SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Injectable Dermal Filler
Device Trade Name:	*Restylane® Lyft with Lidocaine*
Device Procode:	PKY, LMH
Applicant's Name and Address:	Galderma Laboratories, LP 14501 N. Freeway Fort Worth, TX 76177
Date of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P040024/S099
Date of FDA Notice of Approval:	May 18, 2018

The original PMA (P040024) for Restylane was approved on March 25, 2005, and is indicated for for mid-to-deep dermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds (NLF). The PMA Supplements for Perlane® (PMA P040024/S006) and Restylane® Lyft with Lidocaine (P040024/S039) were approved on May 11, 2007 and January 29, 2010, respectively for implantation into the deep dermis to superficial subcutis for the correction of moderate to severe facial folds and wrinkles, such as nasolabial folds. The PMA Supplement for Restylane® Lyft with Lidocaine (P040024/S073) was approved on July 1, 2015, for subcutaneous to supraperiosteal implantation for cheek augmentation and correction of age-related midface contour deficiencies over the age of 21. The SSEDs to support the indication are available on the CDRH website and is incorporated by reference here. The current supplement was submitted to expand the indication for *Restylane Lyft with Lidocaine*.

II. INDICATIONS FOR USE

Restylane® Lyft with Lidocaine is indicated for implantation into the deep dermis to superficial subcutis for the correction of moderate to severe facial folds and wrinkles, such as nasolabial folds.

Restylane® Lyft with Lidocaine is indicated for subcutaneous to supraperiosteal implantation for cheek augmentation and correction of age-related midface contour deficiencies in patients over the age of 21.

Restylane® Lyft with Lidocaine is indicated for injection into the subcutaneous plane in the dorsal hand to correct volume deficit in patients over the age of 21.

III. DEVICE DESCRIPTION

Restylane® Lyft with Lidocaine contains 0.3% lidocaine and is a transparent, viscous, sterile gel of hyaluronic acid (HA) isolated from a *Streptococcus* species that is chemically crosslinked with 1,4-butanediol diglycidyl ether (BDDE), stabilized, and suspended in phosphate buffered saline at pH = 7 and a concentration of 20 mg/mL.

IV. CONTRAINDICATIONS

- *Restylane® Lyft with Lidocaine* is contraindicated for use in patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.

- *Restylane® Lyft with Lidocaine* contains trace amounts of gram positive bacterial proteins, and is contraindicated for patients with a history of allergies to such material.

- *Restylane® Lyft with Lidocaine* is contraindicated for patients with bleeding disorders.

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

A. Warnings and Precautions

A detailed description of warnings and precautions can be found in the *Restylane® Lyft with Lidocaine* package insert (Warnings and Precautions).

V. ALTERNATIVE PRACTICES AND PROCEDURES

Practices and procedures for making the aging hand look younger typically target skin rejuvenation including topicals, chemical peels, microdermabrasion, intense pulsed light, and laser energy devices. Sclerotherapy, endovenous vascular ablation and phlebectomy is used to reduce visibility of veins. Dorsal hand injections for improved skin appearance have been performed in markets outside the US with products in the *Restylane®* family. Currently approved filler alternatives available in the US include calcium hydroxylapatite (a semi-permanent filler), and autologous fat injections.

VI. MARKETING HISTORY

Perlane and *Restylane® Lyft with Lidocaine* have been available in the United States for the correction of moderate to severe facial folds and wrinkles and age-related midface contour deficiencies since May 2, 2007 and January 29, 2010, respectively. *Restylane® Lyft with Lidocaine* (also known previously as Restylane Perlane Lidocaine outside of the US) has been commercially available in the European Union and EES countries since 2009. *Restylane® Lyft with Lidocaine* has not been removed from the marketplace for any reasons related to safety, effectiveness, patient or physician complaint, or dissatisfaction.

VII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The safety of *Restylane® Lyft with Lidocaine* for injection in the dorsal hand to correct for volume deficit was assessed in study 43USH1501. Treatment Emergent Adverse Events (TEAEs) that occurred in ≥ 2.5% of subjects in the study, whether related or unrelated to the study product or procedure, included peripheral swelling, laceration, scratch, pain in extremity, bruising, itching, pain, redness, swelling, tenderness, and impaired hand function. Adverse events were obtained from the patient's diary as well as from the study Investigator at all visits.

For further detail regarding specific TEAEs that occurred in clinical study 43USH1501, please see Section X (sub-section D) below.

VIII. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

There are no manufacturing or specification changes due to this supplement.

B. Biocompatibility Studies

This supplement describes clinical data to support approval of a new indication for use. Because no change in product manufacture or specification was conducted, the nonclinical data previously presented in PMA P040024 and supplements support the new proposed indication for use.

IX. SUMMARY OF PRIMARY CLINICAL STUDY

The sponsor performed a clinical study to establish a reasonable assurance of safety and effectiveness for *Restylane® Lyft with Lidocaine* for injection in the dorsal hand to correct volume deficit in patients over the age of 21.

A summary of the clinical study is presented below.

A. Study Design

The 43USH1501 study was a prospective, multi-center, randomized, evaluator-blinded, paired (split-hand) study designed to evaluate the safety and effectiveness of *Restylane® Lyft with Lidocaine* for injection in the dorsal hand to correct volume deficit in patients over the age of 21. The U.S. study enrolled 90 patients who were injected using a co-packed Terumo 29G x 1/2" thin-walled sharp needle. In addition, a cohort study with cannula injection of *Restylane Lyft with Lidocaine* was performed on 25 subjects [24 Fitzpatrick Skin Type (FST) I-IV subjects and 1 FST V-VI subjects] in two U.S. sites.

Primary Clinical Study (Needle only)

The study was a multi-center, prospective, randomized, split-hand pivotal clinical study. The

duration of the study was 6 months. The treating investigator was not masked but the evaluator assessing the hands live was masked. Subjects had one hand randomized to treatment and the other hand served as a no treatment control. The hand randomized to initial treatment received an optional touch up treatment 4 weeks later and an optional re-treatment at 6 months. The hand randomized to no treatment control received treatment at 6 months and an optional touch-up treatment 4 weeks later. The database for this PMA reflected data collected through December 5, 2016 and included 90 treated patients. Patients were enrolled and treated between December 16, 2015 and December 5, 2016 at 5 investigational sites.

1. Follow-up Schedule

All patients were scheduled for follow-up at 72 hours (telephone call), 2 weeks (visit), 4 weeks (visit – optional touch-up [72 hour telephone all post-touch-up]), 6 weeks (visit if touch-up performed), 8 weeks (visit if touch-up performed), 12 weeks, 16 and 20 weeks, and 24 weeks after Baseline; and 72 hours, 2 weeks, and 4 weeks, after 6-month treatment. Subjects who opted for treatment of the fellow hand at 6 months could obtain a touch-up treatment on that hand at 4 weeks after the 6-month treatment with additional follow up at 72 hours (telephone), 2 weeks (visit), and 4 weeks (visit) post fellow hand touch-up.

2. Clinical Inclusion and Exclusion Criteria

Enrollment in the 43USH1501 trial was limited to patients who met the following key inclusion criteria:

- Subjects who were willing to comply with the requirements of the study and provided a signed written informed consent including release of copyright of hand images.
- Males or females, 22 years of age or older.
- Grade 2-4 on the Merz Hand Grading Scale (MHGS), as assessed by blinded evaluator as well as the treating Investigator (note, up to 10 subjects with FST V-VI were not required to meet this inclusion criterion).
- Subjects who were willing and able to perform hand functionality tests.

Patients were not permitted to enroll in the 43USH1501 trial if they met any of the following key exclusion criteria:

- History of allergy or hypersensitivity to injectable HA gel or to gram positive bacterial proteins.
- History of allergy or hypersensitivity to lidocaine or other amide type anesthetics.
- Previous hand surgery including sclerotherapy, or history of hand trauma.
- Advanced photo-aged/photo-damaged skin or skin condition with very crinkled or fragile skin on the dorsal hands.

