# *Restylane® Silk*
# Injectable Gel with 0.3% Lidocaine

**Caution:** Federal Law restricts this device to sale by or on the order of a physician or licensed practitioner.

## DESCRIPTION

*Restylane Silk* is a gel of hyaluronic acid generated by *Streptococcus* species of bacteria, chemically crosslinked with BDDE, stabilized and suspended in phosphate buffered saline at pH=7 and concentration of 20 mg/mL with 0.3% lidocaine.

## INDICATION

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

## CONTRAINDICATIONS

- *Restylane Silk* is contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.
- *Restylane Silk c*ontains trace amounts of gram positive bacterial proteins, and is contraindicated for patients with a history of allergies to such material.
- *Restylane Silk* is contraindicated for patients with bleeding disorders.
- *Restylane Silk* is contraindicated for implantation in anatomical spaces other than the dermis or submucosal implantation for lip augmentation.
- *Restylane Silk* should not be used in patients with previous hypersensitivity to local anesthetics of the amide type, such as lidocaine.

## WARNINGS

- Defer use of *Restylane Silk* 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.
- Injection site reactions (e.g., lip swelling, lip pain, and contusion) to *Restylane Silk* have been observed as consisting mainly of short-term minor or moderate inflammatory symptoms starting shortly after treatment, with an average of less than 18 days duration in the lips. In some cases delayed onset of these events has been observed with a range of 21 to 142 days after treatment. Most events with delayed onset resolved within 18 days. Injection site swelling appears to occur more frequently with the linear antegrade method of injection. Rare post-market Restylane reports of immediate post-injection reactions included extreme swelling of lips, the whole face and symptoms of hypersensitivity such as anaphylactic shock.
- Introduction of product 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 practitioner specialist should an intravascular injection occur.

- *Restylane Silk* must not be implanted into blood vessels. Localized superficial necrosis and scarring may occur after injection in or near vessels, such as in the lips, nose, or glabellar area. It is thought to result from the injury, obstruction, or compromise of blood vessels.
- Delayed onset inflammatory papules have been reported following the use of dermal fillers. Inflammatory papules that may occur rarely should be considered and treated as a soft tissue infection.
- Injections of 3.0 mL or greater (upper and lower lip combined) per treatment session increases the occurrence of injection site reactions. If a volume of more than 3 mL is needed to achieve optimal correction, a follow-up treatment session is recommended.
- As with all dermal filler procedures, *Restylane Silk* should not be used in vascular rich areas. Use of similar products in these areas, such as glabella and nose, has resulted in cases of vascular embolization and symptoms consistent with ocular vessel occlusion, such as blindness. For additional information please see the Post-Marketing Surveillance in Adverse Events.

**PRECAUTIONS**

- Restylane Silk is packaged for single patient use. Do not resterilize. Do not use if package is opened or damaged.
- Health care practitioners 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.
- In order to minimize the risks of potential complications, this product should only be used by health care practitioners who have appropriate training, experience, and who are knowledgeable about the anatomy at and around the site of injection.
- The safety or effectiveness of *Restylane Silk* for the treatment of anatomic regions other than lips or perioral rhytids has not been established in controlled clinical studies. Refer to the clinical studies section for more information on implantation sites that have been studied.
- The safety and effectiveness of cannula injection of *Restylane Silk* have only been clinically evaluated in two brands of blunt-tip cannulas (DermaSculpt and Softfil) that are 25G-27G and 1 1/2 inches in length.
- The safety or effectiveness of *Restylane Silk* for the treatment of perioral rhytids with a small bore, blunt tip cannula has not been established in controlled clinical studies.
- The safety and effectiveness of *Restylane Silk* for lip augmentation has not been established in patients under the age of 22 years. There is limited information on the safety of *Restylane Silk* in patients less than 36 years of age. In a premarket study of *Restylane Silk* with needle injection (MA-1700-04), the incidence of injection site reactions in 60 patients less than 36 years was similar to the 157 patients between the ages of 36 and 65 years. The majority of these injection site reactions were mild in severity. In the premarket study of *Restylane Silk* with cannula injection (43USC1505), 17 subjects less than 36 years of age were studied, and the incidence of injection site reactions were similar to the 43 subjects between the ages of 36 and 72 years.
- As with all transcutaneous procedures, *Restylane Silk* implantation carries a risk of infection. Standard precautions associated with injectable materials should be

followed.

- The safety of *Restylane Silk* for use during pregnancy, in breastfeeding females or in patients under 18 years has not been established
- The safety in patients with known susceptibility to keloid formation has not been studied. Formation of keloids may occur after dermal filler injections including *Restylane Silk.* In a premarket study of *Restylane Silk* with needle injection (MA-1700-04), the incidence and severity of adverse events in 51 subjects with Fitzpatrick Skin Types IV (n=48) and V (n=3) was similar to that reported in the general population and no unique adverse events associated with these patient subgroups was observed. In the premarket study of *Restylane Silk* with cannula injection (43USC1505), the incidence and severity of adverse events in 13 subjects with Fitzpatrick Skin Types IV (n=8), V (n=3), and VI (n=2) were similar to those reported in the general population and no unique adverse events associated with these patient subgroups was observed.
- Hyperpigmentation may occur after dermal filler injections including *Restylane Silk.* Hyperpigmentation was not observed in the two *Restylane Silk* studies of 281 total subjects including subjects with Fitzpatrick Skin Types IV (n=56), V (n=6), and VI (n=2).
- The safety profile for Restylane Silk lip augmentation in persons of color is based upon information from 64 total subjects with Fitzpatrick Skin Types IV, V and VI from two clinical studies (MA-1700-04 and 43USC1505). Within this population, the incidence of adverse events was similar to the overall study population.
- *Restylane Silk* should be used with caution in patients on immunosuppressive therapy.
- Bruising or bleeding may occur at *Restylane Silk* injection sites. Patients who have undergone therapy with thrombolytics, anticoagulants, or inhibitors of platelet aggregation in the 3 weeks preceding treatment with *Restylane Silk* have not been studied.
- After use, syringes and needles/blunt cannula should be handled as potential biohazards.
- Disposal should be in accordance with accepted medical practice and applicable local, state and federal requirements.
- The safety of *Restylane Silk* with concomitant dermal therapies such as epilation, UV irradiation, or laser, mechanical or chemical peeling procedures has not been evaluated in controlled clinical trials.
- 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.
- If laser treatment, chemical peeling or any other procedure based on active dermal response is considered after treatment with *Restylane Silk,* there is a possible risk of eliciting an inflammatory reaction at the implant site. This also applies if *Restylane Silk* is administered before the skin has healed completely after such a procedure.
- Injection of *Restylane Silk* into patients with a history of previous herpetic eruption may be associated with reactivation of the herpes.
- *Restylane Silk* 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 and notify Galderma Laboratories, L.P. at 1-855-425-8722. Glass is subject to breakage under a variety of unavoidable conditions. Care should be taken with the handling of the glass syringe and with disposing of broken glass to avoid laceration or

other injury.
- *Restylane Silk* should not be mixed with other products before implantation of the device.

**ADVERSE EXPERIENCES**
There were two U.S. studies that reported adverse experiences. One study was conducted in support of the indication for submucosal implantation for lip augmentation and dermal implantation for correction of perioral rhytids, and one study was conducted in support of using a small bore, blunt-tip cannula for submucosal implantation for lip augmentation.

**Study conducted for submucosal implantation for lip augmentation and dermal implantation for correction of perioral rhytids**
The U.S. pivotal study (MA-1700-04) involved 221 subjects at 14 centers. At baseline, subjects were randomized to receive *Restylane Silk* injections in the lips and perioral rhytids (as needed) or no treatment (control group). At 6 months, all subjects were eligible to receive treatment or re-treatment in the lips and perioral rhytids with *Restylane Silk.*

Of the 221 subjects enrolled in the study, 218 subjects received their first treatment with *Restylane Silk* at either baseline/Day 0 or at 6 months, and 133 subjects received a second treatment at 6 months. Safety was also evaluated for subjects with Fitzpatrick skin types IV and V (n=52) and for the subgroup of subjects ≤ 35 years of age (n=60).

