SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Injectable Dermal Filler

Device Trade Name: *Restylane® Lyft with Lidocaine* Injectable Gel

Device Procode: LMH

Applicant's Name and Address: Galderma Laboratories, L.P.
14501 N. Freeway
Fort Worth, Texas 76177

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P040024/S073

Date of FDA Notice of Approval: July 1, 2015

Priority Review: Not Applicable

The PMA Supplements for Perlane® (PMA P040024/s06) 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 SSEDs to support these indications are available on the CDRH website and incorporated by reference herein. The purpose of this supplement (P040024/S073) is to add "for subcutaneous to supraperiosteal implantation for cheek augmentation and correction of age-related midface contour deficiencies in patients over the age of 21" as a new Indication for Use.

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; and for subcutaneous to supraperiosteal implantation for cheek augmentation and correction of age-related midface contour deficiencies in patients over the age of 21.

III. CONTRAINDICATIONS

- *Restylane® Lyft with Lidocaine* is contraindicated for 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.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the *Restylane® Lyft with Lidocaine* labeling.

V. DEVICE DESCRIPTION

Restylane® Lyft with Lidocaine contains 0.3% lidocaine and is a gel of hyaluronic acid (HA) isolated from a *Streptococcus* species that is chemically crosslinked with 1,4-butanediol diglycidyl ether (BDDE), stabilized, and suspended in phosphate buffered saline at pH = 7 and a concentration of 20 mg/mL. *Restylane® Lyft with Lidocaine* is a transparent, viscous, and sterile gel that is supplied in a disposable glass syringe. The product is approved in 1 mL and 2 mL fill sizes. The syringe is co-packed in a blister together with sterile 29 G TW and 27 G TW needle(s).

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for cheek augmentation and correction of age-related midface contour deficiencies: surgical implants, autologous fat injections, face-lift surgery, approved soft tissue filler for this indication, and off-label use of soft tissue fillers. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

Perlane and *Restylane® Lyft with Lidocaine* have been sold in the United States since May 2, 2007 and January 29, 2010, respectively. *Restylane® Lyft with Lidocaine* (also known as Restylane Perlane Lidocaine outside of the US) has been commercially available in the European Union and EES countries since 2009. Neither Perlane nor *Restylane® Lyft with Lidocaine* has been removed from the marketplace for any reasons related to safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The safety of *Restylane® Lyft with Lidocaine* for cheek augmentation and correction of age-related midface contour deficiencies in patients over the age of 21 was evaluated in a premarket study. Potential adverse effects (AEs, i.e., complications) associated with the use of the device and occurring in < 2% of subjects whether related or not related were sunken eyes, nausea, implant site infection/abscess, implant site inflammation, implant site mass, implant site warmth, implant site irritation, induration, muscle tightness, muscle twitching, pain in jaw, presyncope, 7th nerve paralysis, acne, needle track marks, rosacea, conjunctivitis, eyelid cyst, colitis ischemic, dental carries, gingival swelling, tooth ache, cyst, discomfort, injection site pain, general swelling, ulcer, acarodermatitis, bronchitis, eye infection, implant site cellulitis, influenza, oral herpes, pneumonia, soft tissue infection, arthropod sting, incision site pain, exposure to toxic agent, facial injury, ligament sprain, meniscus lesion, thermal burn, tooth

fracture, type 2 diabetes, arthralgia, back pain, bursitis, myalgia, neck pain, pain in extremity, basal cell carcinoma, pancreatic carcinoma, metastatic carcinoma, carpal tunnel syndrome, abortion spontaneous, depression, prostatitis, pulmonary vascular disorder, dermatitis contact, rash, urticaria, neurectomy, and hypertension.

Events reported in patient diaries or physician reported adverse events that occurred in ≥ 2% of subjects in the study were implant site hematoma (bruising), implant site hemorrhage (bleeding and ecchymosis), implant site mass, implant site pain/tenderness, implant site swelling, implant site erythema, implant site pruritus, nasopharyngitis, upper respiratory tract infection, headache, and hypoaesthesia. For the specific adverse events that occurred in the clinical studies, please see Section X (sub-section D) below.

