

## ***Restylane*<sup>®</sup> *Kysse***

**Caution:** Federal (USA) law restricts this device to sale by or on the order of a licensed physician or properly licensed practitioner.

### **BEFORE USING PRODUCT, READ THE FOLLOWING INFORMATION THOROUGHLY.**

## **1 DEVICE DESCRIPTION**

*Restylane*<sup>®</sup> *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*<sup>®</sup> *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.

## **2 INTENDED USE/INDICATIONS**

*Restylane*<sup>®</sup> *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.

## **3 CONTRAINDICATIONS**

- *Restylane*<sup>®</sup> *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*<sup>®</sup> *Kysse* may contain trace amounts of gram-positive bacterial proteins and is contraindicated for patients with a history of allergies to such material.
- *Restylane*<sup>®</sup> *Kysse* contains lidocaine and is contraindicated for patients with a history of allergies to such material or other amide type anesthetics.

## **4 WARNINGS**

- Introduction of *Restylane*<sup>®</sup> *Kysse* into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction. Take extra care when injecting soft tissue fillers, for example inject the product slowly and apply the least amount of pressure necessary. Rare but serious adverse events associated with the intravascular injection of soft tissue fillers in the face have been reported and include temporary or permanent vision impairment, blindness, cerebral ischemia or cerebral hemorrhage, leading to stroke, skin necrosis, and damage to underlying facial structures. Immediately stop the injection if a patient exhibits any of the following symptoms, including changes in vision, signs of a stroke, blanching of the skin or unusual pain during or shortly after the procedure. Patients should receive prompt medical attention and possibly evaluation by an appropriate health care professional specialist should an intravascular injection occur (see Health Care Professional Instructions).
- Defer use of *Restylane*<sup>®</sup> *Kysse* at specific sites in which an active inflammatory process (skin eruptions such as cysts, pimples, rashes, or hives) or infection is present until the process has been controlled.

- *Restylane*<sup>®</sup> *Kysse* must not be implanted into blood vessels and should not be used in vascular rich areas. Localized superficial necrosis and scarring may occur after injection in or near vessels, such as in the lips. It is thought to result from the injury, obstruction, or compromise of blood vessels. Special caution should be taken if the patient has undergone a prior surgical procedure in the planned treatment area.
- Delayed onset inflammatory papules have been reported following the use of dermal fillers. Inflammatory papules should be considered and treated as a soft tissue infection. For additional information please see Adverse Events section.

## 5 PRECAUTIONS

- *Restylane*<sup>®</sup> *Kysse* is packaged for single-patient and single-session use only. Do not resterilize. Do not use if package is open or damaged.
- *Restylane*<sup>®</sup> *Kysse* is to be used as supplied. Modification or use of the product outside the Directions for Use may adversely impact the sterility, homogeneity, and performance of the product.
- In order to minimize the risks of potential complications, this product should only be used by health care professionals who have appropriate training, experience, and who are knowledgeable about the anatomy at and around the site of injection.
- Health care professionals are encouraged to discuss all potential risks of soft tissue injection with their patients prior to treatment and ensure that patients are aware of signs and symptoms of potential complications.
- The recommended maximum injected volume per subject and treatment is 6 mL (i.e., 3 mL for lips and 3 mL for perioral area).
- As with all transcutaneous procedures, dermal filler implantation carries a risk of infection. Standard precautions associated with injectable materials should be followed.
- Avoid injecting *Restylane*<sup>®</sup> *Kysse* into areas in close proximity to permanent implants, as this could potentially aggravate latent adverse events or interfere with the aesthetic outcome of the treatment. Limited data is available on injecting *Restylane*<sup>®</sup> *Kysse* into an area where an implant other than hyaluronic acid has been placed.
- Post inflammatory pigmentation changes may occur after dermal filler injections in people with dark skin (Fitzpatrick Type IV-VI).
- Injections of *Restylane*<sup>®</sup> *Kysse* into patients with a history of previous herpetic eruption may be associated with reactivation of the herpes.
- *Restylane*<sup>®</sup> *Kysse* should be used with caution in patients on immunosuppressive therapy.
- *Restylane*<sup>®</sup> *Kysse* should be used with caution in patients with bleeding disorders.
- Patients who are using substances that can prolong bleeding (such as aspirin, nonsteroidal anti-inflammatory drugs, and warfarin) may, as with any injection, experience increased bruising or bleeding at treatment sites.
- The safety of *Restylane*<sup>®</sup> *Kysse* with concomitant dermal therapies such as epilation, UV irradiation, or laser, mechanical or chemical peeling procedures has not been evaluated in controlled clinical trials. If laser treatment, chemical peeling or any other procedure based on active dermal response is considered after treatment with *Restylane*<sup>®</sup> *Kysse*, there is a possible risk of eliciting an inflammatory reaction at the implant site. This also applies if *Restylane*<sup>®</sup> *Kysse* is administered before the skin has healed completely after such a procedure.
- Patients should minimize exposure of the treated area to excessive sun, UV lamp exposure and extreme cold weather at least until any initial swelling and redness has resolved.