An adverse event (AE) was defined as any untoward medical occurrence or an unintended sign, symptom, or disease temporally associated with the use of the device, whether or not considered related to the device. An AE was further defined as:
• any diagnosis, sign, symptom, or abnormal laboratory value not present, detected or complained of at the baseline assessment.
• any diagnosis, sign, symptom, or abnormal laboratory value noted at baseline that worsened in severity or intensity or increased in frequency during the study.

An AE that occurred during the study was considered a treatment emergent adverse event (TEAE) if:
• it was not present prior to receiving treatment (as determined by onset date of event and date treatment was received), or
• it was present prior to receiving treatment but the severity increased after treatment (as determined by onset date of the severity increase of the event and date treatment was received).

The investigator was to classify the severity of an adverse event according to the following definitions:
• Mild: did not interfere with routine activities, could perform daily functions
• Moderate: interfered with routine activities, could perform daily functions, but with concerted effort
• Severe: unable to perform routine activities

A Serious Adverse Device Event (SADE) was defined as an AE that:
• results in death;
• is life-threatening;
• results in permanent impairment of a body function;

• results in permanent damage to a body structure; or,
• necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

Subjects were asked to grade symptoms of bruising, redness, swelling, pain, tenderness and itching. Subject's scores for the severity of these events are presented in Table 2 and durations are provided in Table 3. The majority of events (>85%) were mild in intensity and resolved in 2 – 7 days. Eight patients reported diary symptoms of "Affects Daily Activities" and "Disabling" that lasted longer than 7 days. These events were: Swelling (n=6), pain (n=2), tenderness (n=3), bruising (n=3), itching (n=2), and redness (n=1).

## Table 1: MA-1700-04 Maximum Intensity of Symptoms after Initial Treatment from Subject Diary (N=218)

| | None n (%) | Tolerable n (%) | Affected Daily Activities n (%) | Disabling n (%) |
|---|---|---|---|---|
| **Upper and Lower Lip Combined (N=215)** | | | | |
| Bruising | 39 (18%) | 142 (66%) | 25 (12%) | 9 (4%) |
| Redness | 63 (29%) | 129 (60%) | 19 (9%) | 4 (2%) |
| Swelling | 2 (<1%) | 111 (52%) | 84 (39%) | 18 (8%) |
| Pain | 48 (22%) | 123 (57%) | 38 (18%) | 6 (3%) |
| Tenderness | 16 (7%) | 146 (68%) | 48 (22%) | 5 (2%) |
| Itching | 151 (70%) | 59 (27%) | 5 (2%) | 0 |

## Table 2: MA-1700-04 Duration of Symptoms from Patient Diary

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

The treatment-emergent adverse events (TEAEs) reported during the study are presented in Table 1. The number of events and subjects reporting TEAEs decreased between the first and second treatments. Seventy-eight percent (169/281) of subjects receiving their first treatment reported a total of 632 TEAEs while 63% (84/133) of subjects that received a second treatment reported a total of 196 TEAEs. Furthermore, an overwhelming majority of these TEAEs were mild in intensity (540/632; 85%, and
178/196; 91%; first and second treatment respectively), and were transient in nature, resolving in a mean of 17.4 days (median 10 days).

The most common TEAEs occurring after initial treatment with *Restylane Silk* were lip swelling (43%), contusion (44%), and lip pain (10%). There was no increased risk with additional treatment with *Restylane Silk.* After the second treatment, the reported incidence decreased to 35%, 31%, and 7%, respectively.

In the overall population of subjects receiving their initial treatment with *Restylane Silk*, 12 severe events occurred in 6 subjects. Ten of the severe events were Lip Swelling which occurred in 5 subjects. There were 80 moderate events which occurred in 34 subjects (16%). There were 5 serious adverse events in three patients during the study. In the No Treatment group there were incidences of Clostridial Infection (n=1), and Urinary Tract Obstruction (n=1). In the *Restylane Silk* group there were Cystitis (n=1), Intervertebral Disc Protrusion (n=1), and Nephrolithiasis (n=1). None of the serious events were reported as related to treatment with *Restylane Silk*.

Nineteen subjects reported AEs associated with treatment of the lip whose onset was more than 3 weeks after a *Restylane Silk* injection. There were a total of 35 events in the lip reported in these 19 subjects. Most of the events were Lip Swelling (26/35; 745) and also included Lip Disorder (6/35; 17%), Lip Pain/Pain 2/35; 6%), and Contusion (1/35;
3%). None of the events were reported as serious and all of the events were reported as either mild (24/35; 69%) or moderate (11/35; 31%).

| Table 3: MA-1700-04 Summary of Treatment Emergent Adverse Events | | | | | | | |
|---|---|---|---|---|---|---|---|
| **System Organ Class/ Preferred Term** | **Severity** | **No Treatment at Baseline (N=44)** | | **First Treatment with Restylane Silk (N=218)** | | **Second Treatment with Restylane Silk (N=133)** | |
| Any TEAE | | Events | Subjects | Events | Subjects | Events | Subjects |
| | Total | 20 | 12 (27%) | 632 | 169 (78%) | 196 | 84 (63%) |
| | Mild | 16 | 10 (23%) | 540 | 129 (59%) | 178 | 73 (55%) |
| | Moderate | 2 | 1 (2%) | 80 | 34 (16%) | 18 | 11 (8%) |
| | Severe | 2 | 1 (2%) | 12 | 6 (3%) | 0 | 0 |
| **Gastrointestinal Disorders** | | | | | | | |
| Lip Disorder | Total | 0 | 0 | 17 | 11 (5%) | 1 | 1 (<1%) |
| | Mild | 0 | 0 | 17 | 11 (5%) | 1 | 1 (<1%) |
| | Moderate | 0 | 0 | 0 | 0 | 0 | 0 |
| | Severe | 0 | 0 | 0 | 0 | 0 | 0 |
| Lip Pain | Total | 0 | 0 | 34 | 21 (10%) | 12 | 9 (7%) |
| | Mild | 0 | 0 | 30 | 19 (9%) | 12 | 9 (7%) |
| | Moderate | 0 | 0 | 4 | 2 (<1%) | 0 | 0 |
| | Severe | 0 | 0 | 0 | 0 | 0 | 0 |
| Lip Swelling | Total | 0 | 0 | 186 | 94 (43%) | 74 | 46 (35%) |
| | Mild | 0 | 0 | 154 | 77 (35%) | 65 | 41 (31%) |
| | Moderate | 0 | 0 | 22 | 12 (6%) | 9 | 5 (4%) |
| | Severe | 0 | 0 | 10 | 5 (2%) | 0 | 0 |
| **General Disorders and Administrative Site Conditions** | | | | | | | |
| Pain | Total | 0 | 0 | 32 | 18 (8%) | 6 | 4 (3%) |
| | Mild | 0 | 0 | 24 | 13 (6%) | 4 | 3 (2%) |
| | Moderate | 0 | 0 | 8 | 5 (2%) | 2 | 1 (<1%) |
| | Severe | 0 | 0 | 0 | 0 | 0 | 0 |
| **Injury, Poisoning, and Procedural Complication** | | | | | | | |
| Contusion | Total | 0 | 0 | 145 | 96 (44%) | 55 | 41 (31%) |
| | Mild | 0 | 0 | 134 | 87 (40%) | 53 | 39 (29%) |
| | Moderate | 0 | 0 | 11 | 9 (4%) | 2 | 2 (2%) |
| | Severe | 0 | 0 | 0 | 0 | 0 | 0 |
| **Nervous System Disorders** | | | | | | | |
| Headache | Total | 7 | 4 (9%) | 11 | 10 (5%) | 3 | 2 (2%) |
| | Mild | 7 | 4 (9%) | 10 | 9 (4%) | 2 | 1 (<1%) |
| | Moderate | 0 | 0 | 1 | 1 (<1%) | 1 | 1 (<1%) |
| | Severe | 0 | 0 | 0 | 0 | 0 | 0 |

