SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Injectable Dermal Filler

Device Trade Name: *Restylane® Kysse*

Device Procode: LMH

Applicant's Name and Address:

Q-Med AB, a Galderma affiliate
Seminariegatan 21
SE-752 28 Uppsala, Sweden

Galderma Research and Development, LLC, a Galderma affiliate
14501 North Freeway
Fort Worth, TX 76177

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P140029/S021

Date of FDA Notice of Approval: March 26, 2020

The original PMA for *Restylane® Refyne* and *Restylane® Defyne* (P140029) was approved on December 9, 2016. *Restylane® Refyne* is indicated for injection into the mid-to-deep dermis for the correction of moderate to severe facial wrinkles and folds (such as nasolabial folds) in patients over the age of 21 and *Restylane® Defyne* is indicated for injection into the mid-to-deep dermis for the correction of moderate to severe, deep facial wrinkles and folds (such as nasolabial folds) in patients over the age of 21.

The SSED to support the prior indication is available on the CDRH website and is incorporated by reference here. *Restylane® Kysse* is being submitted as a panel-track supplement (P140029/S021) to the *Restylane® Refyne* and *Restylane® Defyne* PMA (P140029). The current supplement was submitted for *Restylane® Kysse* to include injection into the lips for lip augmentation and for correction of upper perioral rhytids in patients over the age of 21.

II. INDICATIONS FOR USE

Restylane® Kysse is indicated for injection into the lips for lip augmentation and the correction of upper perioral rhytids in patients over the age of 21.

III. CONTRAINDICATIONS

- *Restylane® Kysse* is contraindicated for patients with severe allergies such as manifested by a history of anaphylaxis or history or presence of multiple severe allergies.

- *Restylane® Kysse* may contain trace amounts of gram-positive bacterial proteins and is contraindicated for patients with a history of allergies to such material.

- *Restylane® Kysse* contains lidocaine and is contraindicated for patients with a history of allergies to such material.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the *Restylane® Kysse* physician labeling.

V. DEVICE DESCRIPTION

Restylane® Kysse is a sterile, biodegradable, viscoelastic, non-pyrogenic, clear, colorless, flexible and homogeneous gel composed of hyaluronic acid of bacterial origin, with a moderate lifting capacity. *Restylane® Kysse* is crosslinked with BDDE (1,4-butanediol diglycidylether). The product has a sodium hyaluronate concentration of 20 mg/mL in phosphate buffered saline at pH 7 and contains 3 mg/mL lidocaine hydrochloride.

The gel is supplied in a prefilled plastic syringe. The contents of the syringe are sterilized using moist heat. The syringe is packaged individually in a blister, with two 30G x ½" ultra-thin wall (UTW) needles.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are other approved injectable gels and procedures in the United States for lip augmentation and correction of perioral rhytids such as fat grafting, implants, and surgical lip lifts. 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® Kysse was approved for marketing and sale in the European Union (EU) in January 2010. The product has since been approved in multiple countries globally; Argentina, Armenia, Australia, Azerbaijan, Bahrain, Belarus, Brazil, Canada, Chile, Colombia, Ecuador, Egypt, El Salvador, EU/EFTA, Guatemala, Hong Kong, India, Indonesia, Israel, Kazakhstan, Kuwait, Lebanon, Macedonia, Malaysia, Mauritius, Mexico, Moldova, Morocco, New Zealand, Nicaragua, Philippines, Qatar, Saudi Arabia, Serbia, Singapore, South Africa, Taiwan, Tunisia, Turkey, Ukraine, United Arab Emirates, and Vietnam. *Restylane® Kysse* has not been removed from the marketplace for any reasons related to safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

Injection site reactions events such as bruising, erythema, itching, swelling, pain, lumps/bumps, discoloration, and tenderness are anticipated and expected to generally resolve spontaneously within one week after injection. Lumps/bumps may last longer, but typically resolve in less than 30 days.

For the specific adverse events that occurred in the clinical studies, please see Section 10 below.

Post-marketing surveillance

The adverse events received from post-marketing surveillance (voluntary reporting and published literature) for the use of *Restylane*® *Kysse* with and without lidocaine from worldwide sources mostly include reports of transient swelling/edema with immediate onset or delayed onset, one to three months after treatment.

The following events were also reported in decreasing order of frequency (non-exhaustive list):

- Mass/induration,
- Device ineffective,
- Papules/nodules,
- Pain/tenderness,
- Bruising/bleeding,
- Ischemia/necrosis including pallor and vascular occlusion,
- Erythema,
- Discoloration,
- Inflammation,
- Hypersensitivity/angioedema,
- Blisters/vesicles,
- Infection/abscess including purulent discharge and pustules,
- Injection site reactions such as warmth and burning sensation,
- Pruritus,
- Neurological symptoms such as hypoesthesia and paresthesia,
- Device dislocation,
- Eye disorders such as lacrimation increased,
- Rash,
- Scar/scab/skin atrophy,
- Capillary disorder including capillary fragility and telangiectasia,
- Reactivation of herpes infection,
- Urticaria,
- Acne,
- Dermatitis,
- Discharge,
- Granuloma/foreign body reaction,
- Overcorrection/asymmetry,
- Non-dermatological events including insomnia, discomfort and dyspnea,
- Other dermatological events such as dry skin and skin tightness.

Symptoms of inflammation at the implant site commencing either shortly after injection or after a delay of one to three months have been reported.

When required, treatments for the reported post treatment adverse events included corticosteroids, antibiotics, antihistamines, NSAIDs and aspiration/drainage or enzymatic degradation (with hyaluronidase) of the product.

Other potential adverse events that have been reported following injection of hyaluronic acid gels in general and may occur when using the product include the following: visual disturbance and encapsulation.

Reports of serious adverse events are rare. The most commonly reported serious adverse events for *Restylane® Kysse* with 3 or more reports from post-marketing surveillance were ischemia/necrosis and swelling with concurrent events of pain and discoloration.

- Serious ischemia/necrosis was mostly reported with immediate onset up to a few days following the injection. The ischemia/necrosis cases mostly resolved within a week up to a month and almost all patients had recovered or were recovering at the time of last contact. The treatments included hyaluronidase, analgesics, corticosteroids, vasodilation agent, antiviral agent, platelet aggregation inhibitor, antihistamine, aspirin and anticoagulant agent.
- Serious swelling was reported with immediate onset up to a few days following the injection. The outcome was mainly recovered or recovering at the time of last contact. The treatments included: analgesics, antihistamine, antibiotics, corticosteroids and hyaluronidase.

Vascular compromise may occur due to an inadvertent intravascular injection or as a result of vascular compression associated with implantation of any injectable product. This may manifest as blanching, discoloration, necrosis or ulceration at the implant site or in the area supplied by the blood vessels affected; or rarely as ischemic events in other organs due to embolization. Vision abnormalities including blindness have been reported following injection of dermal fillers, including HA, into the nose, glabella, periorbital areas, and/or cheek, with a time to onset ranging from immediate to a few days following injection. Isolated cases of ischemic events affecting the brain resulting in cerebral infarction have also been reported. Reported treatments include anticoagulant, epinephrine, aspirin, hyaluronidase, corticosteroid treatment, analgesics, antibiotics, local wound care, drainage, surgery and hyperbaric oxygen. Outcomes ranged from resolved to ongoing at the time of last contact.

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

Restylane® Kysse has been tested and characterized through physical and chemical analyses according to ISO 10993-18, see Table 1.

To ensure that *Restylane® Kysse* degrades naturally during its clinical lifespan, degradation assays have also been performed.

Table 1 Summary of Key Bench Testing *on Restylane® Kysse*

Test	Purpose	Results
Extrusion force (N)	Ensures extrusion force meets specification	Passed
pH	Ensures pH meets specification	Passed
Rheology (tan δ)	Ensures rheological properties meet specification	Passed
HA concentration (mg/mL)	Ensures HA concentration meets specification	Passed
Gel content (%)	Ensures gel content meets specification	Passed
Lidocaine concentration (mg/mL)	Ensures lidocaine concentration meets specification	Passed
Residual crosslinker (ppm)	Ensures residual crosslinker meets specification	Passed
Endotoxin (EU/mL)	Ensures endotoxin meets specification	Passed
Sterility	Ensures device is sterile	Passed

B. Biocompatibility Studies

A biological evaluation was performed on *Restylane® Kysse* according to ISO 10993-1, Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process. In the evaluation of *Restylane® Kysse*, data from a similar product, *Restylane® Defyne*, was also used to assess the biological safety. *Restylane® Kysse®* and *Restylane® Defyne* are manufactured with the same raw materials, the same manufacturing process, the same primary packaging and the same sterilization process. According to ISO 10993-1, both *Restylane® Kysse* and *Restylane® Defyne* are categorized as implant devices in contact with tissue where the contact duration is more than 30 days.

All tests were performed according to GLP and the requirements of each test were met. The conclusion from the biological testing is that *Restylane® Kysse* is safe for the intended use.