3. Clinical Endpoints

Effectiveness analysis was conducted on the Intent-to-Treat (ITT) population, defined as all subjects who were injected at least once who met all inclusion criterion for the Merz Hand Grading Scale (MHGS)[1]. The primary effectiveness endpoint was responder rate at Week 12 based on the blinded-evaluator assessment using the MHGS. A responder was defined as a hand with at least 1 point improvement from Baseline on the MHGS.

The secondary effectiveness endpoints included response rates at Weeks 16, 20, and 24 based on blinded-evaluator live assessments of MHGS, Central Independent Photographic Reviewer's (CIPR) assessment of improvement at Weeks 12, 16, 20, and 24, and aesthetic improvement as assessed by subjects and the treating investigator separately using the Global Aesthetic Improvement Scale (GAIS) at Week 4, at Week 4 following touch-up, Weeks 12, 16, 20, Week 24 prior to treatment, Week 28, and Week 32.

Other assessments included a subject questionnaire for satisfaction and perceived improvement of hand function, and the Michigan Hand Outcomes Questionnaire (Brief MHQ) for assessment of impact on normal daily activities.

Safety analyses were conducted on the safety population, defined as all subjects who were injected at least once. The primary safety objective of study 43USH1501 was to define the incidence of all TEAEs, including safety assessments made by the treating investigator at all visits and subject complaints reported during the first 4 weeks after treatment as recorded in the subject diary. Hand functionality was assessed through active and passive range of motions assessments (extension and flexion for index-, middle-, ring-, small finger and thumb), sensation test, functional dexterity test, and strength test (grip strength, key pinch strength, palmar pinch strength, and tip pinch strength) at all physical visits.

The consistency of the primary effectiveness analysis results and AE data was analyzed across the following subgroups: Baseline MHGS score 2, 3 and 4, FST (I-III versus IV-VI), age (above or below median age), gender, ethnicity, race, dominant hand, initial injection volume (above or below median volume), total injection volume (above or below median volume), and study center.

B. Accountability of PMA Cohort

A total of 5 sites across the United States were used to complete study 43USH1501. Randomization was performed using an Interactive Response Technology (IRT) System by randomly assigning Restylane Lyft to either the right or left hand, and the subject's other hand served as a no treatment control. The randomization was stratified by FST (I-III or IV-

[1]Narins RS, Carruthers J, Flynn TC, Geister TL, Gortelmeyer R, Hardas B, Himmrich S, Jones D, Kerscher M, de Maio M, Mohrmann C, Pooth R, Rzany B, Sattler G, Buchner L, Benter U, Breitscheidel L, Carruthers A. Validated assessment scales for the lower face. Dermatol Surg. 2012 Feb: 38 (2 Spec No.): 333-42

VI) within each study site, using a dynamic allocation algorithm. A total of 99 subjects were screened, 92 subjects randomized, and 90 subjects treated with *Restylane® Lyft with Lidocaine*. One subject did not have at least 1 post-treatment safety assessment and was excluded from the safety analysis leaving a total of 89 subjects in the safety population. Four subjects in the safety population did not meet the inclusion criteria for MHGS; therefore, 85 subjects were included in the ITT population. Over 90% of subjects completed the study with only a single subject discontinuing due to an AE. A summary of subject accountability is provided in Table 1 and a summary of treatment regimen for needle-injected subjects is provided in Table 2.

Table 1: Summary of Subject Disposition

Number of Subjects Screened	99
Number of Subjects Randomized	92
Number of Subjects Treated	90*
Number of Subjects in Safety Population	89** (96.7%)
Number of Subjects in ITT Population	85*** (92.4%)
Number of Subjects in PP Population	83 (90.2%)
Completed Study	
Yes	84 (91.3%)
No	8 (8.7%)
Reason for Discontinuation	
Withdrawal by Subject	4 (4.3%)
Lost to Follow-Up	2 (2.2%)
Adverse Event	1 (1.1%)
Other	1 (1.1%)

* Ninety subjects were randomized and received at least one treatment.
** One treated subject did not have at least 1 post-treatment safety assessment and was excluded from the Safety population.
*** Four FST IV-VI subjects did not meet the MHGS inclusion criteria and were excluded from the ITT population

Table 2: Summary of Treatment Regimen for Needle-Injected Subjects (Safety Population*)

	Subjects (N=89)
First Treatment/Restylane Lyft hand	89
Optional Week 4 touch-up/ Restylane Lyft hand	74
6 month/optional re-treatment/Restylane Lyft hand	70
6 month/first treatment/fellow hand	77
Optional 6 month + 4 week touch-up/fellow hand	44

* Ninety subjects were randomized and received at least one treatment. One treated subject did not have at least 1 post-treatment safety assessment and was excluded from the Safety population.

C. Study Population Demographics and Baseline Parameters

Most of the subjects were white (non-Hispanic or Latino) females with a mean age of 55.7 years. Subject demographics (age group, sex, ethnicity, and race) and Baseline characteristics for the ITT population are presented in Table 3.

Table 3: Summary of Subject Demographics (ITT Population)

	Intent-to-Treat Subjects (N=85)
Age (years)	
Mean	55.7
SD	9.13
Median	54.0
Sex	
Male	3 (3.5%)
Female	82 (96.5%)
Ethnicity	
Hispanic or Latino	9 (10.6%)
Not Hispanic or Latino	76 (89.4%)
Race	
White	71 (83.5%)
Black or African American	5 (5.9%)
Asian	0
American Indian or Alaska Native	0
Native Hawaiian or Other Pacific Islander	4 (4.7%)
Other	5 (5.9%)
Hand dominance	
Left	7 (8.2%)
Right	78 (91.8%)
Both	0
Fitzpatrick skin type (FST)	
I Always burns, never tans	4 (4.7%)
II Usually burns, tans with difficulty	21 (24.7%)
III Sometimes mild burns, gradually tans	39 (45.9%)
IV Rarely burns, tans with ease	12 (14.1%)
V Very rarely burns, tans with ease	7 (8.2%)
VI Never burns, tans very easily	2 (2.4%)
Subjects with FST V-VI who met MHGS inclusion criteria	9 (10.6%)
Subjects with FST V-VI who did not meet MHGS inclusion criteria	0
MHGS – Treated Hand (blinded-evaluator)	
0	0
1	0
2	27 (31.8%)
3	31 (36.5%)
4	27 (31.8%)
MHGS – Fellow Hand (Blinded-evaluator)	
0	0
1	0
2	18 (21.2%)

	Intent-to-Treat Subjects (N=85)
3	39 (45.9%)
4	28 (32.9%)

Mean volume of injection for the first treatment at Baseline was 2.13 mL (range 1.0 to 3.0) in the treated hand with an average touch-up treatment of 1.13 mL. The mean volume of total injection was 3.07 mL (range 1.0 to 5.0). Mean volume was similar at Baseline treatment (2.13 mL) and first treatment of the fellow hand (2.05 mL at 6 months). All injections were subcutaneous.

D. Safety and Effectiveness Results

1. Safety Results

A total of 37 (41.6%) subjects experienced at least one TEAE, in total 82 events. Of the 37 subjects reporting a TEAE, 7 reported TEAEs related to the product/procedure (with 13 total related events). There were no deaths reported in the study. A complete summary of Investigator reported TEAEs by intensity and preferred term (PT) is provided in Table 4.