- The safety of *Restylane*<sup>®</sup> *Kysse* for use during pregnancy, in breastfeeding females or in patients under 22 years has not been established.
- Individual variation and treatment area may affect the bio-degradation of *Restylane*<sup>®</sup> *Kysse*, product remnants may remain in the tissue even when the clinical effect has returned to baseline.
- Failure to comply with the needle attachment instructions could result in needle disengagement and/or product leakage at the Luer lock and needle hub connection.
- After use, treatment syringes and needles may be potential biohazards. Handle and dispose of these items in accordance with accepted medical practice and applicable local, state, and federal requirements.
- *Restylane*<sup>®</sup> *Kysse* injectable gel is a clear, colorless gel without particulates. In the event that the content of a syringe shows signs of separation and/or appears cloudy, do not use the syringe.
- *Restylane*<sup>®</sup> *Kysse* should not be mixed with other products before implantation of the device.
- Considerations should be given to the total dose of lidocaine administered if dental block or topical administration of lidocaine is used concurrently. High doses of lidocaine (more than 400 mg) can cause acute toxic reactions manifesting as symptoms affecting the central nervous system and cardiac conduction.
- Lidocaine should be used with caution in subjects receiving agents structurally related to amide-type anesthetics, e.g. certain anti-arrhythmics, since the systemic toxic effects can be additive.
- Lidocaine should be used with caution in patients with epilepsy, impaired cardiac conduction, severely impaired hepatic function or severe renal dysfunction.

## 6 ADVERSE EVENTS

### A. US Pivotal Study of *Restylane*<sup>®</sup> *Kysse*

In the randomized, controlled, evaluator-blinded, multi-center clinical trial to evaluate the safety and effectiveness of *Restylane*<sup>®</sup> *Kysse* versus control for lip augmentation and correction of perioral rhytids, in total 273 subjects were randomized and treated in a 2:1 ratio with either *Restylane*<sup>®</sup> *Kysse* or control.

Preprinted diary forms were completed by subjects to record specific signs and symptoms experienced during the 30 days after initial treatment, touch-up treatment (if performed), and retreatment (if performed). Subjects rated each injection site reactions (ISR) as None, Tolerable, Affects Daily Activities, or Disabling.

The intensity and duration of ISRs reported by > 5% of subjects who completed the diary following initial treatment are summarized in Table 1 and Table 2, respectively. Table 3 shows the intensity and duration of ISR after retreatment reported by > 5% of subjects. The majority of ISRs were tolerable in intensity, and lasted less than 2 weeks.

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

**Table 1 Injection Site Reactions in the Lips by Maximum Intensity after Initial Treatment<sup>[1]</sup>**

Diary Symptom	Restylane <sup>®</sup> Kysse (N=185)				Control (N=88)			
	Total % (n/N) <sup>[2]</sup>	Tolerable %	Affects Daily Activities %	Disabling %	Total % (n/N) <sup>[2]</sup>	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
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 2 Injection Site Reactions in the Lips by Duration after Initial Treatment<sup>[1]</sup>**