Table 2 Biological tests performed on *Restylane® Kysse* and *Restylane® Defyne*

Biological endpoint/test method		Test standard/guideline	Test product	Test result
Cytotoxicity		ISO 10993-5	*Restylane® Kysse*	Not cytotoxic
Sensitization		ISO 10993-10	*Restylane® Kysse*	Not sensitizing
Intradermal reactivity		ISO 10993-10	*Restylane® Kysse*	No irritation
Systemic toxicity	**Acute systemic toxicity**	ISO 10993-11 USP <88>	*Restylane® Kysse*	No systemic toxicity
	Sub-chronic systemic toxicity, 13 weeks	ISO 10993-11	*Restylane® Defyne*	No systemic toxicity
	Pyrogen study	ISO 10993-11 <USP 151>	*Restylane® Kysse*	No pyrogenic reaction
Genotoxicity	**Ames test**	ISO 10993-3 OECD 471	*Restylane® Defyne*	No mutagenic response
	Mouse lymphoma	ISO 10993-3 OECD 476	*Restylane® Defyne*	No mutagenic response or chromosomal aberration
	Mouse micronucleus	OECD 474	*Restylane® Defyne*	No induction of micro-nuclei was induced in mice

Implantation	**52 weeks intradermal in rabbits**	ISO 10993-6	*Restylane® Kysse*	Minimal to mild irritation at 1 month and minimal at 3, 6 and 12 months
	26 weeks intradermal in rabbits	ISO 10993-6	*Restylane® Kysse*	Minimal or no reaction at 1, 4, 12 and 26 weeks

C. Additional Studies

Filled syringes are sterilized using a validated moist heat process in a pressurized autoclave. The sterilization cycle has been validated according to ISO 17665-1. The validated sterilization cycle provides a minimum Sterility Assurance Level (SAL) of 10^{-6}.

A shelf life of 24 months for *Restylane® Kysse* has been established. The shelf life is based on stability data collected through 24 months at 25°C/40% and 30°C/35% relative humidity, and through 6 months at 40°C/25% relative humidity. At each time point, product was characterized via microbiological, physical, chemical, lidocaine hydrochloride content, and lidocaine-related degradant parameters. Conformance of real-time aged product with all specifications was confirmed.

X. SUMMARY OF CLINICAL STUDIES

The applicant performed a clinical study to establish a reasonable assurance of the safety and effectiveness of the use of *Restylane® Kysse* for injection into the lips for lip augmentation and for the correction of upper perioral rhytids in patients over the age of 21 in the US under IDE G150110. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Subjects were treated between 13 Nov 2017 and 26 Mar 2019. The database for this PMA reflects data collected through 23 Apr 2019, and included 273 subjects at 14 investigational sites in the US.

The pivotal study (43USK1701) was a randomized, controlled, evaluator-blinded, multi-center study to evaluate the effectiveness and safety of *Restylane® Kysse* for lip augmentation and correction of perioral rhytids. A total of 273 subjects were randomized in a 2:1 ratio to treatment with *Restylane® Kysse* or the control. The control is a legally marketed product in the US with a similar indication for use.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the clinical study (43USK1701) was limited to subjects who met the following key inclusion criteria:

- Males or non-pregnant, non-breastfeeding females, 22 years of age or older.
- Score of 1 (Very Thin) or 2 (Thin) on BOTH upper and lower lips on the Medicis Lip Fullness Scale (MLFS) as assessed by the Blinded Evaluator.
- For treatment of the upper perioral lines, subjects with a score of 3 (moderately deep wrinkles) to 5 (very deep wrinkle) on the Wrinkle Assessment Scale (WAS) as assessed by the Blinded Evaluator.

Subjects were not permitted to be enrolled in the clinical study if they met any of the following key exclusion criteria:

- Known/previous allergy or hypersensitivity to any injectable HA gel or to gram positive bacterial proteins.
- History of allergy or hypersensitivity to lidocaine or other amide-type anesthetics, or topical anesthetics or nerve blocking agents.
- Previous use of any permanent (non-biodegradable) or semi-permanent (e.g., synthetic calcium hydroxylapatite or Poly-L-Lactic acid) facial tissue augmentation therapy, lifting threads, permanent implants or autologous fat below the level of the lower orbital rim.
- Previous use of any HA based or collagen based biodegradable facial tissue augmentation therapy below the level of the lower orbital rim within 12 months prior to the baseline visit.

2. Follow-up Schedule

In the pivotal study (43USK1701), qualified subjects were randomized to receive treatment with *Restylane® Kysse* or the control in the upper and lower lips at baseline. Treatment of the upper perioral rhytids, vermillion border, philtral columns, cupid's bow, and/or oral commissures was performed at the discretion of the Treating Investigator in consultation with the subject.

Subjects had scheduled visits 2 and 4 weeks after treatment at baseline. Optional touch-up treatment with the assigned study product was offered at Week 4 if optional correction was not achieved.

Subjects had in-clinic follow up visits to evaluate safety and effectiveness at 2, 4, 8, 16, 24, 32, 40, and 48 weeks after the last injection. At the 48-week visit after all study procedures were completed, all subjects, regardless of randomization assignment at baseline, were offered optional retreatment with *Restylane® Kysse* if optimal aesthetic improvement was not maintained. If retreatment was performed, a 2-week and 4-week follow-up visits were scheduled.

Subjects were contacted by telephone 72 hours after each treatment (i.e., initial, touch-up, optional retreatment at Week 48, as applicable) for safety follow up. Subjects evaluated injection site reactions in a 30-day diary for the lips, and upper perioral lines and oral commissures as applicable, starting on the day of treatment at each treatment time point.

The method of injection was at the discretion of the Treating Investigator and was recorded. Sufficient amount of study product (*Restylane® Kysse* or control) was injected to achieve optimal correction of the lips. Optimal correction was defined as at least 1 MLFS step improvement from baseline and best correction that could be achieved as agreed by the Treating Investigator and the subject. It was recommended that the dose not exceed 1.5 mL in each lip (including vermillion, vermillion border and cupid's bow) per treatment session. The study product may have also been injected for optimal correction of the upper perioral rhytids, philtral columns, and/or oral commissures. The recommended maximum injected volume per subject and treatment was 6 mL (i.e. 3 mL for lips and 3 mL for perioral area).

3. Clinical Endpoints

With regards to safety, *Restylane*® *Kysse* in the lips, perioral rhytids, and oral commissures was evaluated by: a) the incidence, intensity, and duration of predefined, expected post-treatment injection site reactions using a subject diary for 30 days after each treatment and for each treatment area, b) the incidence, intensity, duration, and onset of related AEs collected during the study, and c) lip safety assessments as evaluated by a qualified study staff member at each study visit.

With regards to effectiveness, primary analysis of non-inferiority of *Restylane*® *Kysse* to the control was evaluated based on the change from baseline in the Blinded Evaluator assessment of the upper and lower lip separately (co-primary endpoints) at 8 weeks after last injection using the MLFS.

Table 3 Medicis Lip Fullness Scale (MLFS)

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

Secondary effectiveness endpoints included: a) change from baseline and responder rates for each lip separately based on the Blinded Evaluated assessment of MLFS, b) change from baseline and responder rates for perioral rhytids, right and left oral commissures separately based on the Blinded Evaluator assessment using the Wrinkle Assessment Scale (WAS), c) responder rates of aesthetic improvement of the lips as assessed by the subject and Blinded Evaluator using the Global Aesthetic Improvement Scale (GAIS), d) change from baseline in the Rasch transformed scores in subject satisfaction using the patient reported outcome measure (PRO), FACE-Q, specifically the scales Satisfaction with Lips and Appraisal of Lines (FACE-Q is a PRO that can be used to measure outcomes of aesthetic facial procedures and products from the patient's prospective), and e) assessment of lip fullness by an Independent Photographic Reviewer (IPR).

Table 4 Wrinkle Assessment Scale (WAS)

Grade	Description
0	No wrinkles
1	Just perceptible wrinkles
2	Shallow wrinkles
3	Moderate deep wrinkles
4	Deep wrinkles, well-defined edges
5	Very deep wrinkle, redundant fold

With regard to success/failure criteria, non-inferiority of *Restylane® Kysse* to the control was demonstrated if the confidence interval (CI) of difference between treatment means (control – Restylane® Kysse) was entirely below 0.5 for both co-primary endpoints in both the ITT and PP populations.

B. Accountability of PMA Cohort

There were 273 subjects randomized in the study; 184 subjects were randomized to *Restylane® Kysse*, and 89 subjects were randomized to the control treatment group.

As noted in the table below, there was one subject that was randomized to the control treatment group at baseline, but received *Restylane® Kysse* in error. For analysis purposes, this subject is included in the control group in the ITT population based on the as-randomized principal, and in the *Restylane® Kysse* treatment group in the Safety population based on the as-treated principal. The Safety population includes all 273 subjects who were randomized and treated with the investigational products. The ITT population includes subjects who were randomized and had a baseline MLFS score less than 5 (very full) for both the upper and lower lips as assessed by the Blinded Evaluator. There were three subjects that was assessed to have a MLFS score of 5 (i.e., very full lips), and were therefore excluded from the ITT population (N=270). The per protocol (PP) population includes all subjects in the ITT population who completed the Week 8 visit without any deviations considered to have a substantial impact on the primary effectiveness outcome (N =261).

At the week 48 visit, all subjects regardless of randomization assignment at baseline were offered optional retreatment with *Restylane® Kysse* if optimal aesthetic improvement was not maintained. A total of 117 subjects in the *Restylane® Kysse* treatment group received optional retreatment and continued in the study for an additional four weeks.

There were 251 subjects that completed the study (i.e., at Week 48 or 4 weeks post optional retreatment, whichever was applicable), and 22 subjects discontinued early. The primary reasons for discontinuation were: lost to follow up (11/273 subjects, 4.0%), and withdrew consent (9/273 subjects, 3.3%). No subject discontinued the study for medical reasons.

