at Week 12 (17/17). 14/19 (74%) of subjects judged themselves as improved at Week 24. Subjects may also have viewed their Baseline photograph to refresh their recollection of their Baseline appearance.

On the GAIS the *Treating Investigator* scored 100% of the Subjects as improved at Week 2 (20/20), Week 6 (18/18), and Week 12 (19/19). 16/19 (84%) were judged improved at Week 24.

The median duration of effect was 92 days for the Blinded Evaluator and 183 days for Subjects.

The Blinded Evaluator's Canfield 3D Imaging GAIS Assessment of subject improvement was 7/20 (35%) at Week 2, 9/17 (53%) at week 6, 10/15 (67%) at Week 12 and 7/19 (37%) at Week 24.

FDA Comments on Effectiveness Outcomes:

- The effectiveness outcomes presented in this study are somewhat unreliable because there was no control arm (i.e., unmasked evaluations), the sample size was small and a non-validated GAIS measure was used to assess the Primary Effectiveness Endpoint.
- It appears that, for the majority of patients, neither pre or post-treatment live assessments were performed. Therefore, all MLFS effectiveness assessments were determined by photographic means.

The following is an in-depth description of a Pilot study performed outside the United States as an initial investigation Restylane injection for augmentation of soft tissue fullness of the lips.

V - Clinical 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” – Non-IDE Study

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.

Primary Aim:

Device safety was assessed by: 1) Investigator assessment of all local and systemic adverse events at each study visit (i.e., Baseline, Treatment, Hour 72 and Weeks 2, 4, 8 and 12) as well as 2) completion of a Subject Diary for the first two weeks posttreatment (i.e., extent and severity of bruising, redness, swelling, pain, tenderness, itching, and mass formation). Concomitant medication use and changes in concomitant medications were recorded at each visit.

Preliminary estimates of device effectiveness were determined by the Blinded Evaluator, Treating Investigator, and each subject, who performed a live lip assessment at Weeks 2, 4, 8, and 12 using separate 5-point MLFS for each lip (i.e., with photo guides to score 1 = Very Thin; 2 = Thin; 3 = Medium; 4 = Full; and 5 = Very Full). The Blinded Evaluator, Treating Investigator and Subject also independently performed a live assessment of lip augmentation at Weeks 2, 4, 8, and 12 weeks (as compared to baseline with photos as needed) on a 5 point global improvement aesthetic scale (GAIS), where (i.e., Worse, No Change, Improved, Much Improved, and Very Much Improved).

Sample Size

This initial evaluation of the safety of Restylane use for lip augmentation was designed to enroll 21 patients. The study did not include randomization of patients to a Control cohort.

Inclusion and Exclusion Criteria:

Eligible patients required upper and lower lips with a MLFS score of 1, 2, or 3 as assessed by the Treating Investigator.

Study Plan:

After screening, subjects had both lips treated with Restylane to optimal lip augmentation (as determined by physician and subject with a dose that did not exceed 1.5 mL per lip).

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 may have been provided at Week 2, if the Treating Investigator and Subject determined that optimal lip augmentation had not been achieved.

VI – Study MA-1300-14 Outcomes

Study MA-1300-14 enrolled 21 subjects and 19 completed the trial. Two subjects discontinued the study. One subject discontinued due to an adverse event (anxiety attack) and one subject discontinued due to non-compliance with the study schedule. Patient accounting is presented below in Table 19.

Table 19. Subject Accountability Study MA-1300-14

	Restylane N=21
Subjects Completing Study	19 (90%)
Withdrew from the study	2 (10%)
Reasons	
Withdrew Consent	0
Lost to Follow-up	0
AER	1 (5%)
Non-compliance with study schedule	1 (5%)

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:

Safety outcomes included evaluations of 1) the incidence and severity of adverse experiences from Restylane when injected in the lips by the Treating Investigator, 2) the 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 by the subjects and 3) identification of the duration of intended palpability of the Restylane in the lip both by subject examination during the initial two week period at 72 hours and 2 weeks and by the Investigator at 72 hours, and 2, 6, 12, and 24 weeks.