Diary Symptom	Restylane <sup>®</sup> Kysse (N=185)					Control (N=88)				
	Total % (n/N) <sup>[2]</sup>	1-3 Days %	4-7 Days %	8-14 Days %	15-30 Days %	Total % (n/N) <sup>[2]</sup>	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

Diary Symptom	<i>Restylane</i> <sup>®</sup> <i>Kysse</i> (N=185)					Control (N=88)				
	Total % (n/N) <sup>[2]</sup>	1-3 Days %	4-7 Days %	8-14 Days %	15-30 Days %	Total % (n/N) <sup>[2]</sup>	1-3 Days %	4-7 Days %	8-14 Days %	15-30 Days %
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 3 Injection Site Reactions in the Lips by Maximum Intensity and Duration after Retreatment**

Subjects Received Re-Treatment (N=117)								
Diary Symptom	Total % (n/N) <sup>[1]</sup>	Intensity			Duration			
		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.

Adverse events (AEs) were evaluated by Investigators throughout entirety of the study. After initial and touch up treatment, treatment-related treatment-emergent AEs were reported in 21.1% (39/185) of subjects treated with *Restylane*<sup>®</sup> *Kysse* and 25.0% (22/88) of subjects treated with control.

Regardless of treatment group, most related TEAEs were mild in severity and required no action. There were no treatment-related serious adverse events reported.

The severity and duration of TEAEs occurring in > 5% of subjects in either treatment group are summarized in Table 4 and Table 5.

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. Treatment-related AEs occurring in ≤ 5% of subject after initial and touch-up treatment 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 4 Treatment Related AEs Occurring ≥ 5% of Subjects by Maximum Severity after Initial/Touch-up Treatment**

Adverse Event	<i>Restylane</i> <sup>®</sup> <i>Kysse</i> (N=185)				Control (N=88)			
	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 5 Treatment Related AEs Occurring ≥ 5% of Subjects by Duration after Initial/Touch-up Treatment**

Adverse Event	<i>Restylane Kysse</i> <sup>®</sup> (N=185)						Control (N=88)					
	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.

There was no significant difference in the reporting frequency of late onset events (i.e., ≥ 21 days) between the *Restylane*<sup>®</sup> *Kysse* and control treatment groups (5.4% and 5.7%, respectively). In the *Restylane*<sup>®</sup> *Kysse* treatment group, 10 subjects reported 16 late onset events, including: injection site mass, injection site swelling, injection site nodule, injection site hypersensitivity, and oral herpes. In the control group, 5 subjects reported 11 late onset events, including: injection site hypersensitivity, injection site oedema, injection site mass, angioedema, injection site bruising, and injection site nodule. All events in both treatment groups were mild or moderate in intensity, and resolved or were assessed as stable.

At the Week 48 visit, a majority of subjects in the *Restylane*<sup>®</sup> *Kysse* treatment group reported no adverse events following retreatment at Week 48 (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. The severity and duration of TEAEs occurring in > 5% of subjects following retreatment are summarized in Table 6 and Table 7.

**Table 6 Treatment Related AEs Occurring  $\geq$  5% of Subjects by Maximum Severity after Retreatment**

Adverse Event	<i>Restylane</i> <sup>®</sup> <i>Kysse</i> (N=117)			
	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 7 Treatment Related AEs Occurring  $\geq$  5% of Subjects by Duration Severity after Retreatment**

Adverse Event	Events	<i>Restylane</i> <sup>®</sup> <i>Kysse</i> (N=117)				
		$\leq$ 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.

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 assessments were remarkable or presented any safety concerns.

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

## B. Other Safety Data

*Restylane*<sup>®</sup> *Kysse* was previously named *Emervel Lips Lidocaine*.

**Study 05DF1210:** In a randomized, evaluator-blinded, comparative 24-week study of the safety and efficacy of lip injections conducted at one site in Europe, 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. 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 a better local 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.

**Study 05DF1215:** In a randomized, evaluator-blinded, comparative, multi-center study at three sites in Europe, 60 subjects were randomized 1:1 to treatment with either *Emervel Lips Lidocaine* or control with Lidocaine. Subjects with very thin, thin or moderately thick lips according to the Merz Lip Fullness Grading Scale (LFGS) were included. Subjects were optimally treated, which was defined as  $\geq 1$  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.