Table 5 Summary of Subject Disposition: All Subjects

	Randomized Treatment Group		
	Restylane® Kysse	**Control**	**Total**
Number of Subjects Screened			326
Number of Subjects Randomized	184	89	273
Number of Subjects in the Safety Population	185 (100.5%)	88 (98.9%)	273 (100.0%)
Number of Subjects in the ITT Population	183 (99.5%)	87 (97.8%)	270 (98.9%)
Number of Subjects in the PP Population	176 (95.7%)	85 (95.5%)	261 (95.6%)
Completed the Study			
Yes	166 (90.2%)	85 (95.5%)	251 (91.9%)
No	18 (9.8%)	4 (4.5%)	22 (8.1%)

	Randomized Treatment Group		
	Restylane*® *Kysse	**Control**	**Total**
Reason for Discontinuation			
Withdrew Consent	8 (4.3%)	1 (1.1%)	9 (3.3%)
Lost to Follow-up	10 (5.4%)	1 (1.1%)	11 (4.0%)
Medical Reasons	0	0	0
Other	0	2 (2.2%)	2 (< 1%)

Note: All subjects are summarized by the randomized treatment group except the Safety population. In the safety population, subject 8280-027 was randomized to control but received *Restylane*® *Kysse* by error. Therefore 8280-027 is included in the *Restylane*® *Kysse* group (n=185) and not the control group (n=88).
Note: Subjects 8280-016, 8284-026, 8482-020 had MLFS=5 at baseline and were excluded from ITT population.

The safety population includes all subjects who received any of the investigational products based on the as-treated principle.

The ITT population includes all subjects who were randomized and had a baseline MLFS score of less than 5 (very full lips) for both the upper and lower lips. ITT analysis based on the as-randomized principle.

The per protocol population includes all subjects in the ITT population who completed the Week 8 visits without any deviations considered to have a substantial impact on the primary effectiveness outcome.

C. Study Population Demographics and Baseline Parameters

The demographics of the study are typical for a pivotal study performed in the US for this indication. The demographics of the study population are present in Table 6.

Overall, the mean age for study subjects was 52.8 years. Most subjects were female and White (96.7% and 94.0%, respectively), and a majority identified as not being of Hispanic or Latino descent (83.7%).

The ITT population included 216 subjects (80.0%) with Fitzpatrick Skin Type (FST) I, II or III, 36 subjects (13.3%) with FST IV, and 18 subjects (6.7%) with FST V, or VI. The vast majority of all subjects (> 90%) had very thin (1) or thin (2) upper and lower lips as assessed by the Blinded Evaluator and Treating Investigator at baseline. There were 20 subjects (7.4%) with FST V or VI that did not meet the MLFS eligibility criterion of very thin (1) or thin (2) upper and lower lips; this exception was allowed per protocol.

Table 6 Summary of Subject Demographic and Baseline Characteristics: ITT Population

		Treatment Group		
Characteristic	**Statistic**	***Restylane®* *Kysse* (N=183)**	**Control (N=87)**	**Total (N=270)**
	n	183	87	270
Age (years)	Mean (S.D.)	52.4 (13.5)	53.6 (10.8)	52.8 (12.7)
	Median	55.0	55.0	55.0
	Min,Max	22, 82	22, 75	22, 82
Gender:				
Male	n (%)	7 (3.8)	2 (2.3)	9 (3.3)
Female	n (%)	176 (96.2)	85 (97.7)	261 (96.7)
Race:				
White	n (%)	173 (94.5%)	81 (93.1%)	254 (94.0%)
Other Races:				
Asian	n (%)	1 (< 1%)	1 (1.1%)	2 (< 1%)
Black or African American	n (%)	7 (3.8%)	2 (2.2%)	9 (3.3%)
Native Hawaiian or Other Pacific Islander	n (%)	0	1 (1.1%)	1 (< 1%)
American Indian or Alaska Native	n (%)	1 (< 1%)	0	1 (< 1%)
Other Race Reported	n (%)	1 (< 1%)	1 (1.1%)	2 (< 1%)
Multiple Races Reported	n (%)	0	1 (1.1%)	1 (< 1%)
Ethnicity:				
Hispanic or Latino	n (%)	29 (15.8%)	15 (17.2%)	44 (16.2%)
Not Hispanic or Latino	n (%)	154 (84.1%)	72 (82.7%)	226 (83.7%)
Fitzpatrick Skin Type:				
I	n (%)	7 (3.8%)	4 (4.5%)	11 (4.0%)
II	n (%)	77 (42.0%)	31 (35.6%)	108 (40.0%)
III	n (%)	63 (34.4%)	34 (39.0%)	97 (35.9%)
IV	n (%)	23 (12.5%)	13 (14.9%)	36 (13.3%)
V	n (%)	10 (5.4%)	4 (4.5%)	14 (5.1%)
VI	n (%)	3 (1.6%)	1 (1.1%)	4 (1.4%)
Baseline MLFS Assessed by Blinded Evaluator (Upper Lip):				
1-Very Thin	n (%)	99 (54.0%)	43 (49.4%)	142 (52.5%)
2-Thin	n (%)	72 (39.3%)	40 (45.9%)	112 (41.4%)
3-Medium	n (%)	4 (2.1%)	1 (1.1%)	5 (1.8%)
4-Full	n (%)	8 (4.3%)	3 (3.4%)	11 (4.0%)
5-Very Full	n (%)	0	0	0

		Treatment Group		
Characteristic	**Statistic**	***Restylane*® *Kysse* (N=183)**	**Control (N=87)**	**Total (N=270)**
Baseline MLFS Assessed by Blinded Evaluator (Lower Lip):				
1-Very Thin	n (%)	71 (38.7%)	46 (52.8%)	117 (43.3%)
2-Thin	n (%)	101 (55.1%)	38 (43.6%)	139 (51.4%)
3-Medium	n (%)	7 (3.8%)	1 (1.1%)	8 (2.9%)
4-Full	n (%)	4 (2.1%)	2 (2.2%)	6 (2.2%)
5-Very Full	n (%)	0	0	0
Wrinkle Assessment Scale by Blinded Evaluator (Upper Perioral Lines):				
0-No wrinkles	n (%)	62 (33.8%)	24 (27.5%)	86 (31.8%)
1-Just perceptible wrinkle	n (%)	40 (21.8%)	16 (18.3%)	56 (20.7%)
2-Shallow wrinkles	n (%)	27 (14.7%)	16 (18.3%)	43 (15.9%)
3-Moderately deep wrinkle	n (%)	36 (19.6%)	19 (21.8%)	55 (20.3%)
4-Deep wrinkle, well-defined edges	n (%)	11 (6.0%)	8 (9.1%)	19 (7.0%)
5-Very deep wrinkle, redundant fold	n (%)	7 (3.8%)	4 (4.5%)	11 (4.0%)

For the *Restylane*® *Kysse* treatment group, the total median volume injected into the upper and lower lips for initial and touch-up treatment combined was 1.75 mL (range 0.60 to 3.90 mL). The median volume injected for retreatment at Week 48 was 1.00 mL (range 0.10 to 2.80 mL). The total median volume injected into the upper perioral lines for initial and touch up-treatment combined was 0.20 mL (range 0.05 to 1.40 mL); at retreatment it was 0.20 mL (range 0.10 to 0.50 mL).

For the control treatment group, the total median volume injected into the upper and lower lips for initial and touch-up treatment combined was 2.20 mL (range 0.60 to 4.40 mL). The total median volume injected into the upper perioral lines for initial and touch up-treatment combined was 0.41 mL (0.10 to 1.40 mL).

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the cohort of 273 subjects available up to the final evaluation (i.e., 4 weeks after retreatment at Week 48). Subject reported injection site reactions are presented in Table 7 – Table 9. Adverse events (AEs) are presented in Table 10 – Table 17.

Injection Site Reactions: Subjects evaluated injection site reactions (ISRs) in a 30-day diary following initial treatment, and touch-up and retreatment, if performed. The presence of pre-defined expected post-treatment events, i.e., pain, tenderness, redness, bruising, swelling, itching, lumps/bumps, and skin discoloration were assessed for the treated area(s). Subjects recorded the presence and level of intensity (i.e., none, tolerable, affects daily activities, or disabling) for each of the pre-defined events. A summary of the maximum intensity and duration of the diary observations in the lips is presented in Table 7 - Table 9.

Following initial treatment, almost all subjects in the *Restylane® Kysse* treatment group reported an ISR (179/183, 97.8%). The most frequently reported ISRs were swelling (165/183, 90.2%), tenderness (160/183, 87.4%), bruising (157/183, 85.8%), and lumps/bumps (154/183, 84.2%). Other ISRs reported were redness (134/183, 73.2%), pain (125/183, 68.3%), skin discoloration (119/183, 65.0%) and itching (64/183, 35.0%). Subjects rated the intensity of the ISRs as tolerable (121/179, 67.6%), affects daily activities (52/179, 29.1%), and disabling (6/179, 3.4%). Most ISRs lasted 2 weeks or less following initial treatment (91/179, 50.7%).

Following retreatment with *Restylane® Kysse*, the ISRs reported by subjects were similar to those reported at initial treatment (Table 9). Most ISRs lasted 2 weeks or less following retreatment (66/97, 68.0%). The most frequently reported ISRs were swelling (92/114, 85.1%), tenderness (88/114, 77.2%), lumps/bumps (79/114, 69.3%), and bruising (78/114, 68.4%). ISRs after retreatment were rated by subjects as tolerable (79/97, 81.4%), affects daily activities (18/97, 18.6%), and none were disabling.

There were no significant differences in the ISRs reported in the *Restylane® Kysse* treatment compared to the control group. ISRs in both treatment groups were typically reported at a lower incident rate and intensity, and shorter duration following touch-up compared to initial treatment.

Table 7 Injection Site Reactions in the Lips by Maximum Intensity after Initial Treatment[1]

	Restylane® Kysse (N=185)				**Control (N=88)**			
Diary Symptom	**Total % (n/N)[2]**	**Tolerable %**	**Affects Daily Activities %**	**Disabling %**	**Total % (n/N)[2]**	**Tolerable %**	**Affects Daily Activities %**	**Disabling %**
Any Symptom	97.8 (179/183)	67.6 121/179	29.1 52/179	3.4 6/179	96.6 (85/88)	72.9 62/85	25.9 22/85	1.2 1/85
Swelling	90.2 (165/183)	73.3 121/165	23.6 39/165	3.0 5/165	92.0 (81/88)	79.0 64/81	21.0 17/81	0
Tenderness	87.4 (160/183)	85.6 137/160	12.5 20/160	1.9 3/160	89.8 (79/88)	91.1 72/79	8.9 7/79	0
Bruising	85.8 (157/183)	82.2 129/157	15.3 24/157	2.5 4/157	80.7 (71/88)	83.1 59/71	16.9 12/71	0
Lumps/Bumps	84.2 (154/183)	83.1 128/154	15.6 24/154	1.3 2/154	79.5 (70/88)	97.1 68/70	2.9 2/70	0
Redness	73.2 (134/183)	88.1 118/134	10.4 14/134	1.5 2/134	68.2 (60/88)	93.3 56/60	5.0 3/60	1.7 1/60
Pain(including burning)	68.3 (125/183)	86.4 108/125	11.2 14/125	2.4 3/125	63.6 (56/88)	91.1 114/125	7.1 9/125	1.8 1/56
Skin Discoloration	65.0 (119/183)	83.2 99/119	13.4 16/119	3.4 4/119	60.2 (53/88)	86.8 46/53	13.2 7/53	0

	Restylane® Kysse (N=185)				Control (N=88)			
Diary Symptom	**Total % (n/N)[2]**	**Tolerable %**	**Affects Daily Activities %**	**Disabling %**	**Total % (n/N)[2]**	**Tolerable %**	**Affects Daily Activities %**	**Disabling %**
Itching	35.0 (64/183)	90.6 58/64	7.8 5/64	1.6 1/64	30.7 (27/88)	100.0 27/27	0	0

[1]: Does not include data after touch-up treatment.

[2]: n is number of subjects reporting a symptom and is the denominator for percentage of subjects with this symptom. N is number of subjects with a diary entry and is the denominator for percentage in 'Total' column.

Table 8 Injection Site Reactions in the Lips by Duration after Initial Treatment[1]

	Restylane® Kysse (N=185)					Control (N=88)				
Diary Symptom	**Total % (n/N)[2]**	**1-3 Days %**	**4-7 Days %**	**8-14 Days %**	**15-30 Days %**	**Total % (n/N)[2]**	**1-3 Days %**	**4-7 Days %**	**8-14 Days %**	**15-30 Days %**
Any Symptom	97.8 (179/183)	6.1 11/179	12.8 23/179	31.8 57/179	49.2 88/179	96.6 (85/88)	14.1 12/85	23.5 20/85	30.6 26/85	31.8 27/85
Swelling	90.2 (165/183)	21.8 36/165	37.0 61/165	27.9 46/165	13.3 22/165	92.0 (81/88)	46.9 38/81	38.3 31/81	12.3 10/81	2.5 2/81
Tenderness	87.4 (160/183)	28.1 45/160	21.9 35/160	35.6 57/160	14.4 23/160	89.8 (79/88)	48.1 38/79	30.4 24/79	16.5 13/79	5.1 4/79
Bruising	85.8 (157/183)	19.1 30/157	45.2 71/157	30.6 48/157	5.1 8/157	80.7 (71/88)	25.4 18/71	57.7 41/71	16.9 12/71	0
Lumps/Bumps	84.2 (154/183)	7.1 11/154	11.0 17/154	29.2 45/154	52.6 81/154	79.5 (70/88)	25.7 18/70	18.6 13/70	22.9 16/70	32.9 23/70
Redness	73.2 (134/183)	42.5 57/183	39.6 53/134	15.7 21/134	2.2 3/134	68.2 (60/88)	71.7 43/60	25.0 15/60	3.3 2/60	0
Pain(including burning)	68.3 (125/183)	55.2 69/125	20.8 26/125	19.2 24/125	4.8 6/125	63.6 (56/88)	71.4 40/56	25.0 14/56	3.6 2/56	0
Skin Discoloration	65.0 (119/183)	36.1 43/119	29.4 35/119	26.1 31/119	8.4 10/119	60.2 (53/88)	58.5 31/53	28.3 15/53	13.2 7/53	0
Itching	35.0 (64/183)	53.1 34/64	29.7 19/64	12.5 8/64	4.7 3/64	30.7 (27/88)	74.1 20/27	18.5 5/27	0	7.4 2/27

[1]: Does not include data after touch-up treatment.

[2]: n is number of subjects reporting a symptom and is the denominator for percentage of subjects with this symptom. N is number of subjects with a diary entry and is the denominator for percentage in 'Total' column.

Table 9 Injection Site Reactions in the Lips by Maximum Intensity and Duration after Retreatment

Subjects Received Re-Treatment (N=117)								
		Intensity			Duration			
Diary Symptom	Total % (n/N)[1]	Tolerable	Affects Daily Activities	Disabling	1-3 Days %	4-7 Days %	8-14 Days %	15-30 Days %
Any Symptom	85.1 (97/114)	81.4 79/97	18.6 18/97	0	13.4 13/97	24.7 24/97	29.9 29/97	32.0 31/97
Swelling	80.7 (92/114)	87.0 80/92	13.0 12/92	0	39.1 36/92	30.4 28/92	23.9 22/92	6.5 6/92
Tenderness	77.2 (88/114)	95.5 84/88	4.5 4/88	0	37.5 33/88	28.4 25/88	26.1 23/88	8.0 7/88
Lumps/Bumps	69.3 (79/114)	93.7 74/79	6.3 5/79	0	24.1 19/79	20.3 16/79	19.0 15/79	36.7 29/79
Bruising	68.4 (78/114)	80.8 63/78	19.2 15/78	0	23.1 18/78	55.1 43/78	20.5 16/78	1.3 1/78
Redness	65.8 (75/114)	96.0 72/75	4.0 3/75	0	56.0 42/75	32.0 24/75	8.0 6/75	4.0 3/75
Pain (including burning)	57.9 (66/114)	95.5 63/66	4.5 3/66	0	68.2 45/66	19.7 13/66	10.6 7/66	1.5 1/66
Skin Discoloration	55.3 (63/114)	90.5 57/63	9.5 6/63	0	46.0 29/63	36.5 23/63	12.7 8/63	4.8 3/63
Itching	19.3 (22/114)	95.5 21/22	4.5 1/22	0	90.9 20/22	9.1 2/22	0	0

[1]: n is number of subjects reporting a symptom and is the denominator for percentage of subjects with this symptom. N is number of subjects with diary entry (Three subjects did not complete the diary.) for a symptom and is the denominator for percentage in 'Total' column.

Device and Injection Related Events: AEs were evaluated by Investigators throughout entirety of the study. An overall summary of treatment-emergent adverse events (TEAEs) following initial and touch-up treatment is presented in Table 10. There were 72 subjects (72/185, 38.9%) in the *Restylane® Kysse* treatment group that reported a total of 192 TEAEs; of which, 120 (62.5%) were considered to be related to the product and/or injection procedure. In the control treatment group, there were 31 subjects (31/88, 35.2%) that reported a total of 129 TEAEs; 81 (81/129, 62.8%) were considered to be related to the product and/or injection procedure. Regardless of treatment group, most related TEAEs were mild in severity and required no action. There were two serious AEs reported during the study; both events were assessed as unrelated to treatment. For the *Restylane® Kysse* treatment group, related TEAEs treatment typically occurred on the day of treatment (i.e., median time to onset was 0.0 days); for the control group the median time to onset was 1.0 day For the *Restylane® Kysse* group, the median duration of a related TEAE was 13.5 days; it was 15.0 days for the control group.

There were 15 subjects with a related TEAE that had an onset of ≥ 21 days after the last injection. In the *Restylane® Kysse* treatment group, 10 subjects reported 16 late onset events. By preferred term, they included: injection site mass (8 events), injection site swelling (3 events), injection site nodule (2 events), injection site hypersensitivity (2 events), and oral herpes (1 event). All events

were assessed as mild in intensity and resolved or were assessed as stable. In the control group, 5 subjects reported 11 late onset events. By preferred term, they included: injection site hypersensitivity (3 events), injection site edema (3 events), injection site mass (2 events), angioedema (1 event), injection site bruising (1 events), and injection site nodule (1 event). A majority of the late onset events in the control group were assessed as moderate in intensity (7/11 events), four were assessed a mild, and all events resolved. There was no significant difference in the reporting frequency of late onset events between the *Restylane*® *Kysse* and control treatment groups (5.4% [10/185 subjects] and 5.7% [5/88 subjects], respectively).

The severity and duration of TEAEs occurring in > 5% of subjects in either treatment group are summarized in Table 11 – Table 12. Common related TEAEs included injection site mass, bruising, and nodules. Related events of injection site mass or nodules typically lasted less than 30 days, and injection site bruising lasted less than 14 days. In the *Restylane*® *Kysse* treatment group, there were 2 subjects with unresolved masses or nodules at the completion of the study and 1 subject with unresolved masses or nodules that withdrew prior to study completion, which were classified as mild, no treatment was necessary, and they were assessed as stable.