The vast majority of all symptoms reported in subject diaries resolved within 2-7 days of treatment. Furthermore, the duration profiles are similar between first treatment and second treatments with *Restylane Silk.*

| Table 4: Duration of Commonly Occurring Treatment Emergent Adverse Events | | | |
|---|---|---|---|
| **System Organ Class/ Preferred Term** | **No Treatment at Baseline (N=44)** | **First Treatment with *Restylane Silk* (N=218)** | **Second Treatment with *Restylane Silk* (N=133)** |
| **All TEAEs** | | | |
| n | 11 | 168 | 83 |
| Mean (S.D.) | 15.2 (28.8) | 17.7 (29.0) | 9.7 (8.3) |
| Median (min, max) | 6.0 (1, 101) | 10.0 (1, 174) | 7.0 (1, 38) |
| **Gastrointestinal Disorders** | | | |
| Lip Disorder | | | |
| n | 0 | 10 | 1 |
| Mean (S.D.) | - (-) | 49.1 (44.4) | 27.0 (-) |
| Median (min, max) | - | 38.5 (1, 124) | 27.0 |
| Lip Pain | | | |
| n | 0 | 21 | 9 |
| Mean (S.D.) | - (-) | 10.6 (14.5) | 5.2 (2.3) |
| Median (min, max) | - | 7.0 (3, 71) | 6.0 (2, 8) |
| Lip Swelling | | | |
| n | 0 | 94 | 46 |
| Mean (S.D.) | - (-) | 7.3 (4.1) | 7.4 (8.1) |
| Median (min, max) | - | 6.0 (2, 21) | 5.0 (1, 38) |
| **General Disorders and Administrative Site Conditions** | | | |
| Pain | | | |
| n | 0 | 18 | 4 |
| Mean (S.D.) | - (-) | 3.6 (2.3) | 3.5 (1.9) |
| Median (min, max) | - | 3.0 (1, 9) | 3.0 (2, 6) |
| **Injury, Poisoning, and Procedural Complication** | | | |
| Contusion | | | |
| n | 0 | 96 | 41 |
| Mean (S.D.) | - (-) | 8.4 (3.9) | 8.6 (5.9) |
| Median (min, max) | - | 8.0 (2, 20) | 7.0 (3, 32) |
| **Nervous System Disorders** | | | |
| Headache | | | |
| n | 4 | 10 | 2 |
| Mean (S.D.) | 2.8 (2.9) | 1.6 (1.1) | 1.0 (0.0) |
| Median (min, max) | 1.5 (1, 7) | 1.0 (1, 4) | 1.0 (1, 1) |

In addition, subjects with Fitzpatrick skin types IV and V and subjects ≤ 35 years of age had safety results similar to the general study population.

Concomitant treatment of perioral rhytids with lip augmentation does not increase the risk for adverse events. TEAEs for subjects receiving treatment for perioral rhytids were similar in type and frequency to those in the overall population for the common events of lip disorder (bumps), lip pain, lip swelling and contusion. No important differences were noted between those subjects receiving treatment for perioral rhytids and those not receiving treatment for perioral rhytids for first and second injections of *Restylane Silk*.

**Study conducted for the use of a small bore, blunt tip cannula for submucosal implantation for lip augmentation**

Clinical study 43USC1505 was a multicenter, open-label, single-arm prospective study designed to assess adverse experiences identified with the use of Restylane Silk when used in conjunction with a small blunt tip cannula (in the range of 25G-27G) for lip augmentation. Two brands of cannulas, DermaSculpt and Softfil, were evaluated and all were 25G-27G and 1 1/2 inches in length.

The study was conducted at 4 sites in the U.S. with sixty (60) subjects enrolled and treated. Thirteen (13) subjects with Fitzpatrick skin types IV, V and VI were included in the safety analysis. Subjects with these FST were not required to meet the inclusion criterion for MLFS score.

Adverse experiences were assessed by collecting Adverse Events (AEs) throughout the study. A subject diary was used for documentation of pre-defined, expected post-treatment injection site reactions (i.e. bruising, redness, swelling, pain, tenderness, and itching) during the first two (2) weeks after the treatment.

An adverse event (AE) was defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical sign (including abnormal laboratory findings) in subjects (whether or not considered related to the device or procedure), users or other persons (definition restricted to events related to the investigational device or procedure).

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

- Mild: Awareness of symptoms or signs, but easily tolerated (acceptable)
- Moderate: Enough discomfort to interfere with usual activity (disturbing)
- Severe: Incapacity to work or to do usual activity (unacceptable)

A Serious Adverse Event (SAE) was defined as an AE that:
- led to death;
- led to serious deterioration in the health of the subject, that either resulted in
    - a life-threatening illness or injury
    - a permanent impairment of a body structure or body function
    - in-patient or prolonged hospitalization
    - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
- led to fetal distress, fetal death, or a congenital abnormality or birth defect

Pre-defined, expected post-treatment events occurring after lip treatment were collected in a subject diary by day during a 14-day period, starting on the day of treatment. Except for swelling, which was primarily assessed as moderate or severe in intensity, the majority of subjects assessed all other diary symptoms as mild. Of the subjects that reported a severe upper and/or lower lip symptom, the majority of the severe diary symptoms started on day 1 of the diary and lasted 2-7 days.

**Table 5: Duration of symptoms by maximum intensity (mild, moderate, severe) recorded from the patient diary**

| Duration of Symptoms from Patient Diary | | | | | | |
|---|---|---|---|---|---|---|
| Max Intensity | Event | Number of days, Upper and Lower Lip combined | | | | |
| | | Any n (%) | 1 n (%) | 2-7 n (%) | 8-13 n (%) | 14 n (%) |
| Mild | Bruising | 25 (41.7) | 4 (16.0) | 20 (80.0) | 1 (4.0) | 0 (0.0) |
| | Redness | 32 (53.3) | 9 (28.1) | 23 (71.9) | 0 (0.0) | 0 (0.0) |
| | Swelling | 12 (20.0) | 1 (8.3) | 8 (66.7) | 2 (16.7) | 1 (8.3) |
| | Pain | 27 (45.0) | 13 (48.1) | 14 (51.9) | 0 (0.0) | 0 (0.0) |
| | Tenderness | 33 (55.0) | 6 (18.2) | 22 (66.7) | 5 (15.2) | 0 (0.0) |
| | Itching | 12 (20.0) | 6 (50.0) | 5 (41.7) | 1 (8.3) | 0 (0.0) |
| Moderate | Bruising | 10 (16.7) | 0 (0.0) | 8 (80.0) | 2 (20.0) | 0 (0.0) |
| | Redness | 12 (20.0) | 1 (8.3) | 11 (91.7) | 0 (0.0) | 0 (0.0) |
| | Swelling | 28 (46.7) | 0 (0.0) | 18 (64.3) | 9 (32.1) | 1 (3.6) |
| | Pain | 16 (26.7) | 2 (12.5) | 14 (87.5) | 0 (0.0) | 0 (0.0) |
| | Tenderness | 19 (31.7) | 0 (0.0) | 11 (57.9) | 5 (26.3) | 3 (15.8) |
| | Itching | 5 (8.3) | 0 (0.0) | 5 (100.0) | 0 (0.0) | 0 (0.0) |
| Severe | Bruising | 1 (1.7) | 0 (0.0) | 0 (0.0) | 1 (100.0) | 0 (0.0) |
| | Redness | 4 (6.7) | 0 (0.0) | 4 (100.0) | 0 (0.0) | 0 (0.0) |
| | Swelling | 20 (33.3) | 0 (0.0) | 11 (55.0) | 6 (30.0) | 3 (15.0) |
| | Pain | 1 (1.7) | 0 (0.0) | 1 (100.0) | 0 (0.0) | 0 (0.0) |
| | Tenderness | 5 (8.3) | 0 (0.0) | 2 (40.0) | 3 (60.0) | 0 (0.0) |
| | Itching | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

Apart from the expected post-treatment events collected in subject diaries, the majority of subjects (49/60 [81.7%]) had no treatment emergent adverse event (TEAE). In total, there were 27 TEAEs occurring in 11 subjects.