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 were three SAEs in the study; none were treatment related.

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, hyperaesthesia, 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.

### C. Post-Market Surveillance

The adverse event reports received from post-marketing surveillance (voluntary reporting and published literature) for the use of *Restylane*<sup>®</sup> *Kysse* with and without lidocaine from worldwide sources mostly reports of transient swelling/edema with immediate onset or delayed onset, up to several weeks after treatment.

The following events were also reported in decreasing order of frequency:

- 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 hypoaesthesia and paraesthesia,
- Device dislocation,
- Eye disorders such as lacrimation increased,
- Rash,
- Scar/scab/skin atrophy,
- Capillary disorders including capillary fragility and telangiectasia,
- Reactivation of herpes infection,
- Urticaria,
- Acne,
- Dermatitis,
- Discharge,
- Granuloma/foreign body reaction,

- Overcorrection,
- Non-dermatological events such as insomnia, discomfort and dyspnoea and
- Other dermatological events such as dry skin and skin tightness.

Injection related adverse events such as bruising, erythema, itching, swelling, pain and tenderness are anticipated and expected to generally resolve spontaneously within one week after injection.

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 impairment and encapsulation.

When required, treatments for these events included corticosteroids, antibiotics, antihistamines, NSAIDs and aspiration/drainage or enzymatic degradation (with hyaluronidase) of the product. Reports of serious adverse events are very 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. Isolated rare cases of ischemic events affecting the eye leading to visual loss, and the brain resulting in cerebral infarction, following facial aesthetic treatments have been reported. Reported treatments include anticoagulant, epinephrine, aspirin, hyaluronidase, corticosteroid treatment, analgesics, antibiotics, local wound care, drainage, surgery and hyperbaric oxygen.

Symptoms of inflammation at the implant site commencing either shortly after injection or after a delay of up to several weeks have been reported. In case of unexplained inflammatory reactions, infections should be excluded and treated if necessary since inadequately treated infections may progress into complications such as abscess formation. Treatment using only oral corticosteroids without concurrent antibiotic treatment is not recommended. The prolonged use of any medication, e.g., corticosteroids or antibiotics in treatment of adverse events has to be carefully assessed, since this may carry a risk for the patient. In case of persistent or recurrent inflammatory symptoms, consider removal of the product by aspiration/drainage, extrusion or enzymatic degradation (use of hyaluronidase has been described in scientific publications). Before any removal procedure is performed, the swelling may be reduced by using e.g. NSAID for 2-7 days or a short course of corticosteroids for less than 7 days, in order to more easily palpate any remaining product.

## 7 Clinical Studies

### A. Pivotal Study of *Restylane*<sup>®</sup> *Kysse*

#### **Pivotal Study Design**

A randomized, controlled, evaluator-blinded, multi-center study was conducted to evaluate the safety and effectiveness of *Restylane*<sup>®</sup> *Kysse* versus control for lip augmentation and correction of perioral rhytids. 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. There were 273 subjects randomized in the study and treated in a 2:1 ratio with either *Restylane*<sup>®</sup> *Kysse* or control.

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*<sup>®</sup> *Kysse* if optimal aesthetic improvement was not maintained. If retreatment was performed, a 2-week and 4-week follow-up visits were scheduled.

#### **Study Endpoints**

The primary analysis of non-inferiority of *Restylane*<sup>®</sup> *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 Medicis Lip Fullness Scale (MLFS).

Secondary effectiveness measures included: a) change from baseline and responder rates for each lip separately based on the Blinded Evaluator 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 FACE-Q scales Satisfaction with Lips and Appraisal of Lines, and e) responders rates as assessed by a Independent Photographic Reviewer (IPR).

Safety measures included a) the incidence, intensity, and duration of predefined, expected post-treatment events collected 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.

#### **Subject Demographics**

Subject demographics and pretreatment characteristics for the *Restylane*<sup>®</sup> *Kysse* to the control groups are presented in Table 8.