Treatment-related AEs occurring in ≤ 5% of subject after initial and touch-up treatment are summarized in Table 12, and included injection site swelling, injection site pain, oral herpes, injection site hypersensitivity, injection site hypertrophy, angioedema, herpes simplex, injection site discharge, dryness, hemorrhage, induration, edema, papule, and vesicles.

Table 10 Summary of Treatment-Emergent AEs After Initial/Touch-up Treatment

	Restylane® Kysse		Control	
	Events	**Subjects (N = 185) n (%)**	**Events**	**Subjects (N=88) n (%)**
TEAES Overall	192	72 (38.9%)	129	31 (35.2%)
Related TEAEs	120	39 (21.1%)	81	22 (25.0%)
Upper Lip	42	29 (15.7%)	23	13 (14.8%)
Lower Lip	51	27 (14.6%)	28	16 (18.2%)
Perioral lines	5	4 (2.2%)	3	2 (2.3%)
Oral Commissures	22	9 (4.9%)	27	10 (11.4%)
Severity of Related TEAEs	--	--	--	--
Mild	115	36 (19.5%)	74	20 (22.7%)
Moderate	5	3 (1.6%)	7	2 (2.3%)
Severe	0	0	0	0
Action Required	--	--	--	--
None	100	34 (18.4%)	58	16 (8.2%)
Medication	7	4 (2.2%)	11	6 (6.8%)
Non-Pharmacological	13	8 (4.3%)	14	5 (5.7%)
Withdrawal	0	0	0	0
Mean Onset of Related TEAEs	18.7	39	22.0	22
Minimum	0	--	0	--
Maximum	335	--	207	--
Mean Duration of Related TEAEs	24.0	38	40.2	22
Minimum	1	--	4	--
Maximum	129	--	285	--
Unrelated AEs	72	44 (23.8%)	48	22 (25.0%)
Serious AEs	2	2 (1.1%)	0	0
No TEAEs	--	113 (61.1%)	--	57 (64.8%)
Related to product and/or injection procedure.				

Table 11 Treatment Related AEs Occurring ≥ 5% of Subjects by Maximum Severity after Initial/Touch-up Treatment

	Restylane® Kysse (N=185)				Control (N=88)			
Adverse Event	**Subjects**	**Mild**	**Moderate**	**Severe**	**Subjects**	**Mild**	**Moderate**	**Severe**
Injection site mass	19 (10.3%)	19 (10.3%)	0	0	10 (11.4%)	10 (11.4 %)	0	0
Injection site bruising	14 (7.6%)	13 (7.0 %)	1 (<1%)	0	9 (10.2 %)	9 (10.2 %)	0	0
Injection site nodule	10 (5.4%)	10 (5.4 %)	0	0	6 (6.8 %)	6 (6.8 %)	0	0
Table is sorted in descending order by overall incidence rate.								

Table 12 Treatment Related AEs Occurring ≥ 5% of Subjects by Duration after Initial/Touch-up Treatment

	Restylane® *Kysse* (N=185)						Control (N=88)					
Adverse Event	**Events**	**=< 7 Days %**	**8-14 Days %**	**15-30 Days %**	**> 30 Days %**	**Not yet Resolved %**	**Events**	**=< 7 Days %**	**8-14 Days %**	**15-30 Days %**	**> 30 Days %**	**Not yet Resolved %**
Injection site mass	34	8.8%	8.8%	35.3%	38.2%	8.8%	22	0%	13.6%	54.5%	31.8%	0%
Injection site bruising	37	40.5%	54.1%	5.4%	0%	0%	26	69.2%	30.8%	0%	0%	0%
Injection site nodule	18	11.1%	16.7%	44.4%	16.7%	11.1%	18	16.7%	27.8%	33.3%	22.2%	0%
The percentages by duration are based on the number of events for the corresponding treatment-related adverse event.												

Table 13 Treatment Related AEs Occurring ≤ 5% of Subjects by Maximum Severity after Initial/Touch-up Treatment

	Restylane® *Kysse* (N=185)				Control (N=88)			
Adverse Event	**Subjects**	**Mild**	**Moderate**	**Severe**	**Subjects**	**Mild**	**Moderate**	**Severe**
Injection site swelling	4 (2.2 %)	3 (1.6 %)	1 (0.5 %)	0	1 (1.1 %)	1 (1.1 %)	0	0
Injection site pain	3 (1.6 %)	2 (1.1 %)	1 (0.5 %)	0	1 (1.1 %)	1 (1.1 %)	0	0
Oral herpes	1 (0.5 %)	1 (0.5 %)	0	0	3 (3.4 %)	3 (3.4 %)	0	0
Injection site hypersensitivity	1 (0.5 %)	1 (0.5 %)	0	0	1 (1.1 %)	0	1 (1.1 %)	0
Injection site hypertrophy	2 (1.1 %)	2 (1.1 %)	0	0	0	0	0	0
Angioedema	0	0	0	0	1 (1.1 %)	0	1 (1.1 %)	0
Herpes simplex	1 (0.5 %)	1 (0.5 %)	0	0	0	0	0	0
Injection site discharge	1 (0.5 %)	1 (0.5 %)	0	0	0	0	0	0
Injection site dryness	1 (0.5 %)	1 (0.5 %)	0	0	0	0	0	0
Injection site haemorrhage	1 (0.5 %)	1 (0.5 %)	0	0	0	0	0	0
Injection site induration	1 (0.5 %)	1 (0.5 %)	0	0	0	0	0	0
Injection site oedema	0	0	0	0	1 (1.1 %)	0	1 (1.1 %)	0
Injection site papule	0	0	0	0	1 (1.1 %)	1 (1.1 %)	0	0
Injection site vesicles	1 (0.5 %)	1 (0.5 %)	0	0	0	0	0	0
Table is sorted in descending order by overall incidence rate.								

TEAEs occurring after retreatment with subjects in the *Restylane*® *Kysse* treatment group at Week 48 are summarized in Table 14. In general, a majority of subjects reported no adverse events following retreatment (103/117, 88.0%). Of the subjects with a TEAE or TEAE related to the product and/or injection procedure following retreatment, they occurred at a lower incidence rate compared to initial treatment. Also see Table 15 – Table 17. There were no SAEs reported during this timeframe.

Table 14 Summary of Treatment-Emergent AEs After Retreatment

	Restylane® Kysse	
	Events	**Subjects (N = 117) n (%)**
TEAEs Overall	29	14 (12.0%)
Related TEAEs	24	12 (10.3%)
Upper Lip	6	4 (3.4%)
Lower Lip	9	8 (6.8 %)
Perioral lines	0	0
Oral Commissures	9	6 (5.1 %)
Severity of Related TEAEs	--	--
Mild	21	11 (9.4 %)
Moderate	3	1 (<1%)
Severe	0	0
Action Required	--	--
None	23	12 (10.3%)
Medication	0	0
Non-Pharmacological	1	1 (<1%)
Withdrawal	0	0
Mean Onset of Related TEAEs	6.7	12
Minimum	0	--
Maximum	17	--
Mean Duration of Related TEAEs	14.8	12
Minimum	3	--
Maximum	41	--
Unrelated AEs	5	3 (2.6%)
Serious AEs	0	0
No TEAEs	--	103 (88.0%)

Table 15 Treatment Related AEs Occurring ≥ 5% of Subjects by Maximum Severity after Retreatment

	Restylane Kysse® **(N=117)**			
Adverse Event	**Subjects**	**Mild**	**Moderate**	**Severe**
Injection site mass	6 (5.1%)	6 (5.1%)	0	0
Injection site bruising	6 (5.1%)	5 (4.3%)	1 (<1%)	0

Table 16 Treatment Related AEs Occurring ≥ 5% of Subjects by Duration after Retreatment

	Restylane® Kysse **(N=117)**					
Adverse Event	**Events**	**=< 7 Days %**	**8-14 Days %**	**15-30 Days %**	**> 30 Days %**	**Not yet Resolved %**
Injection site mass	12	8.3%	0%	66.7%	16.7%	8.3%
Injection site bruising	10	50.0%	50.0%	0%	0%	0%

The percentages by duration are based on the number of events for the corresponding treatment-related adverse event.

Table 17 Treatment Related AEs Occurring ≤ 5% of Subjects by Maximum Severity after Retreatment

	Restylane® *Kysse* (N=117)			
Adverse Event	**Subjects**	**Mild**	**Moderate**	**Severe**
Injection site bruising	4 (3.4 %)	3 (2.6 %)	1 (0.9 %)	0
Injection site nodule	1 (0.9 %)	1 (0.9 %)	0	0
Injection site vesicles	1 (0.9 %)	1 (0.9 %)	0	0
Oral herpes	1 (0.9 %)	1 (0.9 %)	0	0

Lip Safety Assessments: A study staff member who was qualified by training and experience performed the lip safety assessments at specified study time points. Lip safety assessments included "normal" or abnormal" ratings of lip palpation, texture, symmetry, movement, function, and sensation. None of the lip safety assessments were remarkable or presented any safety concerns.

Serious Adverse Events: There were no treatment-related serious adverse events reported in the study.

Exploratory Subgroup Analyses: Exploratory safety analyses by subgroup (i.e., study site, median injection volume of ≤ 2.7 mL and > 2.7 mL, and FST) were evaluated.

At the site level, the incident rate of subjects with related TEAEs was similar between the *Restylane*® *Kysse* and control treatment groups, and the majority of site-specific events were assessed by the Investigators as mild; this observation is consistent with the summary of related TEAEs overall. Larger differences in the reporting rates was influenced by the small site sample size; however, it does not have a significant impact on the AE profile overall.

The total median injection volume for subjects in the *Restylane*® *Kysse* treatment group was 2.50 mL; for subjects in the control group it was 3.35 mL. For subjects that received > 2.7 mL of investigational product, a slightly higher percentage of subjects in the *Restylane*® *Kysse* and control treatment groups reported related TEAEs compared to overall. Conversely, for subjects that received ≤ 2.7 mL of investigational products, a smaller percentage of subjects in each treatment group reported related TEAEs compared to overall. Regardless of injection volume (i.e., ≤ 2.7 mL or > 2.7 mL), the majority of all related TEAEs in each treatment group were assessed as mild and classified as general disorders and administrative site conditions.

Related TEAES by FST subgroup were fairly consistent with related events reported overall. The majority of all related events in each FST subgroup and treatment group were assessed as mild and classified as general disorders and administrative site conditions. For FST I-III subjects, a slightly higher percentage of subjects in the *Restylane*® *Kysse* and control treatment groups reported related TEAEs compared to overall. For subjects in the FST VI and FST V-VI subgroups, the percentage of subjects with related TEAEs in each treatment

group was slightly lower compared to overall; however, this may be due to the smaller subgroup sample sizes.

Following retreatment with *Restylane® Kysse* at Week 48, a general decrease in the reporting frequency of related TEAEs was also observed across the different subgroups.

Table 18 Incidence of Related TEAEs after Initial/Touch-up Treatment by Subgroup

	Restylane® Kysse **% (n/N)**	**Control % (n/N)**
Investigational Site		
Site 8113	0	25.0% (1/4)
Site 8126	50.0% (9/18)	50.0% (4/8)
Site 8280	10.0% (2/20	11.1% (1/9)
Site 8284	0	0
Site 8476	0	14.3% (1/7)
Site 8481	27.3% (3/11)	20.0% (1/5)
Site 8482	0	0
Site 8496	7.1% (1/14)	0
Site 8629	85.7% (12/14)	100.0% (8/8)
Site 8631	9.1% (1/11)	33.3% (2/6)
Site 8632	75.0% (6/8)	100 % (3/3)
Site 8633	13.3% (2/15)	20.0% (1/5)
Site 8634	20.0% (2/10)	0
Site 8635	7.1% (1/14)	0
Median Injection Volume		
≤ 2.7 mL	19.8% (21/106)	12.9% (4/31)
>2.7 mL	22.8 % (18/79)	31.6% (18/57)
FST		
FST I-III	23.0% (34/148)	27.9 % (19/68)
FST IV	17.4% (4/23)	15.4% (2/13)
FST V-VI	7.1% (1/14)	14.3% (1/7)

2. Effectiveness Results

The analysis of effectiveness was based on the cohort of 270 subjects available up to the Week 48 evaluation. Key effectiveness outcomes are presented in the Table 19 – Table 21.

Primary Endpoint: The primary objective of the study was to demonstrate non-inferiority of *Restylane® Kysse* versus a control in lip fullness augmentation by comparing change from baseline in the Blinded Evaluator assessment of MLFS in the upper and lower lip separately at 8 weeks after last injection. Non-inferiority was established if the CI of difference between treatment means (control – *Restylane® Kysse*) was entirely below 0.5 for both co-primary endpoints in both the ITT and PP populations (i.e., two co-primary endpoints). Confidence intervals were two-tailed and constructed at a confidence level of 95%.

The mean change from the baseline MLFS score for the *Restylane® Kysse* treatment group was 1.8 for both the upper and lower lips. For the control group, the mean change from baseline in the upper lip MLFS score was 1.7, and for the lower lip it was 1.8. Similar results were reported for the PP population.

In the ITT population, the CI of the difference between treatment means (control – *Restylane® Kysse*) in the change from baseline MLFS for the upper lip was (-0.31, 0.18), and (-0.32, 0.16) for the lower lip. For the PP population the CI for the upper lip was (-0.32, 0.17), and (-0.30, 0.19) for the lower lip. The CIs for both analysis populations were entirely below 0.5 for the upper and lower lips, demonstrating that non-inferiority of *Restylane® Kysse* to the control was established.

Table 19 Primary Effectiveness Endpoint: Change from Baseline in the Blinded Evaluators Assessment of Lip Fullness (MLFS) for the Upper and Lower Lips at 8 Weeks after the Last Injection

	ITT Population		PP Population	
	***Restylane® Kysse* (N=183)**	**Control (N=87)**	**Restylane® Kysse (N=176)**	**Control (N=85)**
Upper Lip				
Mean	1.8	1.7	1.8	1.7
S.D.	0.98	0.90	0.96	0.91
Median	2.0	2.0	2.0	2.0
Min, Max	-1, 4	0, 4	0, 4	0, 4
Mean of (Control – Restylane Kysse)	-0.07		-0.08	
95% CI	(-0.31, 0.18)		(-0.32, 0.17)	
Lower Lip				
Mean	1.8	1.8	1.8	1.8
S.D.	0.98	0.85	0.98	0.86
Median	2.0	2.0	2.0	2.0
Min, Max	-1, 4	0, 4	-1, 4	0, 4
Mean of (Control – Restylane Kysse)	-0.08		-0.05	
95% CI	(-0.32, 0.16)		(-0.30, 0.19)	

The following secondary endpoints were evaluated for the *Restylane® Kysse* group only.

Blinded Evaluator MLFS: The change from baseline MLFS and responder rates (i.e., at least a 1 point improvement from the baseline MLFS score) based on the Blinded Evaluated assessment was evaluated. For the *Restylane® Kysse* treatment group, upper and lower lip fullness was maintained for 48 weeks after the last injection with at least a 1 point mean change from baseline in MLFS score. For the upper and lower lips combined, 88% (155/177) of *Restylane® Kysse* treatment group subjects were responders at Week 8 after the last injection. By Week 48 after last injection, the majority of subjects (101/169, 60%) were still assessed as a responder.

Table 20 Proportion of MLFS Responders, Upper and Lower Lips Combined

Weeks After Last Injection	*Restylane® Kysse* % (n/N)	95% Confidence Interval
Week 8	88% (155/177)	0.82, 0.92
Week 16	82% (142/174)	0.75, 0.87
Week 24	77% (129/168)	0.70, 0.83
Week 32	69% (115/167)	0.61, 0.76
Week 40	66% (110/166)	0.59, 0.73
Week 48	60% (101/169)	0.52, 0.67

Blinded Evaluator WAS: Aesthetic improvement from baseline of the upper perioral rhytids and oral commissures was evaluated by the Blinded Evaluator using the WAS. A responder was defined as at least a one grade improvement from the Blinded Evaluator's baseline assessment. Subjects treated with *Restylane® Kysse* in the upper perioral rhytids, and left and right oral commissures had at least a 1 point mean decrease in wrinkle severity at all assessment time points. For the upper perioral lines, the proportion of WAS responders was 94% (50/53) at Week 8, 89% (47/53) at Weeks 16-40, and 83% (44/53) at Week 48. For subjects treated in the left and right oral commissures, separately and combined, a majority were assessed as responders at each of the assessment time points (range 79% [106/134] - 57% [74/129]).

Treating Investigator GAIS: The Treating Investigator assessed the global aesthetic improvement (i.e., improvement from baseline) of the subject's upper and lower lips at post treatment visits. A responder was defined as at least "improved" (i.e., improved, much improved, or very much improved) on the GAIS. For the upper and lower lips at Week 8, separately and combined, almost all subjects treated with *Restylane® Kysse* were assessed improved or better from baseline (≥ 98%, 175/178), and the proportion of responders remained high through Week 48 after last injection (71% (120/169) upper lip, 76% (128/169), lower lip, and 67% (114/169) upper and lower lips combined).

Subject GAIS: Independent of the Treating Investigator, subjects also evaluated the global aesthetic improvement their lips following treatment with *Restylane® Kysse.* The majority of subjects assessed their upper and lower lips as at least "improved" from baseline at all post-treatment time points. For the upper and lower lips combined, the proportion of responders was 96% (170/178) at Week 8. By Week 48 after last injection 78% (132/169) of subjects were still responders. Similar responder rates were reported for the upper and lower lips separately.

Subject FACE-Q Questionnaire, Satisfaction with Lips: The FACE-Q Questionnaire was used to assess treatment outcome from the subject's perspective. The higher total score indicated greater subject satisfaction. The mean total score at baseline (prior to treatment) was 28.1 (n=183); by Week 8, the mean total score was 83.3 (n=177). Subjects remained satisfied with how they felt about their lips following treatment with *Restylane® Kysse* throughout

the study with a mean total score of 66.3 (n=169) at Week 48 after last injection, a 38.2 point increase from baseline.

The proportion of subjects satisfied and dissatisfied per FACE-Q question was evaluated. Prior to treatment at baseline, the majority of subjects (124/183, 68%) reported dissatisfaction with their lips on all FACE-Q questions. By Week 8 following treatment, at least 90% (160/177) of subjects reported lip satisfaction on all FACE-Q questions, and lip satisfaction was maintained through Week 48 for the majority of subjects (110/169, 65%).