Table 4: Summary of all Treatment Emergent Adverse Events by Intensity by Preferred Term (Safety Population N=89)

Preferred Term	Grade of Intensity			Number	Number of Subjects	
	Mild	Moderate	Severe	of Events	n	%
Vitreous detachment	1	.	.	1	1	1.1
Cyst rupture	1	.	.	1	1	1.1
Device failure	1	.	.	1	1	1.1
Facial pain	1	.	.	1	1	1.1
Influenza like illness	.	1	.	1	1	1.1
Peripheral swelling	4	2	.	6	4	4.5
Bronchitis	1	1	.	2	2	2.2
Chronic sinusitis	.	2	.	2	1	1.1
Gastroenteritis	1	.	.	1	1	1.1
Nasopharyngitis	2	.	.	2	2	2.2
Onychomycosis	1	.	.	1	1	1.1
Oral herpes	1	.	.	1	1	1.1
Sinusitis	2	.	.	2	2	2.2
Tooth infection	1	1	.	2	2	2.2
Upper respiratory tract infection	1	.	.	1	1	1.1
Animal scratch	1	.	.	1	1	1.1
Burns first degree	1	.	.	1	1	1.1
Contusion	1	2	.	3	2	2.2
Eye injury	1	.	.	1	1	1.1
Laceration	5	1	.	6	6	6.7
Limb injury	1	.	.	1	1	1.1
Nail injury	1	.	.	1	1	1.1
Scratch	7	.	.	7	6	6.7
Thermal burn	2	.	.	2	2	2.2

Preferred Term	Grade of Intensity			Number of Events	Number of Subjects	
	Mild	Moderate	Severe		n	%
Blood cholesterol increased	1	.	.	1	1	1.1
Vitamin D deficiency	1	.	.	1	1	1.1
Back pain	.	1	.	1	1	1.1
Muscle spasms	1	.	.	1	1	1.1
Musculoskeletal pain	.	1	.	1	1	1.1
Pain in extremity	7	.	.	7	5	5.6
Rotator cuff syndrome	1	.	.	1	1	1.1
Basal cell carcinoma	1	.	.	1	1	1.1
Lobular breast carcinoma in situ	1	.	.	1	1	1.1
Thyroid neoplasm	1	.	.	1	1	1.1
Uterine leiomyoma	.	1	.	1	1	1.1
Migraine	1	.	.	1	1	1.1
Urinary tract infection	1	.	.	1	1	1.1
Uterine polyp	.	1	.	1	1	1.1
Cough	.	1	.	1	1	1.1
Actinic keratosis	2	.	.	2	1	1.1
Dermatitis contact	.	1	.	1	1	1.1
Eczema	1	.	.	1	1	1.1
Onycholysis	2	.	.	2	1	1.1
Photosensitivity reaction	1	.	.	1	1	1.1
Pruritus	2	.	.	2	1	1.1
Rash	2	.	.	2	2	2.2
Skin mass	1	.	.	1	1	1.1
Urticaria	1	.	.	1	1	1.1

Adverse events that occurred in >2.5% of the study population consisted of peripheral swelling [4 subjects (4.5%)], laceration [6 subjects (6.7%)], scratch [(6 subjects (6.7%)], and pain in extremity [5 subjects (5.6%)] with the majority of TEAEs being mild in intensity (N=66 mild, 16 moderate, and no severe). There were no serious adverse events (SAEs) related to the study product or procedure reported in this trial.

One device deficiency associated with injection procedure occurred: the needle was not properly attached and disconnected from the syringe. Subject treatment was not affected.

A total of 13 TEAEs (i.e., individual events) affecting 7 patients (7/89 [7.9%]) were classified as related to product and/or injection procedure. These are presented with time to onset and duration in Table 5. Most events related to treatment with *Restylane® Lyft with Lidocaine* resolved within 5 days (median).

Table 5: Summary of TEAEs assessed as related to either the injection procedure or study device by Time to Onset and Duration

System Organ Class/Preferred Term	Time to Onset (Days)	Duration (Days)
Any related TEAE (n=13)		
Mean (SD)	45.2 (42.5)	29.8 (33.9)
Median (min, max)	28.0 (4, 151)	5.0 (1, 96)
General disorders and administration site conditions (n=6)		
Peripheral swelling (n=6)		
Mean (SD)	57.7 (49.3)	42.8 (34.2)
Median (min, max)	38.0 (20, 151)	50.0 (5, 96)
Musculoskeletal and connective tissue disorders (n=4)		
Pain in extremity (n=4)		
Mean (SD)	18.0 (12.0)	8.0 (8.9)
Median (min, max)	20.0 (4, 28)	5.0 (1, 21)
Skin and subcutaneous tissue disorders (n=3)		
Pruritus (n=2)		
Mean (SD)	28.0 (0.0)	5.0 (0.0)
Median (min, max)	28.0 (28, 28)	5.0 (5, 5)
Skin mass (n=1)		
Mean (SD)	113.0 (n/a)	89.0 (n/a)
Median (min, max)	113.0 (113, 113)	89.0 (89, 89)

For the 89 subjects in the Safety population, three hand-specific related TEAEs were reported in 3 subjects (3/89, 3.4%) after first treatment (first treatment in the randomized hand) and included peripheral swelling (2/89, 2.2%), and skin mass (1/89, 1.1%). In the second treatment (treatment in fellow [non-randomized] hand), 5 hand-specific related TEAEs were reported in 3 subjects (3/77, 3.9%) and included peripheral swelling (2/77, 2.6%), pain in extremity (2/77, 2.6%), and pruritis (1/77, 1.3%). Four hand-specific related TEAEs were reported in 2 subjects (2/70, 2.9%) in the 3rd treatment (Re-treatment at 24 weeks).

Of the 7 subjects with product/injection procedure related TEAEs, 4 subjects received medical treatment. Treatment included nonsteroidal anti-inflammatory drugs (NSAIDS), oral antihistamines, topical and oral corticosteroids, hyaluronidase, and antibiotics.

Five of these 7 subjects experienced delayed onset (>21 days) related TEAEs and 2 additional subjects reported delayed onset related AEs after exit from the study. The delayed adverse events were mild to moderate and included swelling, nodules, tenderness, itching, tingling, and granuloma. Five of these subjects received treatment as mentioned above. All events were followed to resolution. A summary of all Delayed Treatment Emergent Adverse Events (TEAE) can be seen in Table 6.

Table 6: Delayed Onset Treatment Emergent Adverse Events (TEAE)

	FST	Injection method	AE start day relative to last treatment	AE duration	Severity Intensity	Reported AE term	Treatment of the AE
Patient 1	TYPE III	Needle	113	89	MILD	SINGLE SUB-CUTANEOUS NODULE	None
Patient 2	TYPE III	Needle	28	5	MILD	ITCHING ON THE DORSUM OF THE LEFT HAND	None
			28	5	MILD	ITCHING ON THE DORSUM OF THE RIGHT HAND	None
			28	5	MILD	SWELLING TO THE DORSUM OF THE LEFT HAND	None
			28	5	MILD	SWELLING TO THE DORSUM OF THE RIGHT HAND	None
			28	5	MILD	TENDERNESS TO THE DORSUM OF THE LEFT HAND	None
			28	5	MILD	TENDERNESS TO THE DORSUM OF THE RIGHT HAND	None
Patient 3	TYPE III	Needle	48	51	MODERATE	SWELLING TO THE DORSUM OF THE LEFT HAND	Ibuprofen, Chloreniramine Maleate, Hydrocortisone Cream, Medrol Dose Pack, Hyaluronidase, Bethamethasone Dipropinate

	FST	Injection method	AE start day relative to last treatment	AE duration	Severity Intensity	Reported AE term	Treatment of the AE
			20	51	MODERATE	SWELLING TO THE DORSUM OF THE RIGHT HAND	Ibuprofen, Chloreniramine Maleate, Hydrocortisone Cream, Medrol Dose Pack, Hyaluronidase, Bethamethasone Dipropinate
Patient 4	TYPE III	Needle	71	96	MILD	PROLONGED SWELLING OF THE DORSUM OF THE RIGHT HAND	Ibuprofen
Patient 5	TYPE V	Needle	151	49	MILD	SWELLING TO THE DORSUM OF THE LEFT HAND	Benadryl Cream, Hydrocortisone Cream, Methlypredisolone, Sulfamethoxazole, Hyaluronidase, Ice
Patient 6*	TYPE II	Needle	300	136	MILD	GRANULOMA	None
Patient 7*	TYPE IV	Needle	210	4	MODERATE	SWELLING	Medrol Dose Pack

*Indicates the adverse event reported post-study exit.