**Table 8 Subject Demographics and Pretreatment Characteristics: ITT Population (N=270)**

		<b>Restylane® Kysse (N=183)</b>	<b>Control (N=87)</b>
<b>Age (years):</b>	Mean (S.D.)	52.4 (13.5)	53.6 (10.8)
	Min,Max	22, 82	22, 75
<b>Gender:</b>	Female	176 (96.2)	85 (97.7)
	Male	7 (3.8)	2 (2.3)
<b>Race:</b>	White	173 (94.5%)	81 (93.1%)
	Black or African American	7 ( 3.8%)	2 (2.2%)
	Asian	1 (< 1%)	1 (1.1%)
	American Indian or Alaska Native	1 (< 1%)	0
	Native Hawaiian or Other Pacific Islander	0	1 (1.1%)
	Other Race Reported	1 (< 1%)	1 (1.1%)
	Multiple Races Reported	0	1 (1.1%)
<b>Fitzpatrick Skin Type:</b>	I	7 (3.8%)	4 (4.5%)
	II	77 (42.0%)	31 (35.6%)
	III	63 (34.4%)	34 (39.0%)
	IV	23 (12.5%)	13 (14.9%)
	V	10 (5.4%)	4 (4.5%)
	VI	3 (1.6%)	1 (1.1%)
<b>Baseline Upper Lip Fullness:</b>	1-Very Thin	99 (54.0%)	43 (49.4%)
	2-Thin	72 (39.3%)	40 (45.9%)
	3-Medium	4 (2.1%)	1 (1.1%)
	4-Full	8 (4.3%)	3 (3.4%)
	5-Very Full	0	0
<b>Baseline Lower Lip Fullness:</b>	1-Very Thin	71 (38.7%)	46 (52.8%)
	2-Thin	101 (55.1%)	38 (43.6%)
	3-Medium	7 (3.8%)	1 (1.1%)
	4-Full	4 (2.1%)	2 (2.2%)
	5-Very Full	0	0

**Treatment Characteristics**

For the *Restylane® Kysse* treatment group, the total median volume injected for initial and touch-up treatment combined and all areas treated was 2.50 mL. Subjects received a total median volume of 0.90 mL in the upper lip, 0.80 mL in the lower lip, 0.73 mL in the oral commissures, and 0.20 mL in the perioral lines. Less injection volume was needed to achieve optimal correction in the lips and other treatment areas at retreatment; the total median volume injected at this time point was 1.30 mL.

For the control treatment group, the total median volume injected for initial and touch-up treatment combined and all areas treated was 3.35 mL. Subjects received a total median volume of 1.13 mL in

the upper lip, 1.00 mL in the lower lip, 1.00 mL in the oral commissures, and 0.41 mL in the perioral lines.

For both treatment groups, the upper and lower lips were primarily injected in the submucosal. For the oral commissures and perioral lines, injections were subcutaneous or in the mid or deep dermis. Most subjects received a combination of injection techniques in each treatment area; most common methods included serial puncture and linear antegrade.

### **Effectiveness Results**

The primary endpoint of the study was met. The mean change from the baseline MLFS score for the *Restylane*<sup>®</sup> *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. The confidence intervals for the Blinded Evaluator MLFS assessment at Week 8 for both the ITT and PP analysis populations were entirely below 0.5 for the upper and lower lips, demonstrating that non-inferiority of *Restylane*<sup>®</sup> *Kysse* to the control was established.

For subjects treated with *Restylane*<sup>®</sup> *Kysse*, lip fullness was maintained throughout the follow up period for a majority of subjects. For the upper and lower lips combined, the proportion MLFS responders by assessment time point is presented in Table 9. A responder was defined as at least a 1-point improvement from the baseline MLFS score.

**Table 9 Effectiveness Results Through Week 48**

	<i>Restylane</i> <sup>®</sup> <i>Kysse</i> % (n/N)
<b>Week 8</b>	88% (155/177)
<b>Week 16</b>	82% (142/174)
<b>Week 24</b>	77% (129/168)
<b>Week 32</b>	69% (115/167)
<b>Week 40</b>	66% (110/166)
<b>Week 48</b>	60% (101/169)

Subjects treated with *Restylane*<sup>®</sup> *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 (44/53, 83%) were responders through Week 48 as assessed by the Blinded Evaluator using the WAS.