Subject FACE-Q Questionnaire, Appraisal of Lines: Lips: The questionnaire measured the appearance of lines around the lips, and how bothersome the lines were to the subject. At baseline (prior to treatment) the mean total score was 41.8 (n=183). At Week 8 it was 76.0 (n=177) indicating that subjects were less bothered by the lines around their lips following treatment with *Restylane® Kysse*. The mean Rasch-transformed total score remained high throughout the study, and at Week 48 the mean total score was 65.8 (n=169), an increase of 23.7 points from baseline.

The majority of subjects (108/182, 59%) reported that they were moderately or extremely bothered by the appearance of lines around their lips prior to treatment at baseline. Following treatment with *Restylane® Kysse* at Week 8, 77% (137/175) of subjects reported that they were not at all or a little bothered by the lines on all FACE-Q questions, and the majority of subjects (≥ 63% (107/169)) were less bothered by the appearance of lines around their lips through Week 48.

Independent Photographic Reviewer (IPR): At the end of the study, the IPR assessed improvement in fullness of each lip by comparison of random, blinded pairings of the baseline and post-baseline subject photographs. For the *Restylane® Kysse* treatment group, the proportion of upper and lower lip responders as assessed by the IPR was high (≥ 84% (138/164)) at each of the assessment time points. At Week 48, the proportion of responders as assessed by the IPR was 91% for the upper lip and 88% for the lower lip.

Exploratory Subgroup Analyses: The exploratory effectiveness analyses by subgroup (i.e., study site, FST, and race) demonstrated that the results at Week 8 were consistent with the primary analysis based on the difference of means in the MLFS for the upper and lower lips (control minus *Restylane® Kysse*).

Table 21 Difference of Means in Blinded Evaluator MLFS at 8 Weeks after Last Injection by Subgroup

	Mean of (Control – *Restylane® Kysse*)
Investigational Site	
Site 8113 (N=14)	
Upper Lip	0.20
Lower Lip	0.25
Site 8126 (N=16)	
Upper Lip	-0.25
Lower Lip	-0.11
Site 8280 (N=28)	
Upper Lip	-0.06
Lower Lip	-0.06
Site 8284 (N=21)	
Upper Lip	0.17
Lower Lip	-0.20
Site 8476 (=18)	
Upper Lip	-0.27
Lower Lip	-0.30
Site 8481 (N=16)	
Upper Lip	0.20
Lower Lip	0.20
Site 8482 (N=19)	
Upper Lip	-0.01
Lower Lip	0.41
Site 8496 (N=20)	
Upper Lip	0.19
Lower Lip	-0.21
Site 8629 (N=22)	
Upper Lip	-0.39
Lower Lip	-0.21
Site 8631 (N=17)	
Upper Lip	0.35
Lower Lip	-0.06
Site 8632 (N=11)	
Upper Lip	0.08
Lower Lip	-0.04
Site 8633 (N=20)	
Upper Lip	0.60
Lower Lip	0.27
Site 8634 (N-17)	
Upper Lip	-0.59
Lower Lip	0.06
Site 8635 (N=21)	
Upper Lip	-0.21
Lower Lip	-0.36
FST	
FST I-III (N=216)	
Upper Lip	0.00
Lower Lip	0.02
FST IV (N=26)	
Upper Lip	-0.61

	Mean of (Control – *Restylane® Kysse*)
Lower Lip	-0.69
FST V-VI (N=18)	
Upper Lip	0.12
Lower Lip	0.06
Race	
White (N=254)	
Upper Lip	-0.06
Lower Lip	-0.06
Other Races (N=16)	
Upper Lip	-0.03
Lower Lip	-0.30

3. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient 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.

Clinical study 43USK1701 included 14 investigators; of which, one Investigator had disclosable financial interests/arrangements as defined in 21 CFR § 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Restylane® Kysse was previously named *Emervel Lips Lidocaine*.

Study 05DF1210: This was a 24-week, randomized, evaluator-blinded, comparative study of the safety and effectiveness of lip injections with *Emervel Lips* and control conducted at one site in Europe. Forty (40) subjects were randomized 1:1 to treatment with either *Emervel Lips* or control. The rationale for this study was to evaluate whether lip injections with *Emervel Lips* was associated with less swelling and higher subject satisfaction than lip injections with control. One single treatment was administered by the treating investigator according to a standardized procedure. A standardized volume of 0.5 mL was injected by retrograde linear threading into the lip line of each of the upper and lower lip resulting in a total volume of 1.0 mL. After treatment and at 1, 3, 7 and 14 days after treatment, a blinded evaluator assessed intensity of signs and symptoms of local tolerability (edema/swelling, erythema, bruising, pain/tenderness and pruritus) and product palpability. The subjects assessed pain during the injection.

For edema/swelling, results showed a lower intensity in the *Emervel Lips* group compared to the control group both for overall highest intensity ($p<0.001$), and for intensity at each time point at Day 0, Day 1, Day 3 and Day 7 ($p<0.001$) after treatment.

For pain/tenderness, results showed a lower intensity in the *Emervel Lips* group compared to the control group both for overall highest intensity (30.0% none, 60.0% mild, 10.0% moderate; versus 15.0% none, 35.0% mild, 40.0% moderate, 10.0% severe; $p<0.05$), and for intensity at each time point at Day 3 ($p<0.01$) and Day 7 ($p<0.05$). Pain occurred in 70.0% of subjects in the *Emervel Lips* groups and in 85.0% of subjects in the control group overall during the evaluation period.

Altogether, no unexpected reactions or AEs were reported and results indicated tolerability of the *Emervel Lips* treatment compared to the control treatment, especially in terms of less edema/swelling after treatment, and a better tolerability profile for erythema and pain. There were no statistically significant differences between the groups with regard to bruising or pruritus intensity.

The GAIS assessments showed high aesthetic improvement of the lips both in the *Emervel Lips* group and in the control group. Based on the subject satisfaction questionnaire, the majority of subjects showed high satisfaction rates in both groups. The Lip Fullness Grading Scale (LFGS) assessments showed a smaller than expected improvement in lip fullness in both treatment groups. However, the validity of this evaluation is limited due to the pre-defined treatment volume (0.5 mL in each lip for all subjects) and no stratification at baseline regarding baseline LFGS scores.

Study 05DF1215: This was a 12-month, randomized, evaluator-blinded, comparative, multicenter study of the safety and effectiveness of lip injections with *Emervel Lips Lidocaine* and control with Lidocaine conducted at three sites in Europe. Sixty (60) subjects were randomized 1:1 to treatment with either *Emervel Lips Lidocaine* or control with Lidocaine. Blinding was accomplished by using a treating investigator to administer the treatments and blinded evaluators, to whom randomization and treatment were concealed, to conduct blinded assessments after study end, based on photographs. Assessments were also performed by the treating investigator.

Subjects with very thin, thin or moderately thick lips according to the LFGS were included. Subjects were optimally treated, which was defined as ≥1 grade improvement in fullness of each lip according to the LFGS. A touch-up treatment could be administered after 2 weeks to achieve optimal result. A maximum volume of 3 mL (1.5 mL in each lip) was injected at the initial and touch-up treatment combined. The study products contained lidocaine hydrochloride, but additional local anesthesia was allowed to be used. After treatment, the subject assessed pain during injection, and the investigator evaluated treatment procedures and product palpability. An optional retreatment was offered at the last visit (month 12). Each subject was involved in the study for approximately 12 months.

Global aesthetic improvement by GAIS score was assessed by the blinded evaluators (after study end, by evaluation of photographs), the treating investigator and the subject at follow-up after treatment. LFGS score was assessed by the blinded evaluators (after study end, by evaluation of photographs) and treating investigator at screening and at follow-up after treatment.

The subject assessed intensity of signs and symptoms of local tolerability (bruising, redness, pain, tenderness, itching and swelling) in a subject diary for 14 days after treatment. A subject satisfaction questionnaire was completed before treatment and at follow-up after treatment. AEs were recorded throughout the study and device deficiency after treatment.

There were no statistically significant differences between the groups regarding aesthetic improvement of both lips up to month 12 based on the treating investigators', blinded evaluators' or subjects GAIS scores. In general, GAIS assessments showed improvement in both lips in the majority of subjects (≥ 80.0%) up to month 6 and in more than a third of subjects (≥ 39.3%) up to month 12.

There were no statistically significant differences between groups at any time point with regard to LFGS improved subjects and similar subject proportions had improvement in the upper and lower lips. There were no statistically significant differences between groups with regard to mean change from baseline in LFGS for the upper or lower lips, based on the treating investigator's assessments.

No statistically significant differences between groups were found in the subject proportions with LFGS improvement in both lips at month 6 or month 12, based on the blinded evaluations. Based on the subject questionnaire, a majority of subjects in both groups were more satisfied with the fullness of their lips after treatment. The improvement was comparable for the two groups. The satisfaction for the Emervel Lips group went from 6.5% before treatment to 64.0% after treatment for subjects who were very or somewhat satisfied at month 12.

All subjects in both groups reported at least one local reaction within 14 days of initial treatment. The most common reactions were swelling, bruising and tenderness, each of which were reported by >93% of subjects in both groups. This was followed by pain, reported by close to 75% in both treatment groups, and redness, reported by 87.1% in the *Emervel Lips* group and 62.1% in the control group. Itching occurred in less than 38% of subjects in both groups.

Most local reactions had a mild or moderate maximum intensity. Most local reactions resolved within 14 days after treatment and very few subjects had reactions later than this, i.e. that were reported as AEs. None of the local reactions that were reported as AEs had a duration of more than 32 days.