IX. SUMMARY OF PRECLINICAL STUDIES

This supplement presented clinical data to support approval of a new indication for use. Because no change in product manufacture or specification was proposed, the supplement did not contain any manufacturing information or preclinical testing. Instead, the data previously presented in PMA P040024 were sufficient to support the new proposed indication for use.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The sponsor, (i.e., Galderma Laboratories, L.P.) performed a clinical study to establish a reasonable assurance of safety and effectiveness for *Restylane® Lyft with Lidocaine* for cheek augmentation and correction of age-related midface contour deficiencies in patients over the age of 21.

A. Study Design

Patients were enrolled and treated between March 9, 2012 and June 27, 2013. The database for this PMA supplement reflected data collected through September 23, 2013 and included 200 patients.

The clinical study (MA-1400-05) was a prospective, randomized, multi-center, evaluator-blinded study of 200 subjects seeking midface fullness augmentation at 12 investigational centers in the US. Subjects who met all inclusion/exclusion criteria were randomized at entry in a 3:1 ratio to *Restylane® Lyft with Lidocaine* injection or no treatment. Of the 200 randomized subjects, 61 subjects had Fitzpatrick skin types IV-VI and 21 subjects had Fitzpatrick skin types V or VI.

Patients randomized to *Restylane® Lyft with Lidocaine* received touch-up injections at 2 weeks, (if appropriate) to achieve optimal correction. At Month 12, subjects who were initially randomized to *Restylane® Lyft with Lidocaine* treatment were offered retreatment with *Restylane® Lyft with Lidocaine*. Subjects initially randomized to no treatment were permitted to cross-over to *Restylane® Lyft with Lidocaine* treatment at Month 12. Touch-up with *Restylane® Lyft with Lidocaine* was also provided at 2 weeks after the Month 12 treatment, (if needed to achieve optimal correction.)

The primary safety objective was to define the incidence of all adverse events for 12 months after the initial treatment and for up to 12 weeks after the *Restylane® Lyft with Lidocaine* retreatment.

The primary effectiveness endpoint was whether *Restylane® Lyft with Lidocaine* was more effective than no treatment in the augmentation or correction of midface contour deficiency as determined by the blinded evaluator (BE) assessment of midface fullness at the 2 Month visit after *Restylane® Lyft with Lidocaine* treatment (which was compared to the baseline assessment), using the Medicis Midface Volume Scale (MMVS) on both the right and left sides of the face.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the MA-1400-05 study was limited to patients who met the following inclusion criteria: males or non-pregnant, non-breastfeeding females aged 18 to 65 years; seeking augmentation therapy for the midface with a MMVS score of 2 (mild loss of fullness in midface area), 3 (moderate loss of fullness with slight hollowing below malar prominence) or 4 (substantial loss of fullness in the midface area, clearly apparent hollowing below malar prominence) on each side of the face as independently assessed by the blinded evaluator and the treating investigator; willingness to comply with the requirements of the study, including sequential photography or imaging; willing to abstain from any other facial plastic surgical or cosmetic procedures for the 15 months of the study (e.g., laser or chemical resurfacing, facelift, etc.), but subjects may have facial cosmetic procedures outside the area of assessment (e.g., botulinum toxin above the orbital rim, etc.) either before or contemporaneously with cheek augmentation; women of childbearing potential using an acceptable form of birth control during the study period and willingness to take a urine pregnancy test at baseline and at the Month 12 visit.

Patients did not enroll in the MA-1400-05 study if they met any of the following exclusion criteria: a history of allergy or hypersensitivity to injectable hyaluronic acid gel or lidocaine; a history of the presence of any disease on entry that may result in changes in facial contour or edema of the face during the course of the study, (e.g., inflammation, infection, facial psoriasis, herpes zoster, acanthosis, cancer, pre-cancer, actinic keratosis, etc.); a history of the use of any non-biodegradable tissue augmentation therapy or aesthetic facial surgical therapy below the level of the lower orbital rim (e.g., injection or other form of implantation of tissue augmenting substