SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Injectable Dermal Filler
Device Trade Name:	Restylane Silk Injectable Gel
Device Procode:	LMH
Applicant's Name and Address:	Valeant Pharmaceuticals North America LLC/Medicis 400 Somerset Corporate Blvd Bridgewater, NJ 08807
Date of Panel Recommendation:	None

Premarket Approval Application (PMA) Number: P040024/s072

Date of FDA Notice of Approval:	June 13, 2014
Expedited:	Not applicable

The original PMA (PMA # P040024) for Restylane was approved on March 25, 2005 for mid-to-deep dermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds. Submucosal implantation for lip augmentation in patients over the age of 21 was added to the indications for Restylane in supplement P040024/S051 and approved on October 11, 2011. These SSEDs to support these indications are available on the CDRH website and are incorporated by reference here. The current supplement is submitted to add Restylane Silk Injectable Gel, (a new product under the PMA), for submucosal implantation for lip augmentation and correction of perioral rhytids in patients over the age of 21.

II. INDICATIONS FOR USE

Restylane Silk is indicated for submucosal implantation for lip augmentation and dermal implantation for correction of perioral rhytids in patients over the age of 21.

III. CONTRAINDICATIONS

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

- Restylane Silk should not be used in patients with previous hypersensitivity to local anesthetics of the amide type, such as lidocaine.

IV. WARNINGS AND PRECAUTIONS

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

V. DEVICE DESCRIPTION

Restylane Silk contains 0.3% lidocaine and is a gel of hyaluronic acid (HA) isolated from a *Streptococcus* species that is chemically crosslinked with 1,4-butanediol diglycidyl ether (BDDE), stabilized, and suspended in phosphate buffered saline at pH = 7 and a concentration of 20 mg/mL. Restylane Silk is a transparent, viscous, and sterile gel that is supplied in a disposable glass syringe. The product is approved in a 1 mL fill size. The syringe is co-packed in a blister together with sterile 30 G TW needle(s).

The HA has a molecular weight of about one million and is stabilized by adding a minimum amount of BDDE to allow formation of a three-dimensional HA molecular network.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

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

VII. MARKETING HISTORY

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

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The safety of Restylane Silk for lip augmentation and correction of perioral rhytids was evaluated in a premarket study. Potential adverse effects (e.g., complications) associated with the use of the device, as well as for other devices in the same category, as reported in the clinical study include tenderness, swelling, firmness (induration), lumps/bumps (mass), bruising, pain, redness, discoloration, and itching. Other adverse effects reported less frequently (in less than 5% of study subjects) include injection site reaction, injection site hypertrophy, nodule, inflammation, injection site anesthesia, injection site dryness, injection site erosion, contusion, and syncope.

Post-Market Surveillance

Potential adverse effects associated with the use of the device known from published or unpublished sources outside of the PMA clinical studies are discussed below. The adverse events received from post-marketing surveillance for the use of *Restylane Silk* when used outside the US for lip augmentation were infrequent and included mostly reports of swelling of the lip. The most frequent events were injection site swelling, pain/tenderness, inflammation, induration, erythema, nodule formation, skin discoloration, hematoma, injection site mass, eye swelling, hypersensitivity reaction, implant site abscess, infection and implant site necrosis. The severe events associated with Restylane Silk implantation included swelling with a time to onset ranging from 0 to 10 days. Treatments for the events of swelling in the lip included corticosteroids, antibiotics, antihistamines, NSAIDs and hyaluronidase. Vision abnormalities including blindness have been reported following injection of hyaluronic acid, with and without lidocaine, into the nose, glabella, periorbital areas, and/or cheek, with a time to onset ranging from immediate to a few days following injection. Reported treatments include anticoagulant, epinephrine, aspirin, hyaluronidase, steroid treatment and hyperbaric oxygen. Outcomes ranged from resolved to ongoing at the time of last contact. Events requiring medical intervention, and events where resolution information is not available were reported after injection of hyaluronic acid with or without lidocaine. In these cases, the product was injected into the highly vascularized areas of the glabella, nose, and periorbital area, which are outside the device indications for use (See Warnings section).

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

SUMMARY OF PRECLINICAL STUDIES

Restylane Silk was extensively tested and characterized through physical and chemical analyses (Table 1) as well as biocompatibility assessments (Table 2). These studies were performed with a product identical to Restylane Silk without lidocaine (i.e., Restylane Touch) and with Restylane Silk. Non-clinical biological evaluation of the gel product intended for facial tissue augmentation is based on *in vitro* and *in vivo* biocompatibility testing performed on small particle hyaluronic acid (Restylane Touch) together with additional studies performed on Restylane Silk (Table 2).

Table 1. Quality Specification – Basic Requirements

Critical Parameter/Characteristic	Specification Limit*	Test Method
Identity (Gel particle size at x_{50})	50 – 220 µm	QMS-5789

Gel particle size at x_{10}	≥ 25 µm	QMS-5789
Gel particle size at x_{90}	≤ 330 µm	QMS-5789
HA-content	17 – 23 mg/mL	QMS-5616 QMS-4387
Sterility	No growth	QMS-1392
Bacterial endotoxins	≤ 0.5 EU/mL	QMS-1222
pH	Release: 6.8 – 7.5 End of shelf-life: 6.0 – 7.5	QMS-1230
BDDE content	≤ 2 ppm	QMS-5276
Lidocaine Hydrochloride content	2.7 – 3.3 mg/mL	QMS-5612
Swelling Factor	Release: ≤ 3.0 mL/g End of shelf-life: ≤ 3.4 mL/g	QMS-4520
Gel content	Release: ≥ 78 % End of shelf-life: ≥ 60%	QMS-4387 QMS-5621
Extractable carbohydrates	Release: ≤ 22 % End of shelf-life: ≤ 40 %	Calculated as 100 – Gel content
Extrusion force	≤ 30 N	QMS-1427
Extrusion force	No peak above 60N for more than 5 seconds	QMS-1427
Impurities deriving from Lidocaine Hydrochloride	2,6-xylidine ≤ 0.05% of lidocaine HCl Specified unidentified impurities ≤ 0.2% of lidocaine HCl Total amount of impurities Release : ≤ 0.2% of lidocaine HCl End of shelf-life: ≤ 0.9% of lidocaine HCl	QMS-5627
Appearance	A legibly labeled glass syringe filled with transparent gel.	QMS-1394

* At end of shelf-life unless otherwise specified

Given the similarity of the chemical compositions of Restylane Silk and Restylane, biocompatibility studies previously conducted for Restylane (PMA P020023) support conclusions of the safety and effectiveness of Restylane Silk (Table 3).

Based on the chemical and physical testing, there was sufficient data to demonstrate that Restylane Silk was appropriate for evaluation in clinical studies as a dermal filler.

Table 2: Overview of Preclinical Bridging Studies

Test	Study Number	Method	Test Article	Results	Location
Cytotoxicity	05T_33501_01	Agarose overlay (liquid). Mouse fibroblasts overlaid with agarose and treated with test article-saturated filter paper for 24 hours. Cytotoxicity examined and reactivity scored based on evidence of lysis (decoloration) and microscopic morphology.	Restylane Touch	Restylane Touch was not cytotoxic based on the absence of cell lysis and no morphology changes. Positive and negative controls performed as expected.	P040024/S072
Cytotoxicity	08T_37549_03	Agarose overlay (liquid). Mouse fibroblasts overlaid with agarose and treated with test article-saturated filter paper for 24 hours. Cytotoxicity examined and reactivity scored based on evidence of lysis (decoloration) and microscopic morphology	Restylane Silk*	NASHA gel with lidocaine was not cytotoxic based on an absence of cell lysis and no morphology changes. Positive and negative controls performed as expected.	P040024/S072
Intracutaneous Irritancy	06T_49609_03	Undiluted test article and sesame oil control were injected intracutaneously to 5 rabbit skin sites each (0.2 mL/site, n = 2 animals). Injection sites scored for erythema and edema immediately after injection (baseline) and at 24, 48 and 72 hours. Edema scores determined by measuring injection site height and width and correcting for baseline measurements.	Restylane Touch	Severe edema observed in 2 test article injection sites (1 per rabbit), and moderate edema in 1 test article and 1 control site at 24 hours; no edema observed at later timepoints. The primary irritation score was 1.0 and Restylane Touch classified as a slight irritant.	P040024/S072
Intracutaneous Irritancy	08T_37549_05	Undiluted test article and 0.9% NaCl control were injected intracutaneously to 5 rabbit skin sites each (0.2 mL/site, n = 2 animals). Injection sites scored for erythema and edema immediately after injection (baseline) and at 24, 48 and 72 hours. Edema scores determined by measuring injection site height and width and correcting for baseline measurements.	Restylane Silk*	NASHA gel with lidocaine produced very slight to well-defined erythema and no edema.	P040024/S072