There were no deaths reported in the study.

Subjects were asked to record symptoms of bruising, redness, swelling, pain, tenderness, itching, and impaired hand function in a 28-Day patient diary. Based on subject diaries, the majority of subjects experienced injection site reactions on Day 1 after initial treatment that included swelling (75.0%), tenderness (75.0%), redness (71.6%), and bruising (60.2%), with pain reported for 44.3% of subjects. Itching (13.6%) and impaired hand function (6.8%) were also reported. Subject's scores for the severity of these events are presented in Table 7 and durations are provided in Table 8. Overall, injection site reaction decreased with time and by Day 8 all injection site reactions had resolved. The number of subjects with injection site reactions decreased following touch-up procedures. On average, following the first injection of *Restylane® Lyft with Lidocaine*, the injection site reactions resolved within 2-3 days, and only swelling and tenderness resolved within 4-5 days (3.4 and 4.5 days, respectively).

Table 7: Maximum Intensity of Post-Treatment Injection Site Reactions Recorded in the Subject Diary (Safety Population)

	Initial Treatment			6 Month Treatment		
	Restylane® Lyft hand		Fellow Hand	Restylane® Lyft hand	Fellow Hand	
Event Severity	Treatment (N=89)[b]	Touch-Up (N=74)[b]	No Treatment[a] (N=89)[b]	Re-treatment (N=70)	Treatment (N=77)	Touch-Up (N=44)
Bruising						
Total	53 (60.2%)	37 (50.7%)	1 (1.1%)	29 (41.4%)	48 (62.3%)	17 (38.6%)
Mild	43 (48.9%)	32 (43.8%)	1 (1.1%)	23 (32.9%)	32 (41.6%)	13 (29.5%)
Moderate	10 (11.4%)	5 (6.8%)	0	6 (8.6%)	15 (19.5%)	4 (9.1%)
Severe	0	0	0	0	1 (1.3%)	0
Itching						
Total	12 (13.6%)	7 (9.6%)	0	8 (11.4%)	10 (13.0%)	10 (22.7%)
Mild	11 (12.5%)	6 (8.2%)	0	6 (8.6%)	6 (7.8%)	10 (22.7%)
Moderate	1 (1.1%)	1 (1.4%)	0	2 (2.9%)	4 (5.2%)	0
Severe	0	0	0	0	0	0
Pain						
Total	39 (44.3%)	26 (35.6%)	0	30 (42.9%)	42 (54.5%)	11 (25.0%)
Mild	30 (34.1%)	25 (34.2%)	0	20 (28.6%)	26 (33.8%)	8 (18.2%)
Moderate	8 (9.1%)	1 (1.4%)	0	10 (14.3%)	13 (16.9%)	2 (4.5%)
Severe	1 (1.1%)	0	0	0	3 (3.9%)	1 (2.3%)
Redness						
Total	63 (71.6%)	41 (56.2%)	0	42 (60.0%)	50 (64.9%)	20 (45.5%)
Mild	52 (59.1%)	39 (53.4%)	0	34 (48.6%)	33 (42.9%)	19 (43.2%)
Moderate	11 (12.5%)	2 (2.7%)	0	7 (10.0%)	16 (20.8%)	1 (2.3%)
Severe	0	0	0	1 (1.4%)	1 (1.3%)	0
Swelling						
Total	66 (75.0%)	43 (58.9%)	1 (1.1%)	31 (44.3%)	47 (61.0%)	22 (50.0%)
Mild	45 (51.1%)	34 (46.6%)	1 (1.1%)	18 (25.7%)	27 (35.1%)	16 (36.4%)
Moderate	19 (21.6%)	9 (12.3%)	0	12 (17.1%)	19 (24.7%)	5 (11.4%)
Severe	2 (2.3%)	0	0	1 (1.4%)	1 (1.3%)	1 (2.3%)
Tenderness						
Total	66 (75.0%)	49 (67.1%)	2 (2.3%)	41 (58.6%)	55 (71.4%)	26 (59.1%)
Mild	51 (58.0%)	42 (57.5%)	2 (2.3%)	28 (40.0%)	31 (40.3%)	21 (47.7%)
Moderate	14 (15.9%)	7 (9.6%)	0	11 (15.7%)	20 (26.0%)	4 (9.1%)
Severe	1 (1.1%)	0	0	2 (2.9%)	4 (5.2%)	1 (2.3%)
Impaired Function						
Total	6 (6.8%)	3 (4.1%)	0	3 (4.3%)	8 (10.4%)	1 (2.3%)

[a] Four subjects reported injection site reactions on the fellow hand during the no treatment phase.
[b] One subject did not hand in the diary from the Initial treatment (first treatment and touch-up)

Table 8: Number of Days with Post-Treatment Injection Site Reactions Recorded in the Subject Diary (Safety Population)

	Initial Treatment			6 Month Treatment		
	Restylane® Lyft hand		Fellow Hand	Restylane® Lyft hand	Fellow Hand	
Event Statistic	Treatment (N=89)	Touch-Up (N=74)	No Treatment [a] (N=89)	Re-treatment (N=70)	Treatment (N=77)	Touch-Up (N=44)
Bruising						
N	53	37	1	29	48	17
Mean	2.7	3.3	1.0	2.9	3.0	3.5
SD	1.66	3.54	N/A	1.58	1.69	1.87
Median	2.0	2.0	1.0	3.0	2.0	3.0
Min. to Max.	1 to 8	1 to 18	1 to 1	1 to 7	1 to 7	1 to 7
Itching						
N	12	7	0	8	10	10
Mean	1.7	1.6		4.4	3.1	2.0
SD	0.89	1.13		3.70	2.51	1.15
Median	1.0	1.0		3.5	3.0	2.0
Min. to Max.	1 to 3	1 to 4		1 to 11	1 to 9	1 to 4
Pain						
N	39	26	0	30	42	11
Mean	2.7	1.9		3.3	2.7	3.2
SD	3.40	1.18		5.02	2.12	3.12
Median	2.0	1.5		2.0	2.0	2.0
Min. to Max.	1 to 21	1 to 5		1 to 28	1 to 9	1 to 10
Redness						
N	63	41	0	42	50	20
Mean	2.2	2.7		2.1	2.5	2.6
SD	1.45	2.32		1.11	1.47	1.90
Median	2.0	2.0		2.0	2.0	2.0
Min. to Max.	1 to 7	1 to 12		1 to 6	1 to 7	1 to 9
Swelling						
N	66	43	1	31	47	22
Mean	3.4	4.3	2.0	5.0	3.3	3.3
SD	2.83	4.60	N/A	5.59	2.43	2.38
Median	3.0	3.0	2.0	3.0	3.0	3.0
Min. to Max.	1 to 16	1 to 21	2 to 2	1 to 28	1 to 15	1 to 11
Tenderness						
N	66	49	2	41	55	26
Mean	4.5	5.1	1.0	4.4	3.9	4.2
SD	5.70	5.46	0.00	4.91	2.72	3.59
Median	3.0	3.0	1.0	3.0	3.0	2.0
Min. to Max.	1 to 27	1 to 27	1 to 1	1 to 28	1 to 17	1 to 14
Impaired Function						
N	6	3	0	3	8	1
Mean	2.0	1.3		2.3	3.1	1.0
SD	1.55	0.58		1.15	1.73	N/A
Median	1.0	1.0		3.0	3.0	1.0
Min. to Max.	1 to 4	1 to 2		1 to 3	1 to 5	1 to 1

[a] Four subjects reported injection site reactions on the fellow hand during the no treatment phase.