Subjects treated with *Restylane*<sup>®</sup> *Kysse* in the oral commissures had at least a 1-point mean decrease in wrinkle severity at all assessment time points, and a majority (74/129, 57%) 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*<sup>®</sup> *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*<sup>®</sup> *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 (132/169, 78%).

Per the Satisfaction with Lips Questionnaire, there was a high level of subject satisfaction following treatment with *Restylane*<sup>®</sup> *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*<sup>®</sup> *Kysse*, and the majority of subjects (107/169, 63%) were less bothered by the appearance of lines around their lips through Week 48.

For the *Restylane*<sup>®</sup> *Kysse* treatment group, the proportion of upper and lower lip responders as correctly identified by the Independent Photographic Reviewer (IPR) based on blinded pairing of the baseline and post-baseline subject photographs was high (138/164, 84%) 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*<sup>®</sup> *Kysse*).

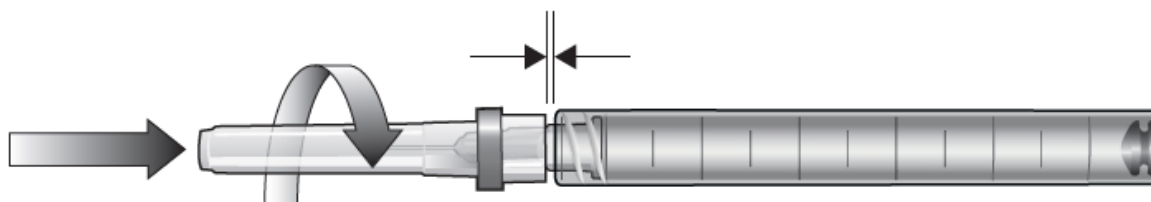
## 8 INSTRUCTIONS FOR USE

### A. To Attach Needle to Syringe

Use surgical gloves, remove the cap from the needle and the tip cap from the syringe. Hold firmly around the syringe barrel and grasp the needle shield with the other hand. Screw the needle tight onto the syringe by simultaneously pushing and rotating firmly until the needle is completely locked. To ensure proper assembly, minimize the gap between the needle shield and the syringe. See the figure below.

Remove the needle shield just before injection by pulling it straight out. Do not rotate.

**Note:** Improper assembly may cause leakage or needle disconnection.



### B. Health Care Professional Instructions

1. *Restylane*<sup>®</sup> *Kysse* contains lidocaine hydrochloride, but additional local anesthesia/nerve block may be used to further reduce pain on injection.
2. Aseptic technique and standard practice to prevent cross-infections should be observed at all

times including the use of disposable gloves during the injection procedure. All traces of make-up below the level of the lower orbital rim should be removed prior to any injection. The treatment site should be cleaned with a suitable antiseptic solution.