Test	Study Number	Method	Test Article	Results	Location
Sensitization	06T_49609_01, 06T_49609_02	Guinea pig maximization study per OECD 406. Guinea pigs (n=10) were induced with intradermal injections of diluted test article (25% in saline) and FCA, followed one week later with an occluded topical dermal application of undiluted test article. Control animals (n=5) were treated similarly with saline. Two weeks after topical induction, animals were challenged with undiluted test article and saline applied occluded topical dermal to flank skin. Skin reactions were scored for erythema and edema 1 and 2 days after challenge.	Restylane Touch	There were no skin reactions after challenge in test article or saline control groups. Restylane Touch was not a skin sensitizer.	P040024/S072
Sensitization	08T_37549_04	Guinea pig maximization study per OECD 406. Guinea pigs (n=10) were induced with intradermal injections of test article and FCA, followed one week later with an occluded topical dermal application of test article. Control animals (n=5) were treated similarly with saline. Two weeks after topical induction, animals were challenged with test article and saline applied occluded topical dermal to flank skin. Skin reactions were scored for erythema and edema 1 and 2 days after challenge.	Restylane Silk*	There were no skin reactions after challenge in test article or saline control groups. NASHA gel with lidocaine was not a skin sensitizer.	P040024/S072

Table 3: Overview of Restylane Preclinical Studies

Test	Study Number	Method	Test Article	Results	Location
Pyrogenicity	99T 11481 00, 99T 11482 00, 99T 11483 00	USP rabbit pyrogen test	Restylane	Three lots of Restylane did not induce fever in any of the tested rabbits	PMA P020023; Vol 04, Section 6.8, Attachment 6:1
Cytotoxicity	00T 02385 00	MEM elution	Restylane	MEM test extracts were not cytotoxic and met the requirements of the test (cytotoxicity grade < 2). The negative controls, reagent controls, and the positive controls performed as anticipated.	PMA P020023; Vol 04, Section 6.8, Attachment 6:3
Cytotoxicity	99-I-099	Colony formation in V79 cells. Restylane concentrations were 0 to 2.0 mg/mL (0 – 10.0%, hyaluronic acid, stabilized)	Restylane	Restylane did not inhibit colony formation in V79 cells and was therefore no cytotoxic. Controls performed as anticipated.	PMA P020023; Vol 04, Section 6.8, Attachment 6:4
Genotoxicity	16513	Ames test (*Salmonella*)	Restylane	Restylane extracts did not increase the number of revertants in any of the tester strains with or without S9 mix. Restylane extracts were not mutagenic.	PMA P020023; Vol 04, Section 6.8, Attachment 6:5
Genotoxicity	31374	Ames test	Restylane	Restylane extracts were not mutagenic.	PMA P020023; Vol 04, Section 6.8, Attachment 6:6
Genotoxicity	99T 02114 00	In vitro chromosomal aberration study in mammalian CHO cells	Restylane	No significant differences in % aberrant cells between test article extract and negative control in the presence or absence of S9. The positive and negative control performed as anticipated, validating the assay. Restylane extract was not genotoxic.	PMA P020023; Vol 04, Section 6.8, Attachment 6:7
Genotoxicity	99T 02114 00	Bone marrow micronucleus assay in mice	Restylane	Test article was not genotoxic. There was no evidence of cellular toxicity. The negative and positive controls performed as expected.	PMA P020023; Vol 04, Section 6.8, Attachment 6:8
Sensitization	16512	Guinea pig maximization test	Restylane	No evidence of delayed contact hypersensitivity observed after treatment with Restylane.	PMA P020023; Vol 04, Section 6.8, Attachment 6:9

Test	Study Number	Method	Test Article	Results	Location
Acute, subchronic and chronic toxicity	99-1	Intradermal injection in rabbit	Restylane	Restylane implants were well tolerated with no adverse reactions and remained within the dermis after 52 weeks. The material became incorporated into the tissue without inducing significant short- or long-term foreign body reaction. Fibrous tissue reaction consisting of collagen, fibrocytes and fibroblasts surrounding Restylane microbeads observed at 7, 14 and 21 days but not at 52 weeks post-injection.	PMA P020023; Vol 04, Section 6.8, Attachment 6:2
Biocompatibility	30440	Muscle implantation test in rabbits (ISO 10993-6) for 4 weeks. Restylane (0.1 mL) and high density polypropylene control implanted intramuscularly to 3 New Zealand White rabbits (4 sites/sample/animal). Macroscopic and microscopic evaluation at necropsy 4 weeks after implantation.	Restylane	Microscopic evaluation indicated that Restylane was well tolerated locally. Minimal to slight chronic inflammatory cell infiltration observed microscopically at test article and control implant sites. Fibrous membrane, minimal to marked, noted at test article implant sites, and minimal to slight at control sites. Except for one test article implant, changes were more pronounced in control implants. Myositis of minimal to moderate severity only adjacent to control implant sites.	PMA P020023; Vol 04, Section 6.8; Attachment 6:10
Biocompatibility	16514	Muscle implantation test in rabbits (ISO 10993-6) for 90 days. Restylane and USP negative control plastic RS implanted intramuscularly to 3 SPF albino rabbits (4 sites/sample/animal). Macroscopic and microscopic evaluation at necropsy 90 days after implantation.	Restylane	No encapsulation observed macroscopically or microscopically with Restylane (vs. mean encapsulation score of 2.2 for negative control). Restylane produced a slight granulomatous cellular response observed as test article fragments separated by a thin fibrous sheet with focal infiltration (primarily lymphocytes). Control implant cavities were lined by a very thin fibrous sheet with no or very few inflammatory cells.	PMA P020023; Vol 04, Section 6.8, Attachment 6:11

* NASHA gel with lidocaine is the basis for Restylane Silk which has been processed through a particle size reduction step to provide smaller particle size

IX. SUMMARY OF PRIMARY CLINICAL STUDY

The sponsor performed a clinical study to establish a reasonable assurance of safety and effectiveness for Restylane Silk for submucosal implantation for lip augmentation and dermal implantation for correction of perioral rhytids in patients over the age of 21.

A. Study Design

Patients were treated between May 7, 2012 and April 13, 2013. The database for this PMA reflects data collected through June 13, 2013 and includes 221 patients. There were 14 investigational sites in the U.S.

The clinical study (MA-1700-04) was a prospective, randomized, multi-center, evaluator-blind study of subjects seeking lip fullness augmentation. Subjects who met all inclusion/exclusion criteria were randomized at in a 3:1 ratio to Restylane Silk treatment or no treatment. The study included 52 subjects with Fitzpatrick skin types IV or V. After treatment, patients attended clinical visits at 72 hours and 2, 4, 8, 12, 16, 20, 24 weeks after Restylane Silk injection as well as 2 and 4 weeks after a Week 24 Restylane re-treatment. The no treatment control subjects had treatment delayed for 6 months.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the MA-1700-04 study was limited to patients who met the following inclusion criteria: males or non-pregnant, non-breast-feeding females, 18 to 65 years of age; seeking augmentation therapy for the lips; had a baseline MLFS score of very thin (1) or thin (2) for both lips (subjects with Fitzpatrick skin types IV, V, and VI need only have one lip eligible by MLFS and subjects ≤ 35 years of age were not required to meet MLFS criteria); had the ability to understand and comply with the requirements of the study; willing to abstain from exclusionary procedures for the duration of the study; willing to give written informed consent to participate in the study; and women of childbearing potential willing to use an acceptable form of birth control during the study period.