Hand function safety assessments, including range of motion , functional dexterity, pinch and grip strength, sensation and dexterity were evaluated at all required study follow up visits. Passive and active range of motion testing in the fingers (extension) revealed negligible change. In the active flexion test for the thumb, there was slightly reduced flexion after treatment. There were 22 subjects out of 89 (24.7%) injected with needle that had at least 10-degree negative change of active flexion for thumb of the treated hand compared to baseline or non-treated hand that remain through the 6-months duration of the study. A summary is provided in Table 9. There was no evidence of loss of sensation for any subject in the study throughout the course of the study. Strength tests revealed no appreciable loss of strength for the pinch strength or grip strength. With the functional dexterity tests, there was no difference between the treated and untreated hands.

Table 9: Active Flexion Range of Thumb Data for Subjects with at least 10-degree negative change

Patient ID	Start Visit of First Episode	Number of Episodes	Duration of Longest Episode (Days)
Patient 1	Week 16	1	76
Patient 2	Week 2 following touch-up	2	>141
Patient 3	Week 2 following touch-up	2	36
Patient 4	Week 2	3	>114
Patient 5	Week 2	2	104
Patient 6	Week 4	2	>176
Patient 7	Week 2	2	>186
Patient 8	Week 4 following touch-up	1	62
Patient 9	Week 2	1	>215
Patient 10	Week 16	1	37
Patient 11	Week 2	3	84
Patient 12	Week 2	2	70
Patient 13	Week 2	1	>189
Patient 14	Week 2	2	129
Patient 15	Week 16	1	52
Patient 16	Week 12	1	31
Patient 17	Week 20	1	30
Patient 18	Week 2	1	>1
Patient 19	Week 20	1	29
Patient 20	Week 4	1	18

Patient ID	Start Visit of First Episode	Number of Episodes	Duration of Longest Episode (Days)
Patient 21	Week 4 following touch-up	1	28
Patient 22	Week 2	1	21

Note: Episode duration is calculated as study day for first visit with no decrease in Active Flexion Range of Thumb after an episode, MINUS study day with first decrease in Active Flexion Range of Thumb.
Note: ">" indicates that there is no assessment with no decrease in Active Flexion Range of Thumb for an episode, and instead the last study day is used as stop day.

Results from subject assessment of the hand-specific impact on daily life activities using the the unvalidated monolateral Michigan Hand Questionnaire (MHQ) showed a negligible effect on subject's daily life activities. The majority of subjects responded with favorable answers to all questions at each study visit assessed (Baseline, Week 12, and Week 24). The majority of subjects were dissatisfied with the appearance of their hands at Baseline with a shift in response to satisfaction at Weeks 12 and 24.

Sub-Group Safety Results

Subgroup analysis examining hand-specific related TEAEs at first treatment on the hand randomized to *Restylane® Lyft with Lidocaine* revealed no clinically relevant differences as a function of Baseline MHGS score, Fitzpatrick Skin Type, age, injection volumes, or number of treatments.

2. Effectiveness Results

The results of the primary efficacy analysis, response rate at Week 12 based on MHGS, which was compared between *Restylane® Lyft with Lidocaine* and no treatment using McNemar's test, demonstrated the superiority of *Restylane® Lyft with Lidocaine* to no treatment ($p<0.0001$). The difference in responder rates at Week 12 was 64.7%, with 85.9% and 21.2% considered responders for Restylane Lyft and no treatment, respectively. Responder rates measured for the treated and fellow hands are summarized in Table 10.

Table 10: Summary of Primary Efficacy Endpoint: Responder Rate at Week 12 (ITT Population)

Restylane Lyft with Lidocaine (N=85) Responder[a] at Week 12			
Active Treatment Group (N=85)	**Fellow Hand [Control] (N=85)**	**Difference in Responder Rate**	**p-value[b]**
85.9%	21.20%	64.7%	<0.0001

[a] A responder is defined as having at least 1-point improvement from baseline on the MHGS by the blinded-evaluator assessment.
[b] P-value calculated using McNemar's test.

Secondary Effectiveness Results

The first secondary efficacy endpoint, responder rates at Weeks 16, 20, and 24, compared rates between *Restylane® Lyft with Lidocaine* and no treatment using McNemar's Test. Statistical significance was achieved at all timepoints ($p<0.0001$) demonstrating a superiority to no treatment. (Table 11).

Table 11: Summary of Responder Rates at Weeks 16, 20, and 24 (ITT Population)

Restylane Lyft with Lidocaine (N=83*) Responder[a] at Week 16			
Active Treatment Group (N=83)	**Fellow Hand [Control] (N=83)**	**Difference in Responder Rate**	**p-value[b]**
91.6%	19.3%	72.3%	<0.0001
Restylane Lyft with Lidocaine (N=82*) Responder[a] at Week 20			
Active Treatment Group (N=82)	**Fellow Hand [Control] (N=82)**	**Difference in Responder Rate**	**p-value[b]**
82.9%	25.6%	57.3%	<0.0001
Restylane Lyft with Lidocaine (N=83*) Responder[a] at Week 24			
Active Treatment Group (N=83)	**Fellow Hand [Control] (N=83)**	**Difference in Responder Rate**	**p-value[b]**
75.9%	30.1%	45.8%	<0.0001

[a] A responder is defined as having at least a 1-point improvement from baseline on the MHGS by the treatment-blinded evaluator.
[b] p-value calculated using McNemar's test.
* N reflects number of subject observations at each timepoint.

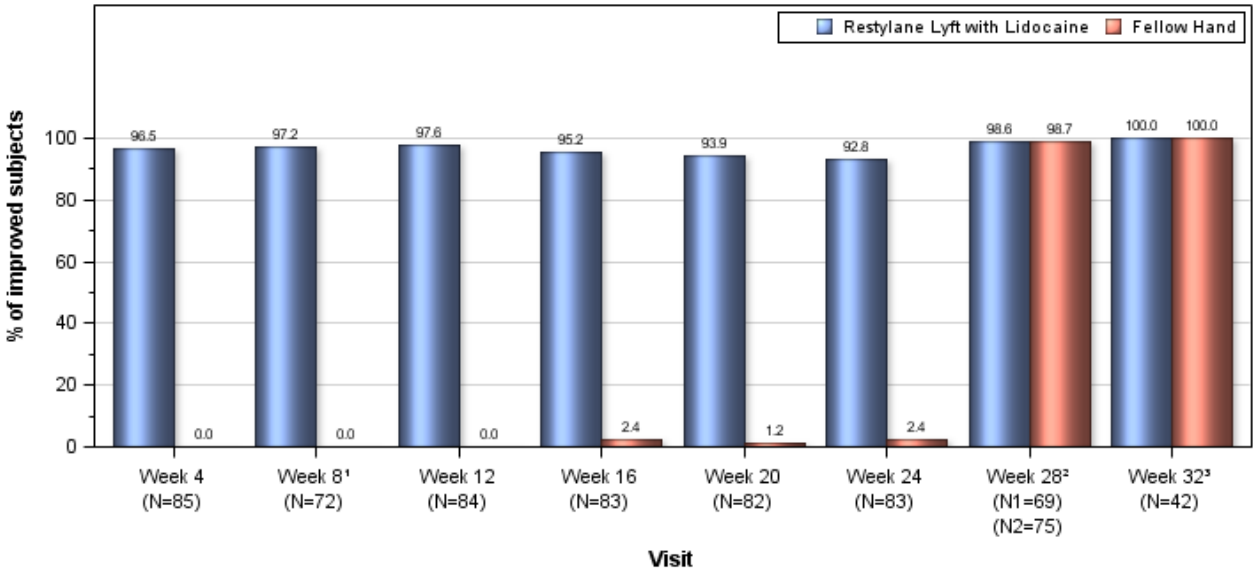
The second secondary efficacy endpoint was a CIPR's assessment of hand improvement at Weeks 12, 16, 20, and 24 that demonstrated an increased improvement in the treatment hand compared to the fellow hand at all study visits. A summary of the hand improvement as observed in the treatment hand and fellow hand are presented in Table 12. The frequency of patients demonstrating improvement in the treatment hand were consistent across all study visits at Weeks 12, 16, 20, and 24 (88.1%, 85.5%, 69.5%, and 85.5%, respectively).