No severe TEAEs were observed and there were no serious adverse events (SAEs). The TEAEs are presented by MedDRA System Organ class (SOC) and Preferred Term (PT) in Table 6. Of these events, six (6) were classified as not related to product or injection procedure.

**Table 6: Summary of TEAEs by Severity – Safety Population**

| **System Organ Class**/ Preferred Term | **Severity** | **Treatment with Restylane Silk (N=60)** | |
|---|---|---|---|
| | | Events | Subjects |
| *Any TEAE* | **Total** | **27** | **11[*] (18.3%)** |
| | Mild | 22 | 11 (18.3%) |
| | Moderate | 5 | 3 (5.0%) |
| | Severe | 0 | 0 |
| **Gastrointestinal Disorders** | | | |
| Chapped lips | **Total** | **2** | **1 (1.7%)** |
| | Mild | 2 | 1 (1.7%) |
| | Moderate | 0 | 0 |
| Colitis ulcerative | **Total** | **1** | **1 (1.7%)** |
| | Mild | 0 | 0 |
| | Moderate | 1 | 1 (1.7%) |
| **General Disorders and Administration Site Conditions** | | | |
| Injection site bruising | **Total** | **5** | **4 (6.7%)** |
| | Mild | 5 | 4 (6.7%) |
| | Moderate | 0 | 0 |
| Injection site pain | **Total** | **2** | **1 (1.7%)** |
| | Mild | 2 | 1 (1.7%) |
| | Moderate | 0 | 0 |
| Injection site swelling** | **Total** | **14** | **8 (13.3%)** |
| | Mild | 10 | 6 (10.0%) |
| | Moderate | 4 | 2 (3.3%) |
| **Infections and Infestations** | | | |
| Sinusitis | **Total** | **1** | **1 (1.7%)** |
| | Mild | 1 | 1 (1.7%) |
| | Moderate | 0 | 0 |
| Upper respiratory tract infection | **Total** | **2** | **1 (1.7%)** |
| | Mild | 2 | 1 (1.7%) |
| | Moderate | 0 | 0 |

*Eleven (11) subjects had TEAEs of mild intensity and three (3) of these also had TEAEs of moderate intensity.
**One of the TEAEs categorized as 'Injection site swelling', was described in the case report form as 'Swelling secondary to cold sore/herpes simplex', and was re- assessed by the Sponsor from unrelated to study product and injection procedure, to be possibly related to the injection procedure.

The time to onset and duration of related TEAEs are presented in Table 7. Most events related to treatment with *Restylane Silk* using cannula emerged on the day of treatment and resolved in a mean of 6.2 days (median 5 days).

**Table 7: Summary of related TEAEs by Time to Onset and Duration - Safety population (N=60)**

| **System Organ Class**/ Preferred Term | **Time to Onset (Days)** | **Duration (Days)** |
|---|---|---|
| *Any related TEAE (n=21)* | | |
| Mean (SD) | 0.4 (0.6) | 6.0 (2.3) |
| Median (min, max) | 0 (0, 2) | 5 (2, 10) |
| **General Disorders and Administration Site Conditions** | | |
| Injection site bruising (n=5) | | |
| Mean (SD) | 0.2 (0.4) | 6.2 (1.3) |
| Median (min, max) | 0 (0, 1) | 6 (5, 8) |
| Injection site pain (n=2) | | |
| Mean (SD) | 1.0 (0.0) | 5.0 (0) |
| Median (min, max) | 1 (1, 1) | 5 (5, 5) |
| Injection site swelling (n=14) | | |
| Mean (SD) | 0.4 (0.6) | 6.1 (2.7) |
| Median (min, max) | 0 (0, 2) | 5 (2, 10) |

Evaluation of adverse events for subjects with Fitzpatrick skin types IV- VI showed no unique TEAEs associated with this subgroup.

One device deficiency associated with injection procedure occurred: at the beginning of injecting, the cannula disconnected from the syringe prior to injecting into the patient.

**POST-MARKETING SURVEILLANCE**

The adverse event reports received from post-marketing surveillance (from voluntary reporting and published literature) of *Restylane Silk* in the U.S. most commonly included reports of transient swelling/edema of the lip or, inflammatory reactions with immediate or delayed onset, up to several weeks after treatment. The following events were also reported: mass/induration, pain/tenderness, lack of effect, bruising/hematoma, erythema, papules/nodules, discoloration/hyperpigmentation, hypersensitivity, angioedema, injection site reactions including exfoliation, burning sensation, irritation, warmth, discomfort, dryness, presumptive bacterial infections and abscess formation, ischemia and necrosis due to unintentional intravascular injection, vascular compression or embolisation, reactivation of herpes infection, pruritus, inflammation, neurological symptoms such as hypoaesthesia and paresthesia, blisters/vesicles, eye disorders including eye swelling, eye irritation and visual disturbance such as transient vision blurred, increased lacrimation, eyelid ptosis and visual impairment, rash, device dislocation, urticaria, fistula/discharge, atrophy/scarring, capillary disorders such as telangiectasia, acne, dermatitis, muscular weakness, and other dermatological events such as dry lips, skin wrinkling, dry skin and skin exfoliation and non-dermatological events such as pyrexia, anxiety, fatigue, insomnia and headache.

When required, treatments for these events included corticosteroids, antibiotics, antihistamines, NSAIDs, aspiration/incision and drainage, surgery or enzymatic degradation (with hyaluronidase) of the product.

Reports of serious adverse events for *Restylane Silk* are rare. The most commonly reported serious adverse events were ischemia/necrosis, infection/abscess and hypersensitivity. Other serious events included concomitant symptoms; swelling, pain/tenderness, erythema and bruising.

In addition to the events listed above, the following adverse events were received from post-marketing surveillance for *Restylane* filler range of products: encapsulation, vasovagal reactions, extrusion of device, granuloma and dermaphytosis.

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 embolisation. 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.

Vision abnormalities including blindness have been reported following injection of hyaluronic acid fillers into the nose, glabella, periorbital areas, and/or cheek, with a time to onset ranging from immediate to a few days following injection. Reported treatments include anticoagulant, epinephrine, aspirin, hyaluronidase, steroid treatment and hyperbaric oxygen. Outcomes ranged from resolved to ongoing at the time of last contact. Events requiring medical intervention, and events where resolution information is not available were reported. In these cases, the product was injected into the highly vascularized areas of the glabella, nose, and periorbital area, which are outside the device indications for use (See Warnings section).

Adverse reactions should be reported to Galderma Laboratories, L.P. at 1-855-425-8722.

## CLINICAL TRIALS

### U.S. Clinical Study

### MA-1700-04

The safety and effectiveness of *Restylane Silk* for lip fullness augmentation and treatment of perioral rhytids was evaluated in a randomized, evaluator blinded, no treatment controlled study.