Patients were not permitted to enroll in the MA-1700-04 study if they met any of the following exclusion criteria: History of allergy or hypersensitivity to injectable hyaluronic acid gel or to lidocaine; history of the presence of any disease on entry which may result 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; history of the use of any non-biodegradable tissue augmentation therapy or aesthetic facial surgical therapy below the level of the lower orbital rim, (e.g., facelift or dental work) in the preceding eight months or plans to use these substances or have these procedures during the study; history of the use of any biodegradable tissue augmentation therapy or aesthetic facial surgical therapy below the level of the lower orbital rim within the last 9 months or plans to use these substances or have these procedures during the study; 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; history of severe allergies or multiple allergies manifested by

anaphylaxis or a history of a hypotensive crisis in response to radio-contrast media or other osmotic agent; the presence of any condition, which in the opinion of the investigator, would make the subject unable to complete the study per protocol; known allergies or hypersensitivity reactions to local topical anesthetics or nerve blocking agents; the presence of cancerous or pre-cancerous lesions in the area to be treated; prior surgery to the upper or lower lip; prior significant trauma, such as dog bite or laceration, to the upper or lower lip resulting in formation of a scar; presence of facial hair that could interfere with Medicis Lip Fullness Scales (MLFS) or the Wrinkle Assessment Scale for Upper Lip Lines (WASULL) evaluation; history of herpes labialis and an outbreak within 4 weeks of study entry or with four or more outbreaks in the 12 months prior to study entry; mild, moderate, or severe abnormal rating for texture or firmness or detection of any abnormal lip structure, such as a scar or lump; moderate or severe abnormal rating for lip symmetry; abnormal rating in lip movement; abnormal rating in lip function; abnormal rating in lip sensation; any mass formation at screening; current use of immunosuppressive therapy; history of connective tissue diseases such as rheumatoid arthritis, systemic lupus erythematosus, polymyositis, dermatomyositis, or scleroderma; participation in any interventional clinical research study within 30 days prior to randomization.

To be randomized the group of subjects with Fitzpatrick skin types IV, V, or VI had the required MLFS score for at least one lip (either upper or lower) as assessed at baseline (prior to randomization) by the blinded evaluator and the treating investigator. Subjects under the age of 36 years met all entry criteria except for the baseline MLFS score may have been enrolled into the non-randomized group.

2. Follow-up Schedule

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

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

Post-Treatment, the parameters measured were: a subject's 14 day treatment diary (after each injection) to record bruising, redness, swelling, pain tenderness, itching, a Treating Investigator assessment of safety outcomes at each visit and a staff member evaluation of abnormal lip texture, lip firmness, and lip symmetry, as well as abnormal lip movement, function, sensation and mass formation at each study visit. The Treating Investigator evaluated lip fullness on the Medicis Lip Fullness Scale (MLFS) and a Global Aesthetic Improvement Scale (GAIS) after each visit, the Blinded Evaluator determined lip appearance (via) MLFS and upper perioral rhytid appearance (via WASULL) at Weeks 8, 12, 16, 20, and 24 as well as 2 and 4 weeks after the Week 24 Restylane Silk re-treatment. Each subject assessed GAIS after each visit and photographs were taken at each visit. Adverse events and complications were also recorded at all visits.

3. Clinical Endpoints

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

An adverse event (AE) was defined as any untoward medical occurrence or an unintended sign, symptom, or disease temporally associated with the use of the device, whether or not considered related to the device. An AE was further defined as:

- any diagnosis, sign, symptom, or abnormal laboratory value not present, detected or complained of at the baseline assessment.
- any diagnosis, sign, symptom, or abnormal laboratory value noted at baseline that worsened in severity or intensity or increased in frequency during the study.

An AE that occurred during the study was considered a treatment emergent adverse event (TEAE) if:

- it was not present prior to receiving treatment (as determined by onset date of event and date treatment was received), or
- it was present prior to receiving treatment but the severity increased after treatment (as determined by onset date of the severity increase of the event and date treatment was received).

The investigator was to classify the severity of an adverse event according to the following definitions:

- Mild: did not interfere with routine activities, could perform daily functions
- Moderate: interfered with routine activities, could perform daily functions, but with concerted effort
- Severe: unable to perform routine activities

A Serious Adverse Device Event (SADE) was defined as an AE that:

- results in death;
- is life-threatening;
- results in permanent impairment of a body function;
- results in permanent damage to a body structure; or,
- necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

The primary effectiveness endpoint was whether Restylane Silk was more effective than No Treatment (as determined by Blinded Evaluator) at 8 weeks after treatment compared to the baseline lip fullness assessment by the Treating Investigator. A Responder was defined as at least one grade increase from Baseline on the MLFS scale for both upper and lower lips. The MLFS is presented below in Table 4.

Table 4. Medicis Lip Fullness Scale (MLFS)

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

The following additional effectiveness endpoints were evaluated: 1) Blinded Evaluator MLFS score at Weeks 12, 16, 20, and 24, as well as 2 and 4 weeks after the Week 24 re-treatment, 2) Treating Investigators' MLFS scores at each time point after treatment, 3) Independent Photographic Reviewers' (IPR) assessment of MLFS score after study completion by an off-site reviewer who compared photos from Baseline and Weeks 4 – 24, 4) the Treating Investigators' GAIS assessment at each time point after treatment, 5) Subjects' GAIS assessment at each time point after treatment (Table 5), 6) the degree of correlation between MLFS and GAIS scores by Treating Investigators, 7) the degree of correlation between Treating Investigators' MLFS and the Subject GAIS scores, 8) the agreement among the proportion of Responders determined by the MLFS and GAIS scales judged by the Treating Investigators, 9) the Agreement among the MLFS for the Treating Investigator, Blinded Evaluator, and IPR assessments, and 10) Treating Investigators' and Blinded Evaluators' assessment of upper perioral rhytid appearance via the WASULL (Table 6). Treatment success was defined as a one grade decrease in the WASULL from baseline.

Table 5. Subject Global Aesthetic Improvement Scale (GAIS)

3	Very Much Improved
2	Much Improved
1	Improved
0	No Change
-1	Worse
-2	Much Worse
-3	Very Much Worse

Table 6. Wrinkle Assessment Scale for Upper Lip Lines (WASULL)

5	Extreme
4	Severe
3	Moderate
2	Mild
1	Very Mild
0	Absent

B. Accountability of PMA Cohort

221 patients enrolled and 158/177 (89%) Restylane Silk and 41/44 (93%) No Treatment (control) subjects completed the study. The two subjects excluded from the ITT population were excluded since they did not have any follow-up assessments. No subject discontinued due to an adverse event. Subject accountability is displayed below in Table 7.

Table 7. Subject Accountability Study MA-1700-04

	No Treatment (N=43)	Restylane Silk (N=176)	Total (N=219)
Subjects Completing Study	41 (95%)	158 (90%)	199 (91%)
Withdrew from the study	2 (5%)	18 (10%)	20 (9%)
Primary Reason for Discontinuation			
Withdrew Consent	0	6 (3%)	6 (3%)
Lost to Follow-up	1 (2%)	12 (7%)	13 (6%)
AER	0	0	0
Other	1 (2%)	0	1 (<1%)

C. Study Population Demographics and Baseline Parameters

Demographic characteristics were similar for the No Treatment and Restylane Silk groups at baseline. The demographics of the entire study population are presented in Table 8. The demographics for patients with Fitzpatrick Skin Types IV and V and patients under the age of 36 were similar to the general study population.

Table 8: Subject Demographics – Safety Population

Characteristic	No Treatment (N=44)	Restylane Silk (N=177)	Total (N=221)
Age (years)			
Mean (S.D.)	49.8 (10.4)	44.4 (12.5)	45.5 (12.3)
Median	51.0	47.0	48.0
Minimum	29	18	18
Maximum	65	65	65
Gender			
Male	1 (2%)	5 (3%)	6 (3%)
Female	43 (98%)	172 (97%)	215 (97%)
Race			
American Indian/Alaskan Native	0	1 (<1%)	1 (<1%)
Black or African American	1 (2%)	0	1 (<1%)
Native Hawaiian or other Pacific Islander	0	0	0
Asian	0	3 (2%)	3 (1%)
White	43 (98%)	168 (95%)	211 (95%)
Other	0	5 (3%)	5 (2%)
Ethnicity			
Not Hispanic or Latino	37 (84%)	141 (80%)	178 (81%)
Hispanic or Latino	7 (16%)	36 (20%)	43 (19%)
Fitzpatrick Skin			
I, II, and III	34 (77%)	135 (76%)	169 (76%)
IV, V, and VI	10 (22%)	42 (24%)	52 (24%)
Baseline MLFS - Treating Investigator (upper lip)			
Very Thin [1]	27 (61%)	76 (43%)	103 (47%)
Thin [2]	15 (34%)	70 (40%)	85 (38%)
Medium [3]	2 (5%)	18 (10%)	20 (9%)
Full [4]	0	10 (6%)	10 (5%)
Very Full [5]	0	3 (2%)	3 (1%)
Baseline MLFS - Treating Investigator (lower lip)			
Very Thin [1]	15 (34%)	53 (30%)	68 (31%)
Thin [2]	24 (55%)	76 (43%)	100 (45%)
Medium [3]	4 (9%)	25 (14%)	29 (13%)
Full [4]	1 (2%)	21 (12%)	22 (10%)
Very Full [5]	0	2 (1%)	2 (<1%)
Baseline MLFS - Blinded Evaluator (upper lip)			
Very Thin [1]	29 (66%)	76 (43%)	105 (48%)
Thin [2]	13 (30%)	69 (39%)	82 (37%)
Medium [3]	2 (5%)	21 (12%)	23 (10%)
Full [4]	0	10 (6%)	10 (5%)
Very Full [5]	0	1 (<1%)	1 (<1%)
Baseline MLFS - Blinded Evaluator (lower lip)			
Very Thin [1]	19 (43%)	53 (30%)	72 (33%)
Thin [2]	21 (48%)	76 (43%)	97 (44%)
Medium [3]	2 (5%)	28 (16%)	30 (14%)
Full [4]	2 (5%)	16 (9%)	18 (8%)
Very Full [5]	0	4 (2%)	4 (2%)

Additional information on the Study Population:

The majority of subjects in the Restylane Silk (81%) and No Treatment (79%) cohorts had a concomitant procedure during the study period. The most commonly reported concomitant procedure for both Treatment Groups was cold compress therapy (as a prophylactic measure for pain and swelling). The Medical Histories for both cohorts were well matched at baseline with the exception that more patients in the No Treatment Group had a prior history of Seasonal Allergy (16%) compared to (2%) the Treatment group. Concomitant medications were taken by 91% of subjects in the No Treatment group and 99% of subjects in the Restylane Silk treatment group. Pretreatment anesthetics (e.g., topical and local anesthetic, infiltrative, and regional blocks) were frequently used by the investigators to help mitigate procedure pain; some of the commonly used anesthetics included: lidocaine, local anesthetics, and xylocaine with ephinephrine.

Injected Volumes of Restylane Silk for Lip and Perioral Rhyids Correction:

For lip treatment, the mean volume of Restylane Silk injected for the initial treatment (and touch-up) sessions was 2.179 mL (range 0.10 – 6.80 ml) for subjects in the Restylane Silk group. While all subjects received a submucosal injection for their first treatment, some subjects also received an injection other than submucosal for their initial and touch-up treatments. A combination of injection methods (i.e., linear retrograde and linear antegrade) was used for both the initial injection and touch-up treatments. The mean length of time for initial treatment of both lips was 9 minutes and 11 seconds (median 7 min, 5 sec). For subjects receiving retreatment at the 6 months, the mean volume of Restylane Silk injected into the lips was 1.495 mL (including touch-up). For subjects randomized to the No Treatment group the mean volumes injected into the lips for the initial sessions as 2.124 mL. The extent of exposure for lip augmentation in the subgroups of subjects with Fitzpatrick skin types IV, V, and VI and subjects less than 36 years of age was similar to the overall population.

For perioral rhytids, 65 subjects received initial treatment. The mean volume of *Restylane Silk* injected at the initial treatment (including touch-up) was 0.475 mL for subjects in the *Restylane Silk* treatment group. While the majority of subjects (51/65) received a mid-dermis injection for their first treatment, some subjects also received a deep dermis (13/65) or other (5/65) injection for their initial and touch-up treatments. There did not appear to be a preferred method of injection. For initial treatment the mean length of time needed to treat perioral rhytids was 2 minutes and 20 seconds (median 1 min, 31 sec). For the touch-up visit the mean treatment time was 1 min and 23 sec (median 50 sec). At the 6 month treatment (including touch-up), 32/65 *Restylane Silk* subjects were re-treated and 18/43 subjects in the No Treatment group received treatment for perioral rhytids. The mean volume of *Restylane Silk* injected for perioral rhytids was 0.697 mL for subjects receiving retreatment. Subjects randomized to the No Treatment group received their first treatment with *Restylane Silk* at 6 months, and the mean volume of 0.885 ml was injected into the mid-dermis for perioral rhytids. The extent of exposure for treatment of perioral rhytids in the subgroup of subjects with Fitzpatrick skin types IV, V, and VI was similar to the overall population. No subjects under the age of 36 years received treatment for perioral rhytids at the initial treatment. Three subjects received treatment at 6 months.

D. Safety and Effectiveness Results

1. Safety Results

218/221 subjects received their first treatment with Restylane Silk at either Baseline/Day 0 or at Week 24. 133 subjects received a second series of treatments at Week 24. There were 20 TEAEs experienced by 12 (27%) No Treatment (control) subjects compared to 632 TEAEs experienced by 169 (78%) subjects receiving their first treatment with Restylane Silk and 196 TEAEs experienced by 84 (63%) of subjects after their second treatment with Restylane Silk. For Restylane Silk patients the majority of the TEAEs were mild in intensity (i.e., 540/632 (85%) and 178/196 (91%)), 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 9.

Table 9: Summary of Treatment Emergent Adverse Events Occurring in ≥ 5% of Subjects by Severity – Safety Population

System Organ Class/ Preferred Term	Severity	No Treatment at Baseline (N=44)		First Treatment with Restylane Silk (N=218)		Second Treatment with Restylane Silk (N=133)	
Any TEAE		Events[1]	Subjects[2]	Events	Subjects	Events	Subjects
	Total	20	12 (27%)	632	169 (78%)	196	84 (63%)
	Mild	16	10 (23%)	540	129 (59%)	178	73 (55%)
	Moderate	2	1 (2%)	80	34 (16%)	18	11 (8%)
	Severe	2	1 (2%)	12	6 (3%)	0	0
Gastrointestinal Disorders							
Lip Disorder	Total	0	0	17	11 (5%)	1	1 (<1%)
	Mild	0	0	17	11 (5%)	1	1 (<1%)
	Moderate	0	0	0	0	0	0
	Severe	0	0	0	0	0	0
Lip Pain	Total	0	0	34	21 (10%)	12	9 (7%)
	Mild	0	0	30	19 (9%)	12	9 (7%)
	Moderate	0	0	4	2 (<1%)	0	0
	Severe	0	0	0	0	0	0
Lip Swelling	Total	0	0	186	94 (43%)	74	46 (35%)
	Mild	0	0	154	77 (35%)	65	41 (31%)
	Moderate	0	0	22	12 (6%)	9	5 (4%)
	Severe	0	0	10	5 (2%)	0	0
General Disorders and Administrative Site Conditions							
Pain	Total	0	0	32	18 (8%)	6	4 (3%)
	Mild	0	0	24	13 (6%)	4	3 (2%)
	Moderate	0	0	8	5 (2%)	2	1 (<1%)
	Severe	0	0	0	0	0	0
Injury, Poisoning, and Procedural Complication							
Contusion	Total	0	0	145	96 (44%)	55	41 (31%)
	Mild	0	0	134	87 (40%)	53	39 (29%)
	Moderate	0	0	11	9 (4%)	2	2 (2%)
	Severe	0	0	0	0	0	0
Nervous System Disorders							
Headache	Total	7	4 (9%)	11	10 (5%)	3	2 (2%)
	Mild	7	4 (9%)	10	9 (4%)	2	1 (<1%)
	Moderate	0	0	1	1 (<1%)	1	1 (<1%)
	Severe	0	0	0	0	0	0

[1] A subject with more than one treatment emergent adverse event within a system organ class and/or preferred term is only counted once.
[2] If a subject has more than one treatment emergent adverse event within a system organ class and/or preferred term, the event with the greatest severity will be counted for that subject.

The durations for TEAEs are presented in Table 10. Most events resolved within a mean of 18 days. Common events related to treatment with Restylane Silk generally resolved within a mean of 3.6 days (Pain) to 10.6 days (Lip Pain). Lip Disorder, which included primarily bumps on the lips, showed the longest duration with a mean of 49 days.

Table 10: Duration of Treatment Emergent Adverse Events – Safety Population

System Organ Class/ Preferred Term	Duration (Days)	No Treatment at Baseline (N=44)	1st Treatment *Restylane Silk* (N=218)	2nd Treatment *Restylane Silk* (N=133)
Any TEAE				
	N	11	168	83
	Mean	15.2 (28.8)	17.7 (29.0)	9.7 (8.3)
	Median	6.0	10.0	7.0
	Range	1, 101	1, 174	1, 38
Gastrointestinal Disorders				
Lip Disorder	N	0	10	1
	Mean	-	49.1 (44.4)	27.0 (-)
	Median	-	38.5	27.0
	Range	-	1, 124	27, 27
Lip Pain	N	0	21	9
	Mean	-	10.6 (14.5)	5.2 (2.3)
	Median	-	7.0	6.0
	Range	-	3, 71	2, 8
Lip Swelling	N	0	94	46
	Mean	-	7.3 (4.1)	7.4 (8.1)
	Median	-	6.0	5.0
	Range	-	2, 21	1, 38
General Disorders and Administrative Site Conditions				
Pain	N	0	18	4
	Mean	-	3.6 (2.3)	3.5 (1.9)
	Median	-	3.0	3.0
	Range	-	1, 9	2, 6
Injury, Poisoning, and Procedural Complication				
Contusion	N	0	96	41
	Mean	-	8.4 (3.9)	8.6 (5.9)
	Median	-	8.0	7.0
	Range	-	2, 20	3, 32
Nervous System Disorders				
Headache	N	4	10	2
	Mean	2.8 (2.9)	1.6 (1.1)	1.0 (0.0)
	Median	1.5	1.0	1.0
	Range	1, 7	1, 4	1, 1

Evaluation of adverse events for subjects with Fitzpatrick skin types IV, V, and VI and subjects less than 36 years of age showed no unique adverse events associated with these subgroups. In addition, the incidence and severity of adverse events was similar to that reported in the general population.

There were 5 serious adverse events in three patients during the study. In the No Treatment group there were incidences of Clostridial Infection (n=1), and Urinary Tract Obstruction (n=1). In the Restylane Silk group there were Cystitis (n=1), Intervertebral Disc Protrusion (n=1), and Nephrolithiasis (n=1).

Adverse outcomes reported in the Patient Diaries by severity are presented In Table 11. A majority of the upper and lower lip symptoms for each treatment cycle were considered tolerable, and a majority of subjects did not experience itching following first or second treatment. Disabling symptoms were reported in the upper lip and lower lip by 11% and 7%,

respectively, of subjects after their first treatment with Restylane Silk and 8% and 6%, respectively, of subjects after their second treatment with Restylane Silk. Most of the disabling symptoms were related to lip swelling which resolved in most subjects within 14 days. The percentage of subjects reporting symptoms and the severity of the symptoms generally reduced with repeat treatment.

Table 11: Overall Summary of Selected Adverse Events as Reported in Subject's Diary by Maximum Severity – Safety Population

System Organ Class/ Preferred Term	Treatment Group		
	No Treatment at Baseline (N=44)	**First Treatment with *Restylane Silk* (N=218)**	**Second Treatment with *Restylane Silk* (N=133)**
Upper and Lower Lip Combined			
Maximum Severity Reported for Any Diary AE			
n	42	215	128
None	41 (98%)	2 (<1%)	2 (2%)
Tolerable	1 (2%)	102 (47%)	74 (58%)
Affects Daily Activities	0	86 (40%)	40 (31%)
Disabling	0	25 (12%)	12 (9%)
Bruising			
None	42 (100%)	39 (18%)	39 (30%)
Tolerable	0	142 (66%)	74 (58%)
Affects Daily Activities	0	25 (12%)	14 (11%)
Disabling	0	9 (4%)	1 (<1%)
Redness			
None	42 (100%)	63 (29%)	39 (30%)
Tolerable	0	129 (60%)	79 (62%)
Affects Daily Activities	0	19 (9%)	9 (7%)
Disabling	0	4 (2%)	1 (<1%)
Swelling			
None	41 (98%)	2 (<1%)	4 (3%)
Tolerable	1 (2%)	111 (52%)	76 (59%)
Affects Daily Activities	0	84 (39%)	38 (30%)
Disabling	0	18 (8%)	10 (8%)
Pain			
None	41 (98%)	48 (22%)	28 (22%)
Tolerable	1 (2%)	123 (57%)	82 (64%)
Affects Daily Activities	0	38 (18%)	13 (10%)
Disabling	0	6 (3%)	5 (4%)
Tenderness			
None	41 (98%)	16 (7%)	10 (8%)
Tolerable	1 (2%)	146 (68%)	93 (73%)
Affects Daily Activities	0	48 (22%)	20 (16%)
Disabling	0	5 (2%)	5 (4%)
Itching			
None	42 (100%)	151 (70%)	91 (71%)
Tolerable	0	59 (27%)	35 (27%)
Affects Daily Activities	0	5 (2%)	2 (2%)
Disabling	0	0	0

Note: Percentages are based on the number of Subjects in the Safety Population with any non-missing assessment for location and parameter (if applicable).

The durations of symptoms reported in subject diaries are summarized in Table 12. For subjects that received either one or two treatments with Restylane Silk, the vast majority of all symptoms for the both the upper and lower lips resolved within 2-7 days of treatment. Furthermore, the duration profiles are similar between first treatment and second treatments with Restylane Silk.

Table 12: Duration of Selected Adverse Events as Reported in the Subject's Diary – Safety Population

Location/ Adverse Event	No Treatment at Baseline (N = 44)				
	Number of Days				
	Any[1] n (%)	1 n (%)	2-7 n (%)	8-13 n (%)	14 n (%)
Upper and Lower Lip Combined					
Bruising	0	0	0	0	0
Redness	0	0	0	0	0
Swelling	1 (2%)	0	1 (100%)	0	0
Pain (includes Burning)	1 (2%)	1 (100%)	0	0	0
Tenderness	1 (2%)	1 (100%)	0	0	0
Itching	0	0	0	0	0
	First Treatment with *Restylane Silk* (N = 218)				
	Number of Days				
	Any[1] n (%)	**1 n (%)**	**2-7 n (%)**	**8-13 n (%)**	**14 n (%)**
Upper and Lower Lip Combined					
Bruising	176 (81%)	10 (6%)	130 (74%)	34 (19%)	2 (1%)
Redness	152 (70%)	40 (26%)	97 (64%)	15 (10%)	0
Swelling	213 (98%)	9 (4%)	149 (70%)	40 (19%)	15 (7%)
Pain (includes Burning)	167 (77%)	43 (26%)	110 (66%)	13 (8%)	1 (<1%)
Tenderness	199 (91%)	17 (9%)	132 (66%)	41 (21%)	9 (5%)
Itching	64 (29%)	21 (33%)	34 (53%)	7 (11%)	2 (3%)
	Second Treatment with *Restylane Silk* (N = 133)				
	Number of Days				
	Any[1] n (%)	**1 n (%)**	**2-7 n (%)**	**8-13 n (%)**	**14 n (%)**
Upper and Lower Lip Combined					
Bruising	89 (67%)	6 (7%)	65 (73%)	17 (19%)	1 (1%)
Redness	89 (67%)	18 (20%)	64 (72%)	7 (8%)	0
Swelling	124 (93%)	2 (2%)	96 (77%)	20 (16%)	6 (5%)
Pain (includes Burning)	100 (75%)	26 (26%)	70 (70%)	4 (4%)	0
Tenderness	118 (89%)	8 (7%)	88 (75%)	19 (16%)	3 (3%)
Itching	37 (28%)	8 (22%)	21 (57%)	8 (22%)	0

[1] Percentages are based on the number of subjects in the Safety population.
Note: Percentages are based on the number of subjects reporting the symptom for the specified lip, unless otherwise noted.
Note: Second Treatment With *Restylane Silk* column only includes diary summaries from subjects who actually received a second treatment at 6 months.

Nine subjects reported events that were coded to either Oral Herpes or Herpes Simplex. All events of Herpes events were reported as mild. In two of the nine subjects the outbreak was reported as related to the device and in five subjects the outbreak was reported as due to the procedure. Three subjects had outbreaks that were not contemporaneous with treatment. Two of these subjects had reported prior outbreaks of Herpes. In summary, nine subjects reported Oral

Herpes or Herpes Simplex during the study. Of these nine subjects, five had a history of Herpes outbreaks prior to study start. Six of the nine subjects reported an outbreak of Herpes within 5 days after treatment with Restylane Silk.

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 13.

Table 13. 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.