The incidence and severity of adverse experiences determined by the Treating Investigator - There were 8 AEs reported in 6 subjects during the study. There were two events of nasopharyngitis and one event each of eyelid boil, influenza, pyelonephritis, contusion, fall, and anxiety. Four of these events were considered severe (i.e., Eyelid Boil, Pyelonephritis, Contusion and Fall), two were mild (i.e., Nasopharyngitis and Anxiety) and two were moderate (i.e., Influenza and Nasopharyngitis) in severity. No AE was considered to be related to study treatment and no SAE was reported.

One AE 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. Hyaluronidase was administered to remove Restylane from both lips.

The 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 by the subjects are presented below in Tables 21 and 22.

Table 21. Maximum Intensity of Symptoms after Treatment, Subject Diary

AER	Restylane: Upper Lip				Restylane: Lower Lip			
	None	Tolerable	Affected Daily Activity	Disabling	None	Tolerable	Affected Daily Activity	Disabling
Bruising	4 (21%)	14 (74%)	1 (5%)	0	5 (26%)	14 (74%)	0	0
Redness	8 (42%)	10 (53%)	1 (5%)	0	11 (58%)	8 (42%)	0	0
Swelling	1 (5%)	13 (68%)	5 (26%)	0	2 (11%)	16 (84%)	1 (5%)	0
Pain	8 (42%)	9 (47%)	1 (5%)	1 (5%)	11 (58%)	8 (42%)	0	0
Tenderness	2 (11%)	15 (79%)	2 (11%)	0	3 (16%)	16 (84%)	0	0
Itching	15 (79%)	4 (21%)	0	0	17 (89%)	2 (11%)	0	0
Mass Formation	12 (63%)	6 (32%)	1 (5%)	0	14 (74%)	5 (26%)	0	0

Table 22. Duration of Adverse Outcomes Reported in the Patient Diary

AER	Restylane: Upper Lip				Restylane: Lower Lip			
	1 day	2-7 day	8-13 day	> 14 days	1 day	2-7 day	8-13 day	> 14 days
Bruising	2 (11%)	11 (58%)	2 (11%)	0	4 (21%)	10 (53%)	0	0
Redness	4 (21%)	7 (37%)	0	0	4 (21%)	4 (21%)	0	0
Swelling	1 (5%)	17 (89%)	0	0	5 (26%)	12 (63%)	0	0
Pain	4 (21%)	6 (32%)	1 (5%)	0	5 (26%)	3 (16%)	0	0
Tenderness	1 (5%)	12 (63%)	4 (21%)	0	3 (16%)	11 (58%)	2 (11%)	0
Itching	0	3 (16%)	1 (5%)	0	0	1 (5%)	1 (5%)	0
Mass Formation	2 (11%)	4 (21%)	1 (5%)	0	1 (5%)	4 (21%)	0	0

FDA Comments on the Safety Outcomes:

- All symptoms reported resolved by day 14.
- The information provided on the Canadian study is general, without numerator or denominator. The types and severities of adverse events and medical interventions are described to be similar to those seen in pivotal study MA1300-15. Information is not included regarding the amount and number of times Restylane was injected in a patient's lips, time required to resolve adverse events or time intervals between the last Restylane injection and the onset of an adverse event. The sponsor does include a comparison to adverse events reported in the nasolabial fold. The major difference seen is an increase in swelling in the lip, which is not unexpected.

Study Effectiveness Endpoint Results:

At Week 8, the Blinded Evaluator scored 89% of subjects with at least a one grade improvement on the MLFS in both upper and lower lips (i.e., the Primary Effectiveness Endpoint). At Week 8, the Treating Investigator also scored 89% of subjects with at least a one grade improvement on the MLFS in both upper and lower lips. At all other time points (Weeks 2, 4, and 12), the percent of MLFS Responders ranged from 75% - 89% for the Blinded Evaluator and 80% - 100% for Treating Investigator.

At Week 8, 100% of Blinded Evaluator and Treating Investigator and 94% of subjects were assessed via the GAIS as "improved", "much improved", or "very much improved." At all other time points (Weeks 2, 4, and 12), the percent of GAIS response ranged from 95% to 100% for both Blinded Evaluator and Treating Investigator.