### MA-1700-04 Randomized Clinical study

| | |
|---|---|
| Design | This was a randomized, evaluator-blinded, no treatment as a control study of 221 subjects who were seeking lip fullness augmentation at 14 U.S. investigational centers. At entry to the study, subjects were randomized 3:1 to (1) Restylane Silk or (2) no treatment. The study recruited a minimum of 30 subjects with Fitzpatrick skin types IV, V, or VI. An additional<br>40 subjects seeking lip fullness augmentation who were ≤ 35 years of age at study entry and met all except the Medicis Lip Fullness Scales (MLFS) thin/very thin lip criterion were to be enrolled; these subjects were not randomized. Subjects may have returned at 2 weeks after the initial injection for touch-up treatment (if necessary). Subjects were also given the opportunity to have their perioral rhytids treated along with the lip augmentation. Each lip that was treated for augmentation was analyzed for effectiveness and all lips were analyzed for safety. Subjects randomized to treatment at baseline were re-treated at 6 months and subjects randomized to no treatment at baseline received their first treatment at 6 months. The safety of all subjects was then monitored for one month after the 6 month treatment.<br><br>There were a total of 177 subjects that received treatment with SPHAL at the Baseline Visit. Of these subjects, 44 subjects did not receive treatment at the Month 6 treatment visit (Visit<br>10). Of these 44 subjects, 11 subjects were lost to follow-up (LTFU) and six subjects withdrew consent (see response to Question 8) prior to Visit 10 |

| | |
|---|---|
| Endpoints | Effectiveness<br>Primary:<br>The Primary effectiveness objective was to identify whether Restylane Silk was more effective in lip augmentation than no treatment. This was determined by the change from baseline in blinded evaluator assessments of lip fullness at 8 weeks after the first treatment, separately in the upper and lower lips (co-primary effectiveness endpoints) in the randomized subjects using separate five grade MLFS with photoguides for each lip. Treatment success was defined as at least a one grade increase from baseline in the MLFS for the blinded evaluator assessment at Week 8 (compared to the baseline assessment).<br><br>The primary safety objective was to determine the incidence of reported treatment emergent adverse events at 72 hours, 2, 4, 8, 12, 16, 20 and 24 weeks after the initial injection(s) and 72 hours, 2 weeks and 4 weeks after the 6 month treatment. Subjects maintained diaries for 14 days after the initial and 6 month treatments to record the severity and duration of bruising, redness, swelling, pain, tenderness and itching.<br><br>Secondary:<br>Secondary effectiveness objectives included:<br>• Assessment of lip fullness augmentation after treatment with Restylane Silk compared to no treatment as assessed by the blinded evaluator, treating investigator, and independent photographic reviewer (IPR) at post-baseline time points as compared to the baseline assessment. Response was defined as at least one grade improvement from baseline in the upper and lower lips using MLFS.<br>• Identification of lip improvement at each time point after treatment with Restylane Silk as compared to no treatment using the Global Aesthetic Improvement Scale (GAIS) by the treating investigator and the subjects. Response was defined as a GAIS rating of<br>• "improved" or better in the upper and lower lips.<br>• Improvement in the appearance of upper perioral rhytids compared to no treatment at each time point using the Wrinkle Assessment for Upper Lip Lines (WASULL) by the assessment of the blinded evaluator and the treating investigator.<br>• Proportion of responders for the co-primary and secondary endpoints for subjects with pre-treatment Fitzpatrick scores IV, V, and VI as well as for subjects ≤ 35 years old at baseline.<br><br>Secondary safety objectives included assessment of lip texture, firmness, symmetry, product palpability, mass formation, lip movement, lip function, and lip sensation. |

Outcomes

Demographics

The study enrolled an adult population of predominately Caucasian healthy females.

| Characteristics | Total (N=221) |
|---|---|
| **Age (years)** | |
| n | 221 |
| Mean (S.D.) | 45.5 (12.3) |
| Median | 48.0 |
| Minimum | 18 |
| Maximum | 65 |
| **Gender** | |
| Male | 6 (3%) |
| Female | 215 (97%) |
| **Race** | |
| American Indian/Alaskan Native | 1 (<1%) |
| Black/African American | 1 (<1%) |
| Native Hawaiian/Pacific Islander | 0 |
| Asian | 3 (1%) |
| White | 211 (95%) |
| Other | 5 (2%) |
| **Ethnicity** | |
| Not Hispanic or Latino | 178 (81%) |
| Hispanic or Latino | 43 (19%) |
| **Fitzpatrick Skin Type** | |
| I, II, and III | 169 (76%) |
| IV, V, and VI | 52 (24%) |

Volume of *Restylane Silk* used

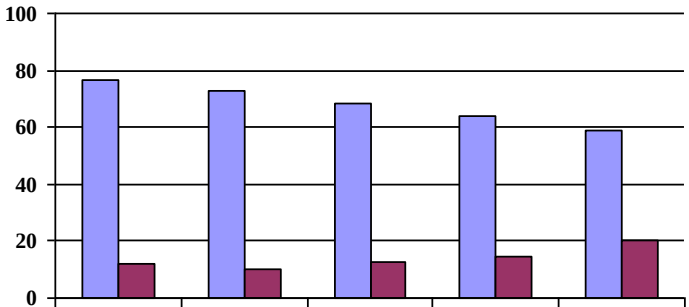
| | Initial Treatment | | 6 Month Treatment | |
|---|---|---|---|---|
| | No Treatment (N=43) | *Restylane Silk* (1st Treatment) | No Treatment (1st Treatment) | *Restylane Silk* (2nd Treatment) |
| **Volume of Injection (mL) for upper and lower lip(s) (includes treatment and touch up)** | | | | |
| n | -- | 176 | 41 | 133 |
| Mean | -- | 2.18 (1.07) | 2.12 (0.74) | 1.50 (0.81) |
| Median | -- | 1.00 | 2.00 | 1.25 |
| Minimum | -- | 0.10 | 1.00 | 0.20 |
| Maximum | -- | 6.80 | 4.00 | 4.40 |
| **Volume of Injection (mL) for perioral rhytids (includes treatment and touch up)** | | | | |
| n | -- | 65 | 18 | 32 |
| Mean | -- | 0.48 (0.44) | 0.89 (0.70) | 0.70 (0.53) |
| Median | -- | 0.30 | 0.90 | 0.60 |
| Minimum | -- | 0.03 | 0.02 | 0.10 |
| Maximum | -- | 1.70 | 1.90 | 2.00 |

It was recommended in the study protocol that the investigator treating the subject not exceed injections of 1.5 mL of *Restylane Silk* per lip per treatment session.

Effectiveness

The purpose of this study was to evaluate the safety and effectiveness of *Restylane Silk* for soft tissue augmentation of the lips and improvement of perioral rhytids. The results of assessments confirm that *Restylane Silk* is effective for adding fullness to both the upper and lower lips for at least 6 months

**Proportion (%) of MLFS Responders Measured by the Blinded Evaluator (Upper and Lower Lip Combined)**

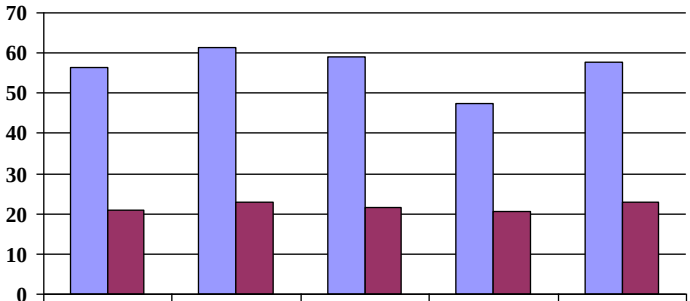



| | Week 8 | Week 12 | Week 16 | Week 20 | Week 24 |
|---|---|---|---|---|---|
| Restylane Silk Treatment | 76.7 | 73.1 | 68.3 | 64 | 58.8 |
| No Treatment | 11.9 | 10 | 12.5 | 14.6 | 20 |

p<0.001 for all time points

The study also showed that the appearance of upper perioral rhytids improved in patients whose perioral rhytids were treated with *Restylane Silk* as assessed by the blinded evaluator.