For Restylane Silk subjects most (90%) had normal upper and lower lip texture at all-time points. For those subjects that were assessed with abnormal upper or lower lip texture (n=18) at any point, all but one were rated as mild, and one was rated as moderate in the lower lip at Week 8. For this subject, the lower lip assessment returned to normal within four weeks.

Subjects in both groups were treated at 6 months (Week 24) either as a first time or retreatment session. The upper and lower lip texture assessments were similar between the groups at 2 and 4 weeks after the 6 month treatment, with a majority of subjects in each group having normal lip texture (99%). For subjects with abnormal upper or lower lip texture that received their first or second treatment at 6 months, all were rated as mild.

Lip firmness was judged via the criteria presented in Table 14.

Table 14: Lip Firmness Scoring Criteria

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

Nearly all Restylane Silk subjects (>93%) had normal upper and lower lip firmness at all assessment time points. For those subjects that were assessed with abnormal lip firmness at any point, almost all were rated as mild. There were two subjects in the No Treatment group and six subjects in the Restylane Silk treatment group that had moderate abnormal lip firmness in the upper and/or lower lip 72 hours after the 6 month treatment. By the Week 2 visit after the 6 month treatment the abnormal firmness reduced to mild in all of these subjects and by Week 4 after the 6 month treatment all but 1 subject in each treatment group returned to normal. In addition, there were no subjects with severe abnormal upper or lower lip firmness at any point in the study.

All subjects in the No Treatment group at baseline had normal upper and lower lip firmness through Week 24. Subjects in this group received their first treatment with Restylane Silk at Week 24 (6 months), and the upper and lower lip firmness assessments were consistent with those subjects in the Restylane Silk treatment group at post-treatment time points.

Lip symmetry was judged with the criteria presented in Table 15.

Table 15: 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.

In the Restylane Silk treatment group, 8 subjects had mild upper lip asymmetry at baseline and two subjects had a mild lower lip asymmetry at baseline. Following treatment at baseline, a vast majority of subjects had normal upper and lower lip symmetry throughout the course of the study, and of those that had abnormal upper (n=57) or lower lip (n=29) symmetry most were

considered to be mildly abnormal. Only one subject was reported to have moderately abnormal lip symmetry at 72 hours after initial treatment and at the first touch-up visit and one subject had moderately abnormal lip symmetry at 72 hours after the second treatment. Both of these subjects had mild abnormal lip symmetry by the 2 week post-treatment visit. No subjects were reported to have severe lip asymmetry (>2 mm) at any time point during the study. No subjects in the No Treatment group reported abnormal lip symmetry through Week 24. After treatment, up to 5 subjects reported to mild lip asymmetry in the upper or lower lip after their first treatment at 6 months. There was no moderately or severely abnormal lip symmetry reported for any subjects at any time point.

Lip movement was tested by the ability to pronounce a preselected series of words. In three cases subjects were unable to pronounce all the words. All subjects were able to pronounce all the words over the period of the study at all visits demonstrating the lip augmentation with Restylane Silk does not impact lip movement.

Lip function was tested by assessing a subject's ability to suck liquid through a straw. All subjects in both groups at all assessment time points were able to complete this activity demonstrating the lip augmentation with Restylane Silk does not impact lip function.

Lip sensation was tested via: 1) the monofilament test (i.e., a subject's ability to feel the sensation of a 0.4G monofilament at three points on the upper lip and three points on the lower lip) and 2) the cotton wisp test (i.e., a subject's ability to feel the sensation of a cotton wisp at three points on the upper lip and three points on the lower lip). Lip sensation was not affected in the monofilament test for almost all subjects at all-time points. For three subjects, the lack of sensation occurred most frequently 72 hours after treatment. There was no specific pattern to which lip or which site on either lip did not have sensation. In the cotton wisp test there were very few instances of loss of sensation by this method (3 events reported by 2 subjects). As with the monofilament test this lip sensation test shows that subjects treated with Restylane Silk do not lose their ability to detect the sensation of touch.

Device palpability in the lips was assessed by a qualified study staff member (other than the treating investigator and blinded evaluator) at all post-treatment time points. The assessor determined palpability by answering the following question: 'Is the product palpable? If yes, is this the expected feel or unexpected feel (non-uniform density or unexpected lumpiness) for the product?

For subjects in the Restylane Silk treatment group, the device was palpable with the expected feel for both the upper and lower lips for a majority of subjects through Week 24 (ranging from (76% - 97%)). Device palpability also decreased over time. Additionally, there were very few subjects (≤ 3%) in the Restylane Silk treatment group that had unexpected feel of the product. In instances of unexpected feel, the treatment for resolution was for the lips to be massaged to help create more uniform density.

Subjects in the No Treatment group were eligible for their first treatment with Restylane Silk at Week 24 (6 Months), and at time points following treatment the device was palpable for almost all subjects (ranging from 88% to 100%). There were reports of an unexpected feel in 2 subjects

72 hours after their first treatment at 6 months. By 2 weeks after the treatment, all of the palpability was reported as an expected (normal) feel.

In the Restylane Silk group, there was infrequent detection of lip masses throughout the study. The majority of masses (17/24; 71%) were detected after the second treatment with Restylane Silk. However, by 4 weeks after the 6 month treatment lip mass formation was only detected in 3 subjects (1.3%). Lip mass formation can often be confused with the feel of the implanted device.

Lip mass was not detected in any subject in the No Treatment group through Week 24. At 72 hours after the 6 month treatment 2 subjects had mass formation in the upper lip and one subject in the lower lip. By 4 weeks after the 6 month treatment no mass was detected in any of the No Treatment group subjects.

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 all of the subjects (100%) the second treatment was not more difficult to complete.

Subjects (44/177) that were eligible to receive re-treatment did not receive treatment at the Month 6 treatment visit. Of these 44 subjects, 11 subjects were lost to follow-up (LTFU) and six subjects withdrew consent prior to Visit 10. 27 subjects who were potentially able to receive treatment at Month 6 were untreated. The reasons for the 27 untreated subjects at Month 6 in the Restylane Silk arm are as follows: 1) subject satisfied with first treatment (n=7), 2) subject refused due to AE with first treatment (n=6), 3) subject decision not to have re-treatment (n= 12) and no reason given (n=2).

There was a higher proportion of AEs reported in subjects receiving more than 3 mL of Restylane Silk. For this reason the label was revised to state: "Injections of 3.0 mL or greater (upper and lower lip combined) per treatment session increased the occurrence of injection site reactions. If a volume of more than 3 mL is needed to achieve optimal correction, a follow-up treatment is recommended."

2. Effectiveness Results

Primary Effectiveness Endpoint Results:

Analysis of the primary endpoint included subjects with a baseline MLFS score of 1 or 2. The results of the primary effectiveness endpoint are presented in Table 16.

Table 16: 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 Silk	172	138 (80.2%)	
	No Treatment	42	5 (11.9%)	
	Difference	--	68.3%	< 0.001
Lower Lip				
Week 8	Restylane Silk	152	128 (84.2%)	
	No Treatment	38	7 (18.4%)	
	Difference	--	(65.8%)	< 0.001
Upper and Lower Lip Combined				
Week 8	Restylane Silk	176	134 (76.1%)	
	No Treatment	43	5 (11.6%)	
	Difference		(64.5%)	< 0.001

* A Responder was defined as a 1 grade or more change from baseline on the MLFS.
Subjects with a missing Blinded Evaluator assessment at 8 week were imputed using the hot deck method.
Only subjects with a baseline score of 1 or 2 were included in the analyses.

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

Secondary Effectiveness Endpoints Outcomes

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

Table 17 presents a summary of the absolute change in MLFS from Baseline for Upper and Lower Lips at Week 8.

Table 17: 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 Silk (N=135)	
		Observed	Change from Baseline	Observed	Change from Baseline
Upper Lip					
Week 8	n	39	39	121	121
	Mean (S.D.)	1.9 (1.0)	0.5 (0.8)	3.4 (1.0)	2.1 (1.0)
	Median	2.0	0.0	3.0	2.0
	Min, Max	1,4	0, 3	1, 5	-1, 4
	P-value	--	--	--	<0.001
Lower Lip					
Week 8	n	35	35	111	111
	Mean (S.D.)	1.9 (0.8)	0.4 (0.6)	3.4 (0.9)	1.8 (0.9)
	Median	2.0	0.0	3.0	2.0
	Min, Max	1, 3	0, 2	1, 5	-1, 4
	P-value	--	--	--	<0.001

A Blinded Evaluator determination of MLFS score was performed at Weeks 12, 16, 20, and 24, as well as 2 and 4 weeks after the Week 24 re-treatment. Success was defined as at least one grade increase from Baseline to the measurement time point for both the upper and lower lips. The statistical difference in the proportion of Restylane Silk and No Treatment Responders (based on the MLFS scores) was evaluated using Fisher's exact tests. The difference in the proportion of Restylane Silk and No Treatment MLFS Responders was significant at all time points, when upper and lower lips were evaluated separately or combined. Table 18 presents the Blinded Evaluators' MLFS scores from Weeks 12- 24 when upper and lower lip outcome measures were combined.