FDA Comments on Effectiveness Outcomes:

- This study was performed outside of the U.S. and hence FDA did not review or comment on the study design. It is included in this summary to insure that all relevant clinical data on the use of Restylane in lip augmentation has been presented to the Advisory Panel.
- The effectiveness outcomes presented in this study are somewhat unreliable because there was no control arm (i.e., unmasked evaluations) and the sample size was small.

VII - Relevant Post Market Experience

The following information on lip area-adverse events found in the *sponsor's global postmarketing safety database* from January 01, 2007 to September 30, 2010 are presented below. The most commonly reported events were: 1) 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 were ongoing at the time of reporting. Reporters were asked to describe the severity of the events using mild, moderate, or severe. The majority of adverse events were reported as mild and moderate. The most commonly reported adverse event was swelling. Reported medical interventions included massage, ice, hyaluronidase, antibiotics, anti-virals, and steroid therapy. As these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency, duration, severity or establish a causal relationship to treatment.

The sponsor stated that the types of commonly reported lip area adverse events identified in the global postmarketing database are similar to the types of events observed in the MA-1300-15 US pivotal study. In the MA-1300-15 study, lip area treatment emergent adverse events (TEAEs) experienced by greater than or equal to 5% of the safety population included: pain, swelling, tenderness, contusion (e.g., bruising and/or ecchymosis), erythema, and skin exfoliation. Table 23 presents the total number of Restylane-reported adverse events from January 1, 2007 to September 30, 2010. Table 24 then compares the incidence of Restylane adverse events from January 1, 2007 to September 30, 2010 reported after nasolabial fold and lips injection.

**Table 23. Total Number of Restylane Reported Adverse Events
from 01/01/2007 to 09/30/2010**

No. of Events	Lips	NLF	Other	Unkown	Total
Restylane	758	634	3200	93	4685

**Table 24. Restylane Adverse Events Related to NLF and Lip Injections
from 01/01/2007 to 09/30/2010**

Adverse Event	Nasolabial Fold		Lip	
	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%
Dermatofytosis	0	0.0%	0	0.0%
Swollen Tongue	0	0.0%	1	0.1%
Unevaluable Event	0	0.0%	0	0.0%

FDA review of the Manufacturer and User Facility Device Experience database (MAUDE) for Medical Device Reports (MDRs) related to Restylane injection in the lip area identified the following information.

Methods The Manufacturer and User Facility Device Experience (MAUDE) database was searched using several combinations of different search criteria. The most effective search was using variations of brand names for “Restylane” without date limitation. The reports from this search were unduplicated and exported to an excel spread sheet for analysis. The reports were then individually reviewed to isolate the reports indicating the injection of Restylane in the “Lips”, “Lip, upper or lower”, and “vermillion border”.

Results The original search generated 121 reports. During the review of the reports it was noticed that 2 of the voluntary reporters had each submitted 2 reports for the same events. The 2 extra reports were deleted bringing the total number of reports considered for analysis to 119 reports. The reports were entered under 2 different product codes: 104 reports with procodes LMH (Implant, Dermal, for aesthetic use), and 15 reports with product code LNM (Agent, Bulking, Injectable for gastro-urology use). However, all 119 reports were related to Restylane. Reports were submitted with 3 different manufacturers’ names; 84 reports by Q-Med AB, 33 reports by Medicis Aesthetic, Inc., one report by Linvatec Corp, and one voluntary report did not include a manufacturer’s name. The Overall data for 119 reports is presented below.

I. Overall counts:

Table 25 summarizes the number of reports submitted by manufacturer by year the report was received.

Table 25. Number of Reports submitted by each manufacturer, and by the Year Reports Received (n=119)

Year Report Received	Q-Med's MDRs	Medicis's MDRs	Linvatec's MDRs	Total # of MDRs
2003	1	0	0	1
2004	2	3	1	6
2005	23	1	0	24
2006	11	5	0	16
2007	23	0	0	23
2008	23	2	0	25
2009	1	20	0	21
2010	0	2	0	2
2011	**0	0	0	0
Total	84	33	1	118*

*Total number of MDR is 118 in this table because one report was missing manufacture's name

**The notable point in the table above is the decreased number of reports since the beginning of 2010.

The report source was as follows: 103 from manufacturer and 16 from voluntary reporters. Types of events were originally reported as 7 injuries, 100 "Other", 10 "Invalid data" one "Malfunction" and in one report the type of event was not specified. All reports categorized as "Other" were submitted by the manufacturer.