**Proportion (%) of Responders Measured by the Blinded Evaluator for Upper Perioral Rhytids**




| | Week 8 | Week 12 | Week 16 | Week 20 | Week 24 |
|---|---|---|---|---|---|
| Treatment of Rhytids + Lip | 56,5 | 61,3 | 59 | 47,5 | 57,6 |
| Treatment of Lip Only | 20,9 | 22,9 | 21,4 | 20,6 | 22,8 |

p<0.001 for all time points

| | |
|---|---|
| | Subjects assessed lip improvement at each time point after treatment with a 7-point GAIS. When upper and lower lip outcomes were combined, the study showed that subjects were pleased with the visual improvement in their lips. No patients in the No Treatment group assessed themselves as improved from baseline at any visit.<br>Subjects assessed lip improvement at each time point after treatment with a 7-point non-validated GAIS. When upper and lower lip outcomes were combined, the following percentage of Restylane Silk subjects assessed themselves as improved or better from Baseline: 97.7% (Week 2), 95.3% (Week 4), 90.1% (Week 8), 87.5% (Week 12), 79.4 % (Week 16), 76.5% (Week 20), and 76.5% (Week 24). No patients in the No Treatment group assessed themselves as improved from Baseline at any visit.<br><br>76% of the eligible subjects elected to receive re-treatment at Week 24 which suggests that subjects believed that the safety concerns associated with Restylane Silk lip and perioral injections were less than the aesthetic value provided by the device. Of the subjects that elected to not receive re-treatment at Week 24, six (3%) reported refusal due to adverse events experienced during their initial treatment.<br>Lip safety assessments, such as lip texture, firmness, symmetry, movement, function, sensation, mass formation, and device palpability were evaluated at the screening visit and throughout the study. None of the lip assessments were remarkable or presented any safety concerns. |

**U.S. Clinical Study**

**43USC1505**

The study was conducted to assess adverse experiences identified with the use of Restylane® Silk in conjunction with a small blunt tip cannula (in the range of 25G-27G) for lip augmentation.

**43USC1505 Multicenter, Open-Label, Prospective Study**

| | |
|---|---|
| Design | This was a multicenter, open-label, 12-week prospective study of cannula injection of Restylane Silk for lip augmentation in 60 subjects. Subjects with Fitzpatrick skin types (FST) I, II, or III were required to have the MLFS scores of 1 (very thin) or 2 (thin) on both the upper and lower lips to be eligible for the study. Thirteen (13) subjects with FST IV, V, or VI were enrolled, of which six were exempt from meeting the inclusion criteria for MLFS scores per protocol. Eligible subjects were injected by the investigator at baseline; the subject's lips and perioral rhytids (if elected) were treated to optimal augmentation. After the initial treatment, follow-up visits occurred at day 3, week 2, week 4, and week 12.<br><br>Safety was evaluated by collecting AEs throughout the study. A subject diary was used for documentation of pre-defined, expected post-treatment injection site reactions (i.e. bruising, redness, swelling, pain, tenderness, and itching) during the first two weeks after the treatment. Other safety assessments included evaluation by a qualified study staff member of lip palpation, texture, symmetry, movement, function, and sensation.<br><br>Effectiveness was evaluated by a change from baseline in the MLFS as assessed by the investigator, and an improvement using the Global Aesthetic Improvement Scale (GAIS) as assessed by the investigator and subject. |

| | |
|---|---|
| Endpoints | Primary:<br>The primary objective of the study was to assess adverse experiences identified with the use of Restylane Silk in conjunction with a small blunt tip cannula (in the range of 25G-27G) for lip augmentation.<br>Adverse experiences were assessed by collecting Adverse Events (AEs) throughout the study. A subject diary was used for documentation of pre-defined, expected post-treatment injection site reactions (i.e. bruising, redness, swelling, pain, tenderness, and itching) during the first two weeks after the treatment. Other safety assessments included evaluation of lip palpation, movement, function, sensation, texture, and symmetry.<br><br>Secondary:<br>The secondary objective of the study was to characterize the effectiveness of Restylane Silk, used in conjunction with a small blunt-tip cannula, for augmentation of soft tissue fullness of the lip as determined by:<br>• investigator assessed global aesthetic improvement at 4 and 12 weeks,<br>• subject assessed global aesthetic improvement at 4 and 12 weeks, and<br>• change from baseline in Investigator assessed Medicis Lip Fullness Scale (MLFS) at 4 and 12 weeks. |

Outcomes

Demographics

Table 8. Demographic summary, all subjects

| Characteristics | Total (N=60) |
|---|---|
| Age (Years) | |
| n | 60 |
| Mean (SD) | 46.5 (14.1) |
| Median | 48.0 |
| Minimum | 23.0 |
| Maximum | 72.0 |
| Gender | |
| Male | 4 (7%) |
| Female | 56 (93%) |
| Race | |
| American Indian/Alaska Native | 1 (2%) |
| Black/African American | 2 (3%) |
| Native Hawaiian/Other Pacific Islander | 1 (2%) |
| Asian | 2 (3%) |
| White | 53 (88%) |
| Other | 1 (2%) |
| Ethnicity | |
| Not Hispanic or Latino | 55 (92%) |
| Hispanic or Latino | 5 (8%) |
| Fitzpatrick skin type | |
| I, II and III | 47 (78%) |
| IV, V and VI | 13 (22%) |

Table 9. Fitzpatrick classification, all subjects.

| Site | Fitzpatrick classification | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | I | | II | | III | | IV | | V | | VI | | Total (N) | |
| | n | % | n | % | n | % | n | % | n | % | n | % | N | % |
| 8302 | 0 | 0.0 | 5 | 33.3 | 5 | 33.3 | 2 | 13.3 | 2 | 13.3 | 1 | 6.7 | 15 | 100.0 |
| 8476 | 0 | 0.0 | 9 | 64.3 | 5 | 35.7 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 14 | 100.0 |
| 8551 | 1 | 6.7 | 6 | 40.0 | 3 | 20.0 | 4 | 26.7 | 1 | 6.7 | 0 | 0.0 | 15 | 100.0 |
| 8552 | 0 | 0.0 | 4 | 25.0 | 9 | 56.3 | 2 | 12.5 | 0 | 0.0 | 1 | 6.3 | 16 | 100.0 |
| Total | 1 | 1.7 | 24 | 40.0 | 22 | 36.7 | 8 | 13.3 | 3 | 5.0 | 2 | 3.3 | 60 | 100.0 |

Extent of exposure

The mean volume of Restylane Silk injected per lip was 1.1mL. The mean total volume for both lips was 2.2mL. The depth of injection for the upper and lower lips for all subjects was submucosal, and a majority of subjects received a combination of injection methods including linear retrograde and linear antegrade, Investigators used the same gauge of cannula when treating the upper and lower lips, and in this study 55.0% of subjects received treatment with a 27G cannula and 45.0% received treatment with a 25G cannula. Treatment of perioral rhytids was optional, and was performed by Investigators at two of the four investigational sites. Six (6) subjects had mid-dermal injections using cannula in both upper and lower perioral rhytids, and three (3) subjects had treatment in the upper perioral rhytids only. The mean total volume for both the upper and lower perioral rhytids was 0.3mL. None of the subjects with Fitzpatrick Skin Types IV, V, and VI were treated in the perioral rhytids with cannula.