Table 18: Proportion of MLFS Responders from Baseline in Upper and Lower MLFS as Measured by the Blinded Evaluator

Assessment/Time point	Treatment Group	Number Subjects in ITT	# (%) responders*	p-value
Upper and Lower Lip combined				
Week 12 (Secondary)	Restylane Silk	167	122 (73.1%)	
	No Treatment	40	4 (10.0%)	
	Difference	--	63.1%	< 0.001*
Week 16 (Secondary)	Restylane Silk	164	112 (68.3%)	
	No Treatment	40	5 (12.5%)	
	Difference	--	55.8%	< 0.001*
Week 20 (Secondary)	Restylane Silk	161	103 (64.0%)	
	No Treatment	41	6 (14.6%)	
	Difference	--	(46.4%)	< 0.001*
Week 24 (Secondary)	Restylane Silk	160	99 (58.8%)	
	No Treatment	40	8 (20%)	
	Difference	--	(38.8%)	< 0.001*

The blinded evaluator assessed the appearance of upper perioral rhytids according to the WASULL scale at each visit for which the MLFS was assessed. The proportion of responders as assessed with at least one grade improvement from baseline in subjects treated for lip augmentation and perioral rhytids was 56.5% of subjects at Week 8, 61.3% at Week 12, 59.0% at

Week 16, 47.5% at Week 20, and 57.6% at Week 24. At 2 and 4 weeks after the 6 month treatment, response improved to 70.4% and 73.7%, respectively. In the group of subjects receiving treatment for lip augmentation only, response was seen in 20.9% of subjects at Week 8, 22.9% at Week 12, 21.4% at Week 16, 20.6% at Week 20 and 22.8% at Week 24. At 2 and 4 weeks after the 6 month treatment, response in the no treatment group was 26.0% and 29.7%, respectively.

A Fischer's Exact test comparing subjects receiving treatment for lip augmentation and perioral rhytids to those subjects receiving treatment for lip augmentation only was statistically significant ($p<0.001$) at all evaluations in favor of subjects receiving the treatment for augmentation and perioral rhytids.

An analysis was conducted to evaluate the improvement in upper perioral rhytids when comparing lips that were treated for augmentation and for perioral rhytids to those that were treated for lip augmentation only. This analysis demonstrated that when subjects were treated for improvement in upper perioral rhytids in addition to lip augmentation, there was statistically significant improvement observed in perioral rhytids.

3. Subgroup Analyses

52 subjects with Fitzpatrick Type IV and V skin were enrolled in the study of which ten were initially randomized to No Treatment. 50 patients received a single Restylane Silk treatment series at Baseline or at the Week 24 visit and 37 patients received a Restylane Silk re-treatment series at Week 24. As with the overall population, the incidence of subjects with TEAEs decreased from the first to the second treatment with Restylane Silk at 76% and 65%, respectively. The common TEAEs were lip disorder, lip pain, lip swelling and contusion. The incidence of these events was similar to the overall population. Table 19 summarizes the TEAEs experienced in 5% or greater of patients with Fitzpatrick Skin Types IV and V.

Table 19: Summary of Treatment Emergent Adverse Events Occurring in ≥ 5% of Subjects for Fitzpatrick Skin Types IV, V, and VI – Safety Population

System Organ Class/ Preferred Term	Treatment Group					
	No Treatment at Baseline (N=10)		First Treatment with SPHAL (N=50)		Second Treatment with SPHAL (N=37)	
	Events	Subjects[1]	Events	Subjects[1]	Events	Subjects[1]
Subjects with Fitzpatrick Skin Types IV, V, and VI						
Any TEAE	2	1 (10%)	116	38 (76%)	49	24 (65%)
Gastrointestinal Disorders						
Lip Disorder	0	0	4	3 (6%)	1	1 (3%)
Lip Pain	0	0	13	8 (16%)	10	7 (19%)
Lip Swelling	0	0	33	20 (40%)	18	12 (32%)
General Disorders and Administration Site Conditions						
Pain	0	0	6	3 (6%)	2	1 (3%)
Infections and Infestations						
Clostridial Infection	1	1 (10%)	0	0	0	0
Oral Herpes	0	0	1	1 (2%)	2	2 (5%)
Injury, Poisoning and Procedural Complications						
Contusion	0	0	32	24 (48%)	13	13 (35%)
Renal and Urinary Disorders						
Urinary Tract Obstruction	1	1 (10%)	0	0	0	0

[1] A subject with more than one treatment emergent adverse event within a system organ class and/or preferred term is only counted once.

Note: For the No Treatment at Baseline group an adverse event is considered treatment emergent if the start date is on or after the Visit 2 (Day 0) date. For the First Treatment with SPHAL group an adverse event is considered treatment emergent if the start date is on or after the date of initial treatment injection. For the Second Treatment with SPHAL group an adverse event is considered treatment emergent if the start date is on or after the date of the second treatment injection.

Note: Percentages are based on the number of Subjects in the Safety population.

Note: No Treatment at Baseline includes subjects who did not receive an initial injection at Visit 2.

The study enrolled 61 subjects ≤ 35 years of age. Six subjects were randomized to No Treatment and 52 subjects were either randomized to treatment with Restylane Silk or were enrolled in the Restylane Silk group (not randomized). 52 patients received a single Restylane Silk treatment at Baseline or at the Week 24 visit and 39 patients received re-treatment with Restylane Silk at Week 24. As with the overall population, the incidence of subjects with TEAEs was 83% after the first and 72% after the second treatment with Restylane Silk. The common TEAEs were lip blister, lip pain, lip swelling, pain, contusion and skin exfoliation. Evaluation of adverse events for subjects ≤ 35 years of age showed no unique adverse events associated with this subgroup and the incidence and severity of adverse events was similar to that reported in the general population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 14 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections

54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

X. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

- **Relevant Post Market Experience**

Review of the global postmarketing safety database was performed to identify additional safety information about the previous use of Restylane Vital Lidocaine (a.k.a. Restylane Silk) for lip augmentation. The Global Postmarketing Safety Database was reviewed for adverse events in general and the lip area-adverse events in specific from August 2011 to December 2012. The most commonly reported events were implant site swelling, pain/tenderness, inflammation, mass (lumps, bumps), erythema, papules/modules, infection/abscess, and bruising/bleeding. The events generally occurred immediately after treatment and the majority were mild or moderate in severity. These events appeared similar to the adverse events observed in the US pivotal study. Table 20 compares the incidence of Restylane Vital Lidocaine adverse events from August 2011 to December 2012 after injection in any location and injection specifically in the lips.

Table 20. Restylane Vital Lidocaine Adverse Events Potentially Related to Treatment

	All locations		Lip	
Adverse Event	**No.**	**%**	**No.**	**%**
Swelling	38	0.022	7	0.004
Pain/Tenderness	9	0.005	0	0
Inflammation	8	0.005	1	0.001
Mass/Induration	7	0.004	0	0
Erythema	6	0.003	0	0
Papules/Nodules	6	0.003	0	0
Infection/Abscess	4	0.002	2	0.001
Bruising/Bleeding	3	0.002	0	0
Non Dermatological Events	3	0.002	0	0
Discolouration	2	0.001	0	0
Capillary Disorder	1	0.001	0	0
Device Ineffective	1	0.001	0	0
Eye Disorders	1	0.001	0	0
Hypersensitivity	1	0.001	0	0
Injection Site Reactions	1	0.001	0	0
Ischemia/Necrosis	1	0.001	0	0
Rash	1	0.001	1	0.001

Adverse events that occurred at the injection site beyond 24 hours up to months after injection included: swelling, oedema, pain, inflammation, induration, nodule, erythema, device ineffective, abscess, necrosis, and papules.