Table 12: Summary of Central Independent Photographic Reviewer's Assessment of Hand Improvement (ITT Population)

Restylane Lyft (N=85)	Week 12	Week 16	Week 20	Week 24
Improvement				
N	84	83	82	83
No	10 (11.9%)	12 (14.5%)	25 (30.5%)	12 (14.5%)
Yes	74 (88.1%)	71 (85.5%)	57 (69.5%)	71 (85.5%)
Fellow Hand				
Improvement				
N	84	83	82	83
No	68 (81.0%)	66 (79.5%)	69 (84.1%)	65 (78.3%)
Yes	16 (19.0%)	17 (20.5%)	13 (15.9%)	18 (21.7%)

The third secondary endpoint, the GAIS, was summarized using dichotomized categories for the following timepoints: Week 4, Week 4 following touch-up, Weeks 12, 16, and 20, Week 24, and Weeks 28 and 32. Subject and Investigator evaluations yielded similar results in the treatment hand at Week 24 (92.8%; 95.2%). Subject and investigator evaluations of improvement for both hands are presented in Figure 1 and 2.

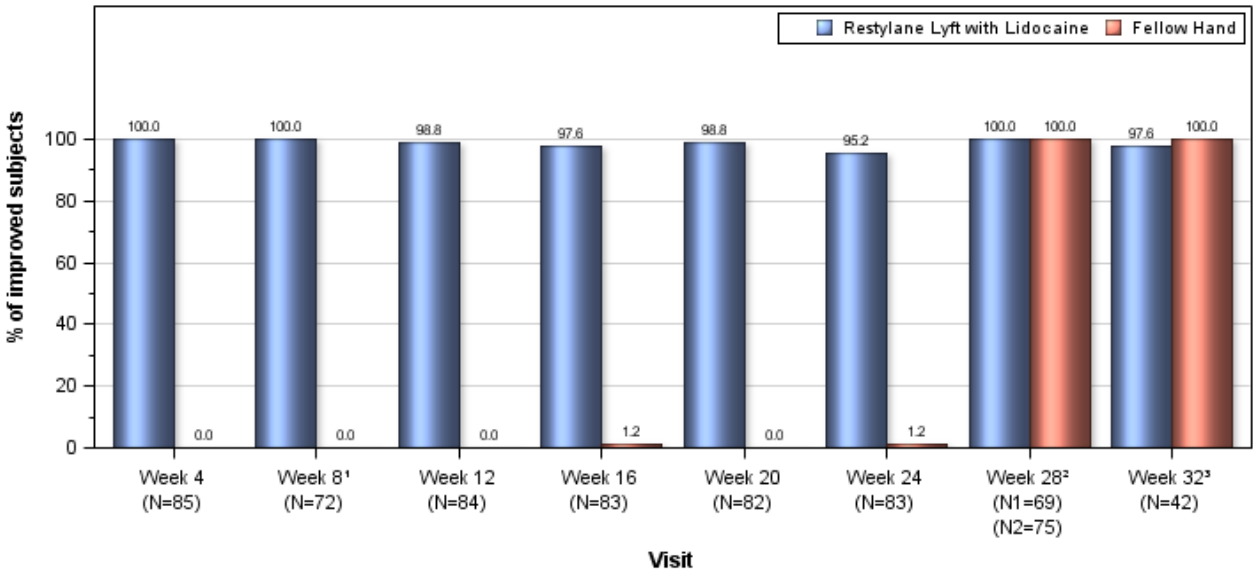
Figure 1: Improved subjects on GAIS by visit, Subject Evaluation (ITT population)



1) Week 8 =Week 4 following touch-up at Week 4.
2) Week 28= 4 weeks post re-treatment of originally treated hands and post initial treatment of fellow hands.
3) Week 32 = 4 weeks post touch-up of fellow hands.

N_1 = Restylane Lyft with Lidocaine
N_2 = Fellow Hand

Figure 2: Improved subjects on GAIS by visit, Treating Investigator Evaluation (ITT population)



1) Week 8 =Week 4 following touch-up at Week 4.
2) Week 28= 4 weeks post re-treatment of originally treated hands and post initial treatment of fellow hands.
3) Week 32 = 4 weeks post touch-up of fellow hands.

N_1 = Restylane Lyft with Lidocaine
N_2 = Fellow Hand

The fourth secondary efficacy endpoint evaluated the patient's satisfaction with *Restylane® Lyft with Lidocaine* and assessed at Week 12 based upon a 13-item questionnaire using a 5-point Likert Response Scale (1=Strongly Agree, 2=Agree, 3=Neither agree or disagree, 4=Disagree, 5=Strongly Disagree). Responses to each item were transformed into percent agreement (percentage of subjects with a score of 1 or 2) and are presented descriptively. Overall, the majority of subjects were satisfied with the appearance of the treated hand compared to the untreated (77/84; 91.7%), agreed that the treatment result looks natural (80/84; 95.2%), felt their treated hand appeared more attractive (74/84; 88.1%) and youthful (75/84; 89.3%), would recommend treatment to a friend (71/84; 84.5%) and would undergo repeat treatment in the future (65/84; 77.4%). A summary of Subject Satisfaction at Week 12 is provided in Table 13.

Table 13: Summary of Subject Satisfaction at Week 12 (ITT Population) (N=85)

		Intent-to-Treat Subjects
I am happier with the overall appearance of my treated hand compared to my untreated hand	Agree	77 (91.7%)
	Do Not Agree	7 (8.3%)
My treated hand appears more attractive than my untreated hand	Agree	74 (88.1%)
	Do Not Agree	10 (11.9%)
My treated hand looks more youthful than my untreated hand	Agree	75 (89.3%)
	Do Not Agree	9 (10.7%)
My treated hand feels softer than my untreated hand	Agree	44 (52.4%)
	Do Not Agree	40 (47.6%)
Skin on my treated hand appears tighter than on my untreated hand	Agree	64 (76.2%)
	Do Not Agree	20 (23.8%)
My treated hand looks less bony than my untreated hand	Agree	78 (92.9%)
	Do Not Agree	6 (7.1%)
Veins on treated hand are less apparent compared to my untreated hand	Agree	81 (96.4%)
	Do Not Agree	3 (3.6%)
Appears at least 5 years younger than my untreated hand	Agree	59 (70.2%)
	Do Not Agree	25 (29.8%)
Appears at least 10 years younger than my untreated hand	Agree	26 (31.0%)
	Do Not Agree	58 (69.0%)
Skin on my treated hand appears hydrated	Agree	57 (68.7%)
	Do Not Agree	26 (31.3%)
The treatment result looks natural	Agree	80 (95.2%)
	Do Not Agree	4 (4.8%)
I would recommend this treatment to a friend	Agree	71 (84.5%)
	Do Not Agree	13 (15.5%)
I would have another treatment	Agree	65 (77.4%)
	Do Not Agree	19 (22.6%)

*One subject did not complete the Subject Satisfacation Questionnaire at Week 12; n=84.

At week 12, subjects completed a single question related to improved hand function of the treated hand post-treatment (i.e, “since receiving treatment my hand function has improved”), which was assessed based on either “yes” or “no” responses. The majority of subjects in the ITT population (63/84; 75.0%) did not perceive an improvement in hand function.