3. To avoid breakage of the needle, do not attempt to bend or otherwise manipulate it before or during treatment. If needle gets bent, discard it and complete the procedure with a replacement needle. Do not re-shield used needles. Recapping by hand is a hazardous practice and should be avoided. Discard unshielded needles in approved sharps collectors.
4. Before injection, press the plunger rod carefully until a small droplet is visible at the tip of the needle and the plunger is at the 1 mL graduation mark.
5. If the needle is blocked, do not increase the pressure on the plunger rod. Instead, stop the injection and replace the needle.
6. After insertion of the needle, and just before injection, the plunger rod should be withdrawn slightly to aspirate and verify the needle is not in a blood vessel. Inject slowly by gently pressing down on the plunger rod with the thumb or palm of the hand. Do not apply excessive pressure to the syringe at any time. Presence of scar tissue may impede advancement of the needle/cannula. If resistance is encountered the needle/cannula should be partially withdrawn and repositioned or fully withdrawn and checked for function.
7. The injection technique may vary based on the subject's treatment needs and the health care professional's experience and preference. The techniques may include:
  - *Linear antegrade threading*: also called push-ahead technique as some product is pushed ahead of the needle. Once the needle is in place, the product is injected on withdrawal of the needle.
  - *Linear retrograde threading*: the needle is threaded into the tissue at the appropriate depth, and the product is injected as a straight line on withdrawal of the needle.
  - *Serial puncture*: numerous small needle insertions to deliver a small bleb or bolus of the product, repeated along a line or regions of the tissues.
  - *Fern pattern*: vertical or diagonal linear threads with needle entry from the centre of line or the edge of vermilion border of the lip with the needle pushing into the body or vermilion of the lip and a taper-shaped pattern of product injected on withdrawal of the needle.
  - *Fan technique*: a number of linear threads to spread the product over a wider area.
  - *Other*: at the choice of the health care professional.
8. For lip augmentation, *Restylane*<sup>®</sup> *Kysse* should be injected into the submucosal layer of the lip. Care should be taken to avoid intramuscular injection. For correction of perioral rhytids and philtral column, *Restylane*<sup>®</sup> *Kysse* should be injected into the mid-dermis to the subcutaneous layer. If *Restylane*<sup>®</sup> *Kysse* is injected too superficially this may result in visible lumps and/or bluish discoloration. It is recommended to change needle for each new treatment site.
9. It is important that the injection is stopped just before the needle is pulled out of the skin to prevent material from leaking out or ending up too superficially in the skin.
10. It is recommended that the dose should not exceed 1.5 mL per upper lip and 1.5 mL per lower lip per treatment (touch-up included). Optional treatment of perioral rhytids and philtral

column may be performed. The recommended maximum injected volume per subject and treatment (touch-up volume included) is 6 mL.

11. Correct to 100% of the desired volume effect. Do not overcorrect.
12. If immediate blanching occurs, the injection should be stopped and the area massaged until it returns to a normal color. Blanching may represent a vessel occlusion. If normal skin coloring does not return, do not continue with the injection. Treat in accordance with American Society for Dermatologic Surgery guidelines, which include hyaluronidase injection.<sup>1</sup>
13. After each injection, the lip should be observed to assess the degree of enhancement and the uniformity of the implant. The lips should be gently palpated to ensure an even deposition of the implant. Palpated “skip areas” (areas not containing product) should be treated with additional implant material or by gentle massage of the area until a uniform implant is palpable.
14. When the injection is completed, the treated site should be gently massaged so that it conforms to the contour of the surrounding tissues. If an overcorrection should occur, the area should be firmly massaged between fingers to obtain optimal results. If the treated area is swollen directly after the injection, an ice pack can be applied on the site for a short period. Ice should be used with caution if the area is still numb from anaesthetic to avoid thermal injury.
15. Monitor the subject for at least one hour after the procedure in order to detect any immediate adverse events. Patients may have mild to moderate injection site reactions, which typically resolve within a few days.

### **C. Patient Instructions**

- The patient should be asked to avoid heat (sun bathing, sauna, steam baths, etc.) or extreme cold until any signs of local inflammation have disappeared.
- The patient should be asked to avoid touching or shaving the treated area and not to apply any creams or cosmetics in the treated area before the skin has healed completely in order to prevent infections or elicit an inflammatory reaction.
- The patient should also be reminded to abstain from prohibited medications, treatments and procedures.



## 9 HOW SUPPLIED

*Restylane*<sup>®</sup> *Kysse* is supplied in individual treatment syringes with needles as indicated on the carton. The volume in each syringe is as stated on the syringe label and on the carton. The content of the syringe is sterile. Do not resterilize. Do not use if package is open or damaged.

## 10 SHELF LIFE AND STORAGE

*Restylane*<sup>®</sup> *Kysse* must be used prior to the expiration date on the package. Store at a temperature of up to 25°C/77°F. Do not freeze. Protect from sunlight. Refrigeration is not required.

*Restylane*<sup>®</sup> *Kysse* injectable gel has a clear appearance. In the event that a syringe contains material that is not clear, do not use the syringe; notify Galderma Laboratories, L.P. immediately at 1-855-425-8722.

To place an order, contact Galderma Laboratories, L.P. at 1-855-425-8722

Rx only

U.S. Patent 8,357,795; 8,450,475; 8,822,676

**Manufactured for:**

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