While there have been no reports of blindness or visual impairment in the *Restylane Silk* or other previous Restylane/Perlane premarket studies, review of the Post Market Surveillance reports indicated that rare reports of visual impairment or blindness have occurred after Restylane or

Perlane injections. Subsequent to review of these reports the sponsor amended the Patient Brochure and the Instructions for Use labels to describe these events. In addition, the following Warning was added to the Package Insert.

"As with all dermal filler procedures, *Restylane Silk* should not be used in vascular rich areas. Use of similar products in these areas, such as glabella and nose, has resulted in cases of vascular embolization and symptoms consistent with ocular vessel occlusion, such as blindness. For additional information please see the Post-Marketing Surveillance in Adverse Events."

XI. ***PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION***

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

XII. ***CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES***

A. Effectiveness Conclusions

Assessment of product effectiveness is based on the results of Pivotal Study MA-1700-04. These submitted data provided a reasonable assurance that the device is effective for use in lip augmentation in patients over the age of 21. The specific conclusions are:

- The study met the pre-specified primary effectiveness criterion. In the Restylane Silk group at week 8, 80.2% (138/172) of the subjects were upper lip responders and 84.2% (128/152) of the subjects were lower lip responders. In the No Treatment group at week 8, 11.9% (5/42) of the subjects were upper lip responders and 18.4% (7/38) of the subjects were lower lip responders as assessed by the blinded evaluator using the MLFS ratings. For upper and lower lips combined, 76.1% (134/176) of the subjects responded to Restylane Silk at week 8 and 11.6% (5/43) of the no treatment subjects were responders at week 8. Each of these differences was statistically significant.

- The study met the pre-specified secondary effectiveness endpoints for lip augmentation, i.e., the proportion of responders when comparing Restylane Silk to No Treatment cohorts was statistically significantly improved for: 1) the Blinded Evaluators' MLFS ratings from weeks 12 to 24 and 2) the subjects' GAIS scores from weeks 2 to 24.

- Lip augmentation was consistently effective when evaluating subjects with Fitzpatrick skin types IV, V, and VI and subjects under the age of 35 years of age compared to the overall population.

- For subjects receiving additional injections for correction of perioral rhytids, there was a statistically significant and clinically meaningful improvement in perioral rhytids as assessed by the Blinded Evaluator at weeks 8 to 24.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and/or animal studies, data collected in a clinical study conducted to support PMA approval as described above and an evaluation of the Post Market Surveillance reports outside the U.S. The specific conclusions are:

- Of the 221 subjects enrolled in the study, 218 subjects received their first treatment with Restylane Silk at either baseline/Day 0 or at 6 months, and 133 subjects received their second treatment at 6 months. 78% of subjects receiving their first treatment reported a total of 632 TEAE while 63% of subjects that received a second treatment reported a total of 196 TEAEs. Most of these TEAEs were mild in intensity after either the first treatment sessions (540/632; 85%) or the repeat treatment sessions at 6 months (i.e., 178/196; 91%).

- A majority of the commonly reported TEAEs were lip pain, lip swelling, and contusion. These TEAEs typically began within a day of being treated and the events were transient in nature, resolving in a mean of 18 days or less. The mean time to onset was similar for subjects receiving first or follow-up treatments with Restylane Silk.

- A majority of subjects received a combination of injection methods, such as linear retrograde and linear antegrade. The incidence of the TEAEs was independent of the methods of injection. A vast majority of subjects were given submucosal injections. Commonly reported TEAEs with this depth of injection were similar to those reported by the study population as a whole. Very few subjects received a different depth of injection for their first or second treatments with Restylane Silk; therefore no conclusions can be drawn from this data due to the low number of "other" depth of injection subjects.

- Lips treated for perioral rhytids showed a safety profile similar to the overall population.

- For subjects with Fitzpatrick skin types IV and V, the common TEAEs of lip pain, lip swelling, and contusion, and were reported in similar proportions to the overall population. For subjects less than 35 years of age, the common TEAEs of lip pain, lip swelling, and contusion, and were also reported in similar proportions to the overall population.

- Specific anticipated events (bruising, redness, swelling, pain, tenderness, itching, and other) were collected in the first 14 days following baseline/Day 0 and at 6 months in the subject diary. A majority of symptoms for each treatment were considered tolerable. Most of the disabling symptoms were related to lip swelling which resolved in most subjects within 14 days. For subjects that received either one or two treatments with Restylane Silk, the vast majority of all symptoms for the both the upper and lower lips resolved within 2-7 days of treatment.

- Lip safety assessments, such as lip texture, firmness, symmetry, movement, function, sensation, mass formation, and device palpability were evaluated at the screening visit

and throughout the study. None of the lip assessments were remarkable or presented any safety concerns.

- There were no deaths reported during the study and no subject discontinued due to an adverse event. Five SADEs were reported in three subjects during the study. All of the events resolved and were considered to be unrelated to either the study device or the injection procedure.

C. Benefit-Risk Conclusions

- The probable benefits of the device are based on data collected in a clinical study conducted to support PMA approval as described above. The study was a well-designed prospective, no-treatment controlled study using a validated scale and blinded, live evaluations. The data are considered to be as robust as possible for an aesthetic endpoint. In the Restylane Silk and No Treatment groups at Week 8, 76.1% and 11.6% of the patients, respectively, were responders when the results of the upper and lower lip assessments were combined. The duration of effect evaluated by responder rate at 6 months was 58.8% for Restylane and 20% for No Treatment patients. Regarding the benefit derived from treatment of Perioral Rhytids, in the Restylane Silk and No Treatment groups at Week 8, 56.5% and 20.9% of the patients, respectively, were responders when the results of the upper and lower lip assessments were combined. The duration of effect evaluated by responder rate at 6 months was 57.6% for Restylane and 22.8% for No Treatment patients. The findings of the primary effectiveness assessment were supported by the secondary endpoints. The subjects' rating themselves as improved or better from baseline on the GAIS was 97.4% at Week 2, 95.1% at Weeks 4 and 8, 90.0% at Week 12, 82.9% at Week 16, 85.4% at Week 20 and 87.2% at Week 24. The majority of the patients elected to undergo retreatment, indicating that they perceive a benefit and that they would like continued benefit.

- Additional factors to be considered in determining probable risks and benefits for Restylane Silk injection included: almost all (98%) of the patients reported adverse outcomes in a Patient Diary (i.e., Tenderness, Swelling, Firmness, Lumps/Bumps, Bruising, Pain, Redness, and Itching). 13.3% of patients reported adverse outcomes in a Patient Diary lasting longer than 14 days. 3 patients had swelling, lumps or bumps which developed more than six weeks after treatment. Seventy-eight percent (169/281) of subjects receiving their first treatment experienced a total of 632 treatment-emergent adverse events (TEAEs) (as judged by the Treating Investigator) and 63% (84/133) of the subjects that received a second treatment reported a total of 196 TEAEs. Most of these TEAEs were mild in intensity (540/632; 85%, and 178/196; 91%; first and second treatment respectively), and were transient in nature, resolving in a mean of 17.4 days (median 10 days). The most common TEAEs occurring after initial treatment were lip swelling (43%), contusion (44%), and lip pain (10%). There was no increased risk with additional treatment with Restylane Silk. After the second treatment, the reported incidence decreased to 35%, 31%, and 7%, respectively. Nineteen subjects reported TEAEs whose onset was more than 3 weeks after a Restylane Silk injection. There were a total of 35 events in the lip reported in these 19 subjects. Most of the events were Lip Swelling (26/35; 745) and also included Lip Disorder (6/35; 17%), Lip Pain/Pain 2/35; 6%), and Contusion (1/35; 3%). None of the events were reported as serious

and all of the events were reported as either mild (24/35; 69%) or moderate (11/35; 31%). Rare risks include vascular occlusion (including ocular) from embolization and infection. Neither was seen in this pivotal study of 221 treated patients.

- In conclusion, given the available information above, the data support the use of Restylane Silk for submucosal implantation for lip augmentation and dermal implantation for correction of perioral rhytids in patients over the age of 21 and the probable benefits outweigh the probable risks, as determined by the short term adverse outcomes and the rare late adverse events seen after injection, balanced against the improvement seen on the Medicis Lip Fullness, Perioral Rhytid and Patient Satisfaction Scales.

D. Overall Conclusions

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

XIII. CDRH DECISION

CDRH issued an approval order on June 13, 2014.

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order