Most subjects reported mild or moderate pain during treatment and pain assessment was overall similar in both groups. At the touch-up treatment, subjects tended to report a lower intensity of pain (mostly mild) than at the initial treatment.

The palpability findings following both the initial and touch-up treatments were comparable in the two groups. Two weeks after the initial treatment, abnormal palpability was reported in the upper lip of two subjects (6.5%) in the *Emervel Lips* group and three subjects (10.3%) in the control group, and in the lower lip of two subjects (6.5%) in the *Emervel Lips* group and one subject (3.4%) in the control group. All abnormal palpability results from this assessment were reported as AEs with the PT.

The total number of subjects reporting AEs was comparable in the two groups: 20 subjects (64.5%) in the *Emervel Lips* group had 61 AEs and 18 subjects (62.1%) in the control group had 42 AEs in the study. There was one death in the study (sudden death in Subject 205, control group) and two non-fatal SAEs (inflammation of the great toe of the right foot in Subject 219, *Emervel Lips*; and acute cholecystitis in Subject 305, *Emervel Lips*). None of the SAEs were judged as related to study treatment.

Most AEs were of mild (51 events) or moderate intensity (39 events). Thirteen AEs were of severe intensity. Of the severe events, three AEs were judged as related to study product and/or to the injection procedure: swelling of the upper and lower lips in Subject 209 (control) and suspected allergic reaction (PT: hypersensitivity) in Subject 318 (control).

The most common AEs that were judged as related to treatment (to study product and/or to the injection procedure) were implant site papules, implant site pain, and implant site swelling. In addition, the following AEs judged as related to treatment occurred in single subjects: implant site erythema, implant site nodule, implant site pruritus, hypersensitivity, oral herpes, hyperesthesia, and skin discoloration. Implant site papules were less common in the *Emervel Lips* group than in the control group (6.5% vs. 24.1% of subjects) and implant site pain was more common in the *Emervel Lips* group (12.9% vs. 3.4% of subjects). The differences in implant site papules and implant site pain were not statistically significant.

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

In accordance with the provisions of section 515(c)(3) 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.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

Assessment of product effectiveness is based on the results of the U.S. pivotal study 43USK1701. These submitted data provided a reasonable assurance that *Restylane® Kysse* is effective for injection into the lips for lip augmentation and the correction of upper perioral rhytids in patients over the age of 21.

Conclusions from this study are:

- The primary objective of the study was met. The CIs for the Blinded Evaluator MLFS assessment at Week 8 for both the ITT and PP analysis populations were below 0.5 for the upper and lower lips, demonstrating that non-inferiority of *Restylane® Kysse* to the control was established. The results of the sensitivity analysis also support the conclusion of non-inferiority of *Restylane® Kysse*.

- For the *Restylane® Kysse* treatment group, a majority of subjects (≥ 60%) were assessed as a MLFS responder by the Blinded Evaluator through Week 48 (upper and lower lips, separately and combined). A responder was defined as at least a 1 point improvement from the baseline MLFS score.

- Subjects treated with *Restylane® Kysse* in the upper perioral rhytids had at least a 1-point mean decrease in wrinkle severity at all assessment time points, and a majority (≥83% (44/53)) were responders through Week 48 as assessed by the Blinded Evaluator using the WAS.

- Subjects treated with *Restylane® Kysse* in the oral commissures had at least a 1-point mean decrease in wrinkle severity at all assessment time points, and a majority (>57%, 74/129) were responders through Week 48 as assessed by the Blinded Evaluator using the WAS.

- For the upper and lower lips at Week 8, separately and combined, almost all subjects in the *Restylane® Kysse* treatment group (175/178, 98%) were assessed as improved or better from baseline according the Treating Investigator's assessment using the GAIS, and the proportion of responders remained high through Week 48 (71% (120/169) upper lip, 76% (128/169) lower lip, and 67% (114/169) upper and lower lips combined). A responder was defined as at least "improved" (i.e., improved, much improved, or very much improved) on the GAIS.

- For the *Restylane® Kysse* treatment group, subject assessment of aesthetic improvement using the GAIS was high at all assessment time points throughout the study. At Week 8, 96% (170/178) of subjects assessed their upper and lower lips, separately and combined, as "improved" or better compared to baseline, and improvement was maintained through Week 48 for a majority of subjects (≥ 78% (132/169)).

- Per the Satisfaction with Lips Questionnaire, there was a high level of subject satisfaction following treatment with *Restylane® Kysse* per the FACE-Q mean total score, and lip satisfaction was maintained through Week 48 for the majority of subjects.

- Per the Appraisal of Lines: Lips FACE-Q Questionnaire subjects were less bothered by the lines around their lips following treatment with *Restylane® Kysse*, and the majority of subjects (≥ 63%, 107/169) were less bothered by the appearance of lines around their lips through Week 48.

- For the *Restylane® Kysse* treatment group, the proportion of upper and lower lip responders as correctly identified by the IPR based on blinded pairings of the baseline and post-baseline subject photographs was high (≥ 84%, 138/164) at each of the assessment time points.

- For the exploratory effectiveness analysis by subgroup (i.e., study site, FST, and race), the results at Week 8 were consistent with the primary analysis based on the difference of means in the MLFS for the upper and lower lips (control minus *Restylane® Kysse*).

B. Safety Conclusions

The assessment of product safety is based on nonclinical laboratory and animal studies as well as data evaluated in clinical study 43USK1701 to support PMA approval as described above. These submitted data provided a reasonable assurance of safety of *Restylane® Kysse* for injection into the lips for lip augmentation and the correction of upper perioral rhytids in patients over the age of 21.

Conclusions from this study are:

- The majority of subjects in the *Restylane® Kysse* and control treatment groups did not report any TEAEs during the initial treatment period (i.e., events occurring after the initial treatment but before retreatment at 48 weeks) (61.1% and 64.8%, respectively).

- Overall, a vast majority of all related TEAEs in each treatment group were assessed as mild (*Restylane® Kysse* 115/120 events [95.8%], control group 74/81 events [91.4%]); few related events were assessed as moderate, and none were assessed as severe.

- Of the commonly reported related TEAEs (i.e., injection site mass, injection site bruising, and injection site nodule), almost all were assessed as mild in both the *Restylane® Kysse* and control treatment groups; only one event of injection site bruising was assessed as moderate.

- For the *Restylane® Kysse* treatment group, related TEAEs typically occurred on the day of treatment (i.e., median time to onset was 0 days); for the control group the median time to onset was 1 day. Following retreatment with *Restylane® Kysse* at Week 48, a similar result was observed (1 day).

- Late onset events (i.e., $\geq$ 21 days) were reported in both the *Restylane® Kysse* and control treatment groups (5.4% [10/185 subjects] and 5.7% [5/88 subjects], respectively). There was no significant difference in the reporting frequency between the treatment groups. All events in both treatment groups were mild or moderate in intensity, and resolved or were assessed as stable.

- For the *Restylane® Kysse* treatment group, the median duration of related TEAEs following initial treatment was 13.5 days; for the control group it was 15.0 days. Following retreatment with *Restylane® Kysse* at Week 48, the median duration of related TEAEs was shorter (9.0 days).

- A similar percentage of subjects in the *Restylane® Kysse* and control treatment groups had unrelated events (23.8% and 25.0%, respectively). Most of the unrelated TEAEs in the *Restylane® Kysse* group were assessed as mild; in the control group, most were assessed as moderate. There were two unrelated SAEs reported. In addition, two pregnancies were reported; both subjects carried to term with no complications.

- TEAE or TEAE related to the product and/or injection procedure following retreatment with *Restylane® Kysse* at Week 48 occurred at a lower incidence rate compared to initial treatment.

- The majority of all symptoms recorded in the subject diaries were considered tolerable (≥ 67.6%), and typically lasted for less than 2 weeks.

- None of the lip safety assessments were remarkable or presented any safety concerns.

- Exploratory safety analyses by subgroup (i.e., study site, injection volume, and FST) were consistent with the AE data overall.

C. Benefit-Risk Determination

The probable benefits of the device are based on data collected in a randomized, controlled, evaluator-blinded, multi-center study in the US. Summary of effectiveness is provided above and includes improved lip fullness as determined by MLFS assessments, improvement of upper perioral rhytids as determined by a blinded evaluator using WAS, and an improved global aesthetic appearance according to investigators' and subjects' GAIS assessments.

Expected injection related adverse reactions such as injection site mass, injection site bruising, and injection site nodule are well known and normally transient. The most common AEs that were judged as related to treatment were implant site papules, implant site pain, and implant site swelling. No related serious adverse event occurred, and sub group analysis did not reveal any concerns. Short term reactions related to the injection procedure are expected and sufficiently well understood for patients to make informed decisions about device use.

Additional factors to be considered in determining probable risks and benefits for *Restylane® Kysse* included:

1. Patient Perspectives
   Patient perspectives considered during the review included:

   - Subject safety diary to record injection site responses (ISRs) for 30 days following each injection.
   - Global Aesthetic Improvement Scale (GAIS) as assessed by the subject at all time points.
   - Effectiveness of study treatment from the subject's perspective as assessed by the Satisfaction with Lips Questionnaire and Appraisal of Lines: Lips FACE-Q Questionnaire patient-reported outcome measurement.

In conclusion, given the available information above, the data support that for injection into the lips for lip augmentation and the correction of upper perioral rhytids in patients over the age of 21, the probable benefits outweigh the probable risks.

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.

XIV. CDRH DECISION

CDRH issued an approval order on March 26, 2020.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. 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.