Review of the reports revealed that the majority of "type of event" specified as "Other", "Invalid data", and "Malfunction" were actually injury reports. Therefore, the "type of event" was corrected to reflect the actual event. In this process, the type of event of 99 of the 100 reports specified as "Other", 9 reports specified as "invalid data", the one "malfunction" report, and the one report that was missing the type of event (total of 110 reports) was changed to "injury". Additionally, one report of "invalid data" was changed to "Other" because the adverse event in this report did not fall into either "injury" or "malfunction". Therefore, the final corrected count of the "type of events" came to 117 "injury", and 2 "other".

Demographics

Reports' country of origin was specified as United States in 109 reports, while 10 reports did not provide this information. Patient age was missing in 20 reports. The age of the patient in 99 reports specified the age as follows: 20-30 years (n=2), 30 to 40 years (n=22), 40 to 50 years (n=32), 50 to 60 years (n=27), and 50 to 60 years (n=13), and 3

patients were in their 70's. Patient gender was "Female" in 110 reports, "Male" in 8 reports and one report was missing the gender information.

Adverse events in 119 reports

The top 10 adverse events in all 119 reports were identified through MAUDE's "Top 100" query function. This function generates a list of adverse events by using the patient problem codes specified in the reports, and then sums up the occurrence of each code in all the reports. The top 10 patient problem codes are provided in Table 26.

Table 26. Top 10 adverse events identified by MAUDE's "Top 100" Function (n= 119)

Rank	Patient Problem	# of MDRs
1	Swelling	44
2	Skin Discoloration	30
3	Erythema	29
4	Pain	23
5	Bruise	16
6	Rash	9
7	Burning sensation	7
8	Infection	6
9	Hypersensitivity	5
10	Scarring/Necrosis	4

*Please note that each report may contain more than one patient problem code. Therefore, the total number of adverse events is larger than total number of reports.

II. Reports associated with lip augmentation

The individual review of the 119 reports revealed 37 reports of injection of the Restylane into "lips", "upper lip" or "lower lip", and "vermillion border". These 37 reports were analyzed for specific issues of interest for the upcoming panel review.

Limitations of data analysis:

- Terminologies to describe the adverse events used in both manufacturers' reports and in voluntary reports are ambiguous and are not uniform.
- Direct association of the adverse events with the product injected is not explicitly identified in the majority of the reports' narratives.
- The type of local anesthetic used pre-procedure is unknown in a number of reports. Therefore, the possible association of the adverse events with the anesthetic drug can not be determined.
- In reports indicating multiple sites of injection the association of adverse events with injection of Restylane in the lips can not be identified

The site of injection in the 37 "lip augmentation" reports was then broken down to more specific locations stated in the event narrative. Table 27 presents the number of MDRs for each site of injection.

Table 27. Number of Reports by the Reported Sites of Injections in the lip augmentation group (n= 37)

Sites of Injections	# of MDRs
Lips. Lower lip, upper lip	15
Lips, upper or lower lip and nasolabial fold	7
Lips and other sites of the face	7
Vermillion border and Nasolabial fold	4
Vermillion border, Nasolabial fold & lower or upper lip	1
Vermillion border, Nasolabial fold, lips & smoker line	1
Vermillion border (single site)	2

Adverse Events

The adverse events were analyzed in two additional categories based on time-to-event; within the first 24 hours post-injection and after 24 hours post-injection.

Post-injection adverse events during the first 24 hours: Sixteen reports indicated that the adverse events occurred immediately after injections or within the first 24 hours.