Sub-Group Effectiveness Results

The primary effectiveness parameter, responder rate at Week 12, was assessed for the following subgroups: age, initial injection volume <2 mL or ≥2 mL, total injection volume <3 mL or ≥3 mL, site, Baseline MHGS score, FST (I-III versus IV-VI), gender, ethnicity, race, and dominant versus non-dominant hand.

There was a negligible difference in responder rates at Week 12 based on age (85.7% versus 86% for patients <53.5 years and ≥53.5 years, respectively). Patients with a higher initial injection volume (≥2 mL) revealed higher responder rates (91% versus 66.7%) compared to those receiving <2 mL. Similarly, patients with a higher total injection volume (≥3 mL) had higher responder rates compared to a lower total injection volume (<3 mL) (87.9% versus 81.5%, respectively). In general, there was no major difference in percentage of responders across all 5 study centers (Range: 77.8%-100.0%). Patients with the highest Baseline MHGS score (i.e., 4) revealed the highest responder rate (100%), followed by patients with a score of 3 and 2 (87.1% and 70.4%, respectively). Patients with a Baseline FST of I-III showed an 87.5% responder rate compared to 81.0% in FST IV-VI patients. Women, who comprised the majority of subjects in this trial, had higher responder rate compared to males at Week 12 (86.6% versus 66.7%, respectively). Ethnicity slightly influenced patient responder rates with Hispanic or Latinos having an 88.9% responder rate and non-Hispanic or Latinos having an 85.5% rate. The majority of patients in this study were white (N=71) with a responder rate of 85.9%, followed by Black or African American (N=5) with a responder rate of 60.0%, Native Hawaiian or Other Pacific Islander (N=4) with a responder rate of 100.0%, and 'Other' (N=5) with a responder rate of 100.0%. Patients whose dominant hand was treated had a higher responder rate than those whose dominant hand was not treated (92.9% and 79.1%, respectively).

Overall, patients with a higher Baseline MHGS score, FST skin type of I-III, receiving a higher initial injection volume and higher total injection volume, and who were female saw the greatest effectiveness from *Restylane® Lyft with Lidocaine*.

Cannula Cohort Results

A cohort study with cannula injection of *Restylane Lyft with Lidocaine* was performed on 25 subjects (24 FST I-IV subjects and 1 FST V-VI subjects) in two U.S. sites. The benefits and risks of injecting *Restylane Lyft with Lidocaine* using a cannula for the hand indication have not been established. The study was not designed or powered to assess the safety and effectiveness of the use of cannula or to compare its performance to the use of a needle. Preliminary results indicate that cannula use was associated with higher number of TEAEs, delayed adverse events and negative change in the active flexion for thumb as compared to needle injections. However, it was not possible to control or adjust for important potential confounders such as injection techniques, cannula size, and physician's skills.

Rates of TEAE were higher in the cannula cohort (41 events in 17 of 25 cannula-injected subjects, 17/25 = 68.0%) compared to those rates observed in subjects who received *Restylane Lyft with Lidocaine* administered with needle (82 events in 37 of 89 needle-injected subjects, 37/89 = 41.6%). When the device was injected with needle (N=89) 12 hand-specific related TEAEs were reported and 3 of them were related to the 1st treatment (3 events occurred in 3 subjects, 3/89 = 3.3%) compared with Cannula injection (N=25) where 15 hand-specific related TEAEs in 7 subjects were reported related to the 1st treatment (15 events occurred in 7 subjects, 7/25 = 28%).

Regarding delayed adverse events, there appeared to be higher rates of delayed AE in the subjects who received *Restylane Lyft with Lidocaine* with cannula compared to those who received needle injections. In 13 subjects with delayed AEs (> 21 day after treatment), 6 subjects who had Needle injection had delayed AE (6/89 = 6.7%) and 7 subjects who received Cannula injection experienced delayed AE (7/25 = 28%).

Regarding negative change in the active flexion for thumb, there were 22 subjects out of 89 (24.7%) injected with the needle that had at least a 10-degree negative change of active flexion for thumb of the treated hand compared to baseline or non-treated hand that remained through the duration of the study. There were 9 subjects out of 25 (36%) injected with the cannula that had at least a 10-degree negative change of action flexion for the thumb of the treated hand compared to baseline or non-treated hand that remained through the duration of the study.

3. Pediatric Extrapolation

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

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 5 principal investigators and 9 sub-investigators, of which none were full-time or part-time employees of the sponsor PMA P040024/S099, and 3 investigators had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0

Significant payment of other sorts: 3

Proprietary interest in the product tested held by the investigator: 0

Significant equity interest held by investigator in sponsor of covered study: 0

Enrollment across study sites was nearly identical (with the exception of Site 8478 who enrolled 12 more subjects than the next highest enrolling site) which minimizes the potential effect that a single study site could have on the study results.

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. The information provided does not raise any questions about the reliability of the data.

F. Summary of Supplemental Clinical Information – Post Marketing Data

The adverse event reports received from post-marketing surveillance (from voluntary reporting and published literature) for the use of *Restylane® Lyft* with Lidocaine and Perlane for all indications (including cheek) included reports of swelling/edema or inflammatory reactions immediate or delayed onset, up to several weeks after treatment. The following events were also reported: short duration of effect, mass formation including lumps or bumps, induration, pain or tenderness, erythema, bruising/hematoma, presumptive bacterial infections and abscess formation, papules or nodules, inflammation, injection site reactions including burning sensation, warmth and irritation, discoloration/hyperpigmentation, neurological symptoms including hypoaesthesia, paraesthesia and facial nerve paralysis, hypersensitivity, angioedema, ischemia and necrosis due to unintentional intravascular injection or embolisation, eye disorders including eye pain, eye swelling, eye irritation, increased lacrimation, eyelid ptosis and visual impairment such as blurred vision, reduced visual acuity and blindness, pruritus, atrophy/scarring, device dislocation, rash, effusion/discharge, granuloma/foreign body reaction, acne, blisters/vesicles, symptoms of reactivation of herpes infection, urticaria, capillary disorder such as telangiectasia, extrusion of device, dermatitis, muscle disorders such as muscle twitching and muscle weakness, encapsulation and other dermatological events including dry skin, skin wrinkling, skin exfoliation and localized alopecia, and non-dermatological events including headache, discomfort, malaise, pyrexia, dizziness, sinusitis, dyspnoea, fatigue, influenza like illness, insomnia, nausea and anxiety.

When required, treatments for these events included ice, massage, warm compress, nitroglycerine paste, corticosteroids, antibiotics, anticoagulants, antihistamines, analgesics, antiviral agents, diuretic agents, aspiration/incision and drainage, surgery or enzymatic degradation (with hyaluronidase) of the product.

Adverse events received from post-marketing surveillance for *Restylane® Lyft* with Lidocaine and Perlane used for cheek augmentation was in line with the reports listed above for all indications. In rare cases, a late onset (weeks to months) and recurrent inflammation was reported post injection. Concurrent localized events/symptoms were nodules or lumps, infection, and redness, swelling and pain. The treatments of these events included hyaluronidase, antibiotics, corticosteroids, analgesics, incision and drainage.

Reports of serious adverse events for *Restylane*® *Lyft* with Lidocaine and Perlane® are rare. The most commonly reported serious adverse events were infection/abscess, ischemia/necrosis, visual impairment, hypersensitivity/allergic reactions, scarring, inflammation, and granuloma including cases of mass/induration. Concurrent serious events/symptoms included: swelling, pain/tenderness, erythema, neurological symptoms such as paresthesia and hypoesthesia, bruising, discoloration, papules/nodules, and overcorrection, overfill and irregular skin.

Serious infections/abscesses were reported with a time to onset ranging from one day to two months following the injection. Most of the patients were recovered or recovering at the time of last contact. The treatments included antibiotics, analgesics, corticosteroids and hyaluronidase.