Safety results (For tabulated data, see Section ADVERSE EXPERIENCES)

Of those subjects that reported an event, all AEs occurred after treatment at baseline. A total of 27 TEAEs were reported by 11 of the 60 enrolled subjects (18.3%). The vast majority of subjects (81.7%) reported no TEAEs during the study period. The most commonly reported TEAEs by preferred term were: injection site swelling (13.3%) and injection site bruising (6.7%). All other TEAEs (i.e., chapped lips, colitis ulcerative, injection site pain, sinusitis, and upper respiratory tract infection) were reported by 1 subject each (1.7%). No serious AEs (SAEs) were reported,

The median time to onset for any related TEAEs was the same day as treatment and median duration was 5 days (mean = 6.2 days). Following treatment at baseline, all subjects completed a 14-day diary. The daily diary listed specific questions about certain pre-defined, expected events for the upper and lower lips separately, including, bruising, itching, pain, redness, swelling, and tenderness. All subjects reported at least one diary symptom in the upper and/or lower lip. The most commonly reported post-treatment symptoms were: swelling (60/60 subjects, 100%), tenderness (57/60 subjects, 95.0%), and redness (48/60 subjects, 80.0%).

With the exception of swelling, which was primarily assessed as moderate or severe in intensity, the majority of all other reported diary symptoms were assessed as mild by the subject. Of the subjects that reported a severe upper and/or lower lip symptom, the majority of the diary symptoms started on day 1 of the diary and lasted 2-7 days. As expected and as diary symptoms resolved, the proportion of subjects reporting diary symptoms at any intensity level decreased over time.

All subjects with FST IV-VI reported at least one diary symptom in the upper and/or lower lip. The most commonly reported post-treatment symptoms were swelling (13/13 subjects, 100%), tenderness (12/13 subjects, 92.3%), and redness (11/13 subjects, 84.6%). Maximum intensity for swelling was assessed as mild, moderate, and severe. Only one subject assessed tenderness intensity as severe. Apart from swelling, the majority of all other reported diary symptoms were assessed as mild by the subject. The majority of the symptoms reported by subjects with FST IV-VI lasted 7 days or less.

All lip safety assessments, with the exception of lip texture, were assessed as normal at all study time points for all subjects. Two subjects had mild abnormal upper or lower lip texture post-treatment that returned to a normal assessment before the end of study.

Effectiveness results:

Assessment of lip fullness included subjects with a baseline MLFS score of 1 or 2. Scoring was based on visual live assessment by the Investigator. Results of the assessment at Baseline, Week 4 and Week 12 are presented in Table 10. All subjects in the ITT population had a clinically significant improvement, i.e. at least one grade improvement from baseline for the upper lip, and the majority (49/51 [96%]) of lower lips were improved at 12 weeks.

**Table 10: MLFS by visit - ITT population**

| MLFS | Baseline | | | | 4 weeks | | | | 12 weeks | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Upper lip | | Lower lip | | Upper lip | | Lower lip | | Upper lip | | Lower lip | |
| | n | % | n | % | n | % | n | % | n | % | n | % |
| 1 – Very thin | 26 | 48.1 | 22 | 40.7 | 0 | 0.0 | 1 | 1.9 | 0 | 0.0 | 2 | 3.9 |
| 2 – Thin | 28 | 51.9 | 32 | 59.3 | 4 | 7.5 | 2 | 3.8 | 8 | 15.7 | 3 | 5.9 |
| 3 – Medium | 0 | 0.0 | 0 | 0.0 | 24 | 45.3 | 13 | 24.5 | 29 | 56.9 | 25 | 49.0 |
| 4 – Full | 0 | 0.0 | 0 | 0.0 | 17 | 32.1 | 29 | 54.7 | 12 | 23.5 | 19 | 37.3 |
| 5 – Very Full | 0 | 0.0 | 0 | 0.0 | 8 | 15.1 | 8 | 15.1 | 2 | 3.9 | 2 | 3.9 |
| **Total (N)** | 54 | 100.0 | 54 | 100.0 | 53 | 100.0 | 53 | 100.0 | 51 | 100.0 | 51 | 100.0 |

% = n/N*100

Further, the Investigator evaluated the degree of improvement from baseline in the visual appearance of the subject's lips using the 7-point non-validated GAIS at Weeks 4 and 12. Improvement (defined as "Improved", "Much improved" or "Very much improved") was noted for the upper and lower lips combined at Weeks 4 and 12 (98.1% and 98.0%, respectively).

**Table11: Investigator assessment of improvement using GAIS - ITT population**

| GAIS Investigator assessment | 4 weeks | | | | 12 weeks | | | |
|---|---|---|---|---|---|---|---|---|
| | Upper lip | | Lower lip | | Upper lip | | Lower lip | |
| | n | % | n | % | n | % | n | % |
| Very Much Improved | 34 | 64.2 | 45 | 84.9 | 23 | 45.1 | 32 | 62.7 |
| Much Improved | 12 | 22.6 | 6 | 11.3 | 13 | 25.5 | 13 | 25.5 |
| Improved | 6 | 11.3 | 2 | 3.8 | 14 | 27.5 | 6 | 11.8 |
| No Change | 1 | 1.9 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Worse | 0 | 0.0 | 0 | 0.0 | 1 | 2.0 | 0 | 0.0 |
| Much Worse | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Very Much Worse | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| **Total (N)** | 53 | 100.0 | 53 | 100.0 | 51 | 100.0 | 51 | 100.0 |

% = n/N*100

Subjects also rated improvement of their lip fullness, relative to pretreatment appearance, using the GAIS at Weeks 4 and 12. For the upper and lower lips combined, the proportion of subjects that assessed themselves as improved or better from baseline was 94.3% at Week 4, and 84.3% at Week 12.

## HOW SUPPLIED

*Restylane Silk* is supplied in a disposable glass syringe with a luer-lock fitting.

*Restylane Silk* is co-packed with sterilized needle(s) 30 G x ½" as indicated on the carton. A patient record label is a part of the syringe label. Remove it by pulling the flap marked with three small arrows. This label is to be attached to patient records to ensure traceability of the product.

The contents of the syringe are sterile.

The volume in each syringe and needle gauge is as stated on the syringe label and on the carton.

## SHELF LIFE AND STORAGE

*Restylane Silk* must be used prior to the expiration date printed on the package. Store at a temperature of up to 25° C (77° F). Do not freeze. Protect from sunlight. Refrigeration is not required.

Do not resterilize *Restylane Silk* as this may damage or alter the product.

Do not use if the package is damaged. Immediately return the damaged product to Galderma Laboratories, L.P.

Rx only

**U.S. PATENT 5,827,937; 8,455,459; 8,778,909; 8,357,795; 8,450,475; 8,822,676**

**Manufactured for**
Galderma Laboratories, L.P.
14501 N. Freeway
Fort Worth, TX 76177 USA
Phone: 1-855-425-8722

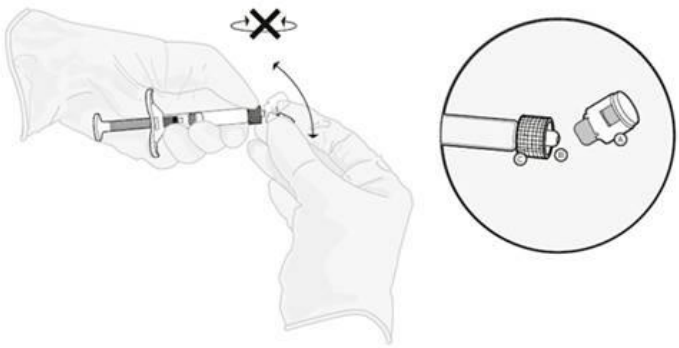
**Manufactured by**
Q-Med AB
Seminariegatan 21
SE-752 28 Uppsala
Sweden