- *Allergic reaction and anaphylactic shock:* Eight patients experienced immediate post injection reactions which included extreme swelling of lips and the whole face. Two of these patients had symptoms of hypersensitivity and one patient experienced anaphylactic shock and presented with shortness of breath, headache, nausea and vomiting. These patients had to be admitted to the emergency room or were hospitalized for immediate medical interventions
- *Vascular accidents and necrosis:* In 5 patients; skin discoloration, bruising, and blanching was seen immediately post- injection due to vascular accidents. The lesions later turned into necrosis and in some cases remained as scarring or dark spots. One example was a patient who had a “mustache-like” mark above her lips, even after receiving treatments. Later, one patient in this group developed hard bumps in her upper lips that looked like” granulomas”.
- *Infection:* Two patients had infections at the site of injection during the first 24 hours with symptoms of fever, pain, and blister. One of the two patients had 2 grape- size lumps that had to be incised and drained and the culture came back “gram positive Cocci”.
- *Angioedema:* One patient developed severe angioedema in the upper lip 2 hours after the injection. The patient was treated with Medrol and Valtrix

Adverse events occurring beyond 24 hours up to months after injection: The 21 remaining reports can be categorized in the following groups:

- *Lumps and bumps:* Eight patients' adverse events were described as having a mass/lesion under skin at the injection site referred to as "lumps, "bumps" and "papules". These non-specific terms could actually be nodules and/or granulomas but no certain conclusion can be drawn from review of the events' narratives.
- *Hyperpigmentation:* Three patients experienced different symptoms at the beginning such as erythema, soreness, "bruise-like", "acne-like" lesions which later were assessed as hyperpigmentation.
- *Dry lips, desquamation/peeling, and product ineffectiveness:* Two patients experienced very dry lips. In one of them dryness was accompanied by peeling of the lips, and in the other the product disappeared and was ineffective.
- *Broken capillaries:* Two patients who had injection of Restylane in both lips and nasolabial fold developed lesions at the nasolabial fold injection sites referred to as "broken capillaries". Patients were scheduled for Intense Pulse Light Therapy.
- *Delayed hypersensitivity:* Two patients developed symptoms of hypersensitivity 7-10 days after injection. One patient experienced severe erythema and swelling in the lips and all over her face to the point that her eyes were shut and the other had swelling of the lips accompanied by dyspnea, lymphadenopathy, peripheral and laryngeal edema.
- *Numbness:* One patient experienced numbness below her lower lip. Treatment with Prednisone was not effective and patient was referred to a neurologist.
- *Hypertrophic scar tissue:* One patient developed a lesion at the vermillion border which was biopsied and cauterized. The pathology result showed hypertrophic scar tissue. The lesion resolved but left a scar on the patient's lip.
- *Herpes:* Two patients had questionable Herpes. The reports indicate that one of the patients developed a vesicular sore at the injection sites (nasolabial fold and sides of the lips) which "looked like Herpes". When patient was evaluated by her physician she was prescribed Valtrex (a drug used for treatment of Herpes). The second patient developed small postulates with burning sensation and severe pain around nasolabial folds, and a sore in the internal mucosa of the mouth. Patient's physician consulted a colleague and diagnosed the patient with Herpes Zoster.

FDA Comments on the Post Marketing Experience with Restylane injections for lip augmentation:

- MDRs related to lip (758/4685 – 16.2%) and nasolabial fold (634/4685 – 13.5%) injections are in the minority of the MDRs submitted to the sponsor. The majority of MDRs are related to "Other" (3200/4684 – 68.3%) uses of Restylane which were not presented in this application.

- Because the frequency of Restylane injections in the lip and nasolabial folds are not known, one cannot meaningfully compare the frequency of MDRs for the approved and proposed indications for use.
- Reports indicate that patients receiving injection of Restylane into lips often receive injections in other areas of the face as well. This is reflected in the combination of symptoms in different areas, and therefore no specific trend of adverse events can be detected for the lip augmentation per se. In the MAUDE database there were only 15 reports indicating lip injection as the single site of injection and the only adverse events in those reports reported more than once were allergic reaction and lesions referred to as “lumps and bumps”. Comparison of the safety profile for Restylane injections in the nasolabial folds and lips is further complicated by the lack of information on the severity and duration or as well as the medical interventions required for these MDRs.

VIII. 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.