Serious hypersensitivity reactions were reported. Most cases had a time to onset ranging from immediately to few weeks post injection and were recovering or recovered at the time of last contact. The treatment included analgesics, antihistamine, antibiotics, and corticosteroids.

Serious granuloma/foreign body reaction including mass/induration, were reported with a time to onset ranging from one day to a year or longer. The outcomes were mostly recovered or recovering at the time of last contact. The treatment included analgesics, antihistamine, antibiotics, corticosteroids and excisions. Biopsies have been taken in some cases, but the majority of cases are non-biopsy confirmed.

Serious inflammation was reported with a time to onset from one to two weeks post injection. Most patients had recovered or were recovering at the time of last contact. Rare cases of inflammation with delayed onset up to several weeks or months post injection has been observed; particularly if the patient experienced local trauma, facial/dental infection, or local infection. The treatment included analgesics, antibiotics, and corticosteroids.

Vascular occlusion resulting in ischemia/necrosis and vision disturbances including blindness have been reported following injection of any soft tissue filler in the face especially in the nose, glabella, periorbital areas, nasolabial folds and cheek, with a time to onset ranging from immediate to a few weeks following injection. 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.

Reported treatments include anticoagulant, epinephrine, aspirin, hyaluronidase, corticosteroid treatment, analgesics, antibiotics, local wound care, drainage, hyperbaric oxygen and surgery. Outcome of the events ranged from resolved to ongoing at the time of last contact. In many of the events requiring medical intervention, the patient was injected into the highly vascularized areas of the glabella, nose, and periorbital area, which are outside the device indications for use.

Injection site bruising, swelling, erythema and pain mostly non-serious generally occurred within 1-2 days after treatment usually resolving within 1 to 4 weeks. Some occurrences have persisted for up to 6 months. Most instances of discoloration including hyperpigmentation, sometimes described as a blue or brown color, have occurred within the same day as treatment but have also occurred up to 6 months post treatment. These events typically resolve within a few days but with some infrequent instances lasting up to 18 months.

X. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The primary effectiveness endpoint of study 43USH1501, responder rate at Week 12 from *Restylane® Lyft with Lidocaine* treatment, was met demonstrating the superiority of treatment versus no treatment (responder rate difference of 64.7%; $p<0.0001$). The secondary endpoint of responder rate at Weeks 16, 20, and 24 also demonstrated superiority to no treatment with a responder rate ≥75.9% at each time point demonstrating statistical separation from no treatment ($p<0.0001$). The CIPR's assessment of improvement demonstrated a higher improvement rate for the *Restylane® Lyft with Lidocaine* treated hand compared to the fellow hand at all study visits where photographs were collected (Week 12 88.1% vs 19.0%; Week 16 85.5% vs. 20.5%; Week 20 69.5% vs. 15.9%' and Week 24 85.5% vs. 21.7%). Both the patients and Investigators satisfaction with treatment remained high as evidenced by the GAIS with 92.8% and 95.2% improvement of the treated hand at Week 24. Overall, the majority of subjects were satisfied with the appearance of the treated hand compared to the untreated (77/84; 91.7%), agreed that the treatment result looks natural (80/84; 95.2%), felt their treated hand appeared more attractive (74/84; 88.1%) and youthful (75/84; 89.3%), would recommend treatment to a friend (71/84; 84.5%) and would undergo repeat treatment in the future (65/84; 77.4%).

Effectiveness was shown in all subgroups, indicating that patients with a higher Baseline MHGS score, FST skin type of I-III, receiving a higher initial injection volume and higher total injection volume, and who were female saw the greatest effectiveness from *Restylane® Lyft with Lidocaine*.

B. Safety Conclusions

Less than half of the subjects in this study experienced TEAEs (N=37 patients [41.6%], which included 82 events). The majority of TEAEs were mild in intensity (N=66 mild, 16

moderate, and no severe) with only the following TEAEs occurring in >2.55% of patients; pain in extremity (5.6%), peripheral swelling (4.5%), laceration (6.7%), and scratch (6.7%). 3 hand-specific related TEAEs were reported in 3 subjects (3.4%) from first treatment (peripheral swelling [2.2%], and skin mass [1.1%]). Adverse event frequency within subgroups FST, age, gender, ethnicity, race, and hand dominance did not reveal a vulnerable population in this study.

In general, injection site reactions decreased with time from treatment. Diary reported events were mostly mild with severe swelling in 2 subjects, and tenderness and pain in 1 subject (first treatment). On average, following the first injection, the events resolved within 2-3 days; only swelling and tenderness resolved after 4-5 days. None of the finger range of motion assessments revealed any appreciable change from administration of *Restylane® Lyft with Lidocaine*. In the active flexion test for the thumb, 24.7% of subjects had at least a 10 degree negative change in thumb flexion which persisted through the course of the 6-months duration study. Change in functional dexterity showed no difference between treated and non-treated hand, and there was no evidence of loss of sensation or appreciable loss of grip or pinch strength.

Injection of *Restylane® Lyft with Lidocaine* did not have an appreciable impact on day to day activities as evidenced by the Brief Michigan Hand Outcome Questionnaire (Brief MHQ)

C. Benefit-Risk Determination

The probable benefits and risks of the *Restylane® Lyft with Lidocaine* device is based on data collected in a clinical study (43USH1501) of *Restylane® Lyft with Lidocaine* for the treatment of dorsal hand volume deficit. This study was a randomized, evaluator-blinded, split-hand study to evaluate the effectiveness and safety of *Restylane® Lyft with Lidocaine* compared to no treatment. A complete summary of effectiveness is provided in Section D and demonstrates the superiority of *Restylane® Lyft with Lidocaine* treatment to no treatment across a variety of analyses metrics (MHGS, CIPR, GAIS, and subject's satisfaction questionnaire). Additionally, there was no evidence for or against a specific subgroup of patients demonstrating a substantial difference in the response to *Restylane® Lyft with Lidocaine* treatment.

A thorough safety assessment was conducted in this study providing a robust safety dataset as further evidence of a positive benefit/risk assessment of treatment with *Restylane® Lyft with Lidocaine*. The majority of related AEs were anticipated from previous exposure to *Restylane® Lyft with Lidocaine* for other indications and included swelling, tenderness, redness, pain, and bruising. No pre-specified subgroup was determined to be a vulnerable population based on AE assessments. Results from the thumb active flexion test demonstrated a slightly reduced flexion after treatment. All other hand functionality testing raised no safety concerns.

1. Patient Perspectives

Patient perspectives considered during the review included:

- A 13-item questionnaire was administered at Week 12 to evaluate patient's satisfaction using a 5-point Likert Response Scale. The majority of patients were happy with the treatment and felt their treated hand appeared more attractive and youthful. Additionally, most subjects would recommend the treatment to a friend and would undergo repeat treatment in the future.

- At week 12, subjects completed a single question related to improved hand function of the treated hand post-treatment. The majority of subjects in the ITT population (63/84; 75.0%) did not perceive an improvement in hand function.

Overall, based on the safety and effectiveness data generated in study 43USH1501 for injection into the subcutaneous plane in the dorsal hand to correct volume deficit in patients over the age of 21, the probable benefits of *Restylane® Lyft with Lidocaine* outweigh the potential risks.

D. Overall Conclusions

Based on the results of the 43USH1501 clinical study, *Restylane® Lyft with Lidocaine* demonstrated a favorable safety and effectiveness profile for injection with needle in the dorsal hand to correct volume deficit in patients over the age of 21, when used in accordance with the indications for use. *Restylane® Lyft with Lidocaine* is shown to be statistically superior to no treatment. The benefits and risks of dermal fillers are sufficiently well understood for patients to make informed decisions about their use.

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

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the General and Plastic Surgery Devices Advisory Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CDRH DECISION

CDRH issued an approval order on May 18, 2018.

XIII. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.