Made in Sweden

## DIRECTIONS FOR ASSEMBLY

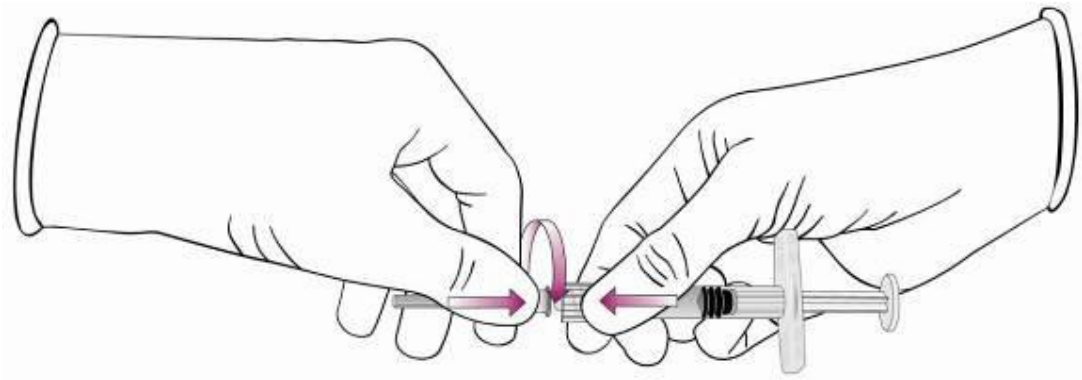
For safe use of *Restylane Silk*, it is important that the needle/blunt cannula is properly assembled.

Hold the syringe on the ribbed part (C) of the white closure system (luer-lock adapter).
With your other hand, take hold of the white cap (A) at the end of the closure system and gently tilt back and forth carefully until cap disconnects and can be pulled off (seal will be broken).
Do not rotate.
Do not touch the syringe tip (B) to keep it sterile.



## ASSEMBLY OF NEEDLE TO SYRINGE

Use the thumb and forefinger to hold firmly around both the glass syringe barrel and the luer-lock adapter. Grasp the needle shield (or hub if using a cannula) with the other hand. To facilitate proper assembly, both push and rotate firmly.



## PRE-TREATMENT GUIDELINES

Prior to treatment, the patient should avoid taking aspirin, nonsteroidal anti-inflammatory medications, St. John's Wort, or high doses of Vitamin E supplements. These agents may increase bruising and bleeding at the injection site.

## TREATMENT PROCEDURE

1. It is necessary to counsel the patient and discuss the appropriate indication, risks, benefits and expected responses to the *Restylane Silk* treatment.
   Advise the patient of the necessary precautions before commencing the procedure.

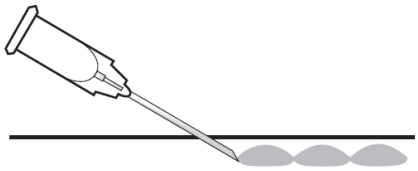
2. Assess the patient's need for appropriate anesthetic treatment for managing comfort, i.e., topical anesthetic, local or nerve block.
3. The patient's face should be washed with soap and water and dried with a clean towel. Cleanse the area to be treated with alcohol or another suitable antiseptic solution.
4. Sterile gloves are recommended while injecting *Restylane Silk*.
5. Before injecting, press rod carefully until a small droplet is visible at the tip of the needle.
6. When using needle, after insertion, and just before injection, the plunger rod should be withdrawn slightly to aspirate and verify that the needle is not intravascular.
7. *Restylane Silk* is administered using a thin gauge needle (30 G x ½") or as an alternative a blunt tip cannula (recommended gauge sizes 25-27G) can be used. Please note use of a cannula is intended for lip augmentation only whereas needles may be used to treat both lips and perioral rhytids.
8. When using a needle, the needle is inserted at an approximate angle of 30° parallel to the length of the wrinkle, fold, or lip. For rhytids, *Restylane Silk* should be injected into the mid-to-deep dermis. *Restylane Silk* should be injected into the submucosal layer for lip augmentation, care should be taken to avoid intramuscular injection. If *Restylane Silk* is injected too superficially this may result in visible lumps and/or bluish discoloration. When using a cannula for lip augmentation, an entry point is made in the skin, e.g. with a sharp needle of appropriate size. Inject slowly.
9. Inject *Restylane Silk* applying even pressure on the plunger rod. 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. Only correct to 100% of the desired volume effect. Do not overcorrect. With cutaneous deformities the best results are obtained if the defect can be manually stretched to the point where it is eliminated. The degree and duration of the correction depend on the character of the defect treated, the tissue stress at the implant site, the depth of the implant in the tissue and the injection technique.
11. Typical usage for each treatment session is specific to the site as well amount of augmentation or rhytids correction desired. Based on U.S. clinical studies, the maximum recommended dose per treatment is 1.5 mL per lip per treatment or 1.0 mL for perioral rhytid correction.

**INJECTION TECHNIQUES**

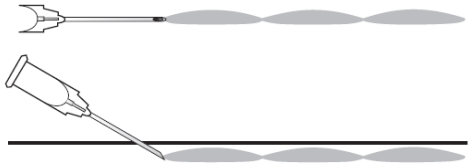
1. *Restylane Silk* can be injected by a number of different techniques that depend on the treating physician's experience and preference, and patient characteristics.
2. **Serial puncture (only recommended for needle)** (A) involves multiple, closely spaced injections along wrinkles or folds. Although serial puncture allows precise placement of the filler, it produces multiple puncture wounds that may be undesirable to some patients.
3. **Linear threading (includes retrograde and antegrade)** (B) is accomplished by fully inserting the needle/cannula into the middle of the wrinkle or fold and injecting the filler along the track as a "thread." Although threading is most commonly practiced after the needle/cannula has been fully inserted and is being withdrawn, it can also be performed while advancing the needle/cannula ("push-ahead" technique). To enhance the vermillion of the lip, the retrograde linear threading technique is the most advisable.
4. Serial threading is a technique that utilizes elements of both approaches

**Note! The correct injection technique is crucial for the final result of the treatment.**

**A. Serial Puncture (only recommended for needle)**



**B. Linear Threading (includes retrograde and antegrade)**



5. Dissection of the sub-epidermal plane with lateral movement of the needle, rapid flows (>0.3 mL/min), rapid injection or high volumes may result in an increase in short-term episodes of bruising, swelling, redness, pain, or tenderness at the injection site.
6. 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 has occurred, massage the area firmly between your fingers or against an underlying area to obtain optimal results.
7. If so called "blanching" is observed, i.e., the overlying skin turns a whitish color, the injection should be stopped immediately 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 the American Society for Dermatologic Surgery guidelines, which include hyaluronidase injection[1].
8. If the wrinkles or lips need further treatment, the same procedure should be repeated until a satisfactory result is obtained. Additional treatment with *Restylane Silk* may be necessary to achieve the desired correction.
9. 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 anesthetic to avoid thermal injury.
10. Patients may have mild to moderate injection site reactions, which typically resolve in less than 18 days in the lip.

**STERILE NEEDLE(S)**
Follow national, local or institutional guidelines for use and disposal of medical sharp devices. Obtain prompt medical attention if injury occurs.

- To help avoid needle breakage, do not attempt to straighten a bent needle. Discard it and complete the procedure with a replacement needle.
- Do not reshield used needles. Recapping by hand is a hazardous practice and should be avoided.
- Discard unshielded needles in approved sharps collectors.
- *Restylane Silk* is provided with a needle that does not contain engineered injury

protection. Administration of *Restylane Silk* requires direct visualization and complete and gradual insertion of the needle making engineered protections infeasible. Care should be taken to avoid sharps exposure by proper environmental controls.

**Ordering Information**
Galderma Laboratories, L.P. and its distributor, McKesson Specialty, are your only sources for FDA-approved Restylane Silk. Purchasing from any other agent is illegal.
To order call 1-855-425-8722

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Part Number: 90-17406-03

[1]Alam M, Gladstone H, Kramer EM, et al. ASDS guidelines of care: injectable fillers. Dermatol Surg. 2008;34(suppl 1):S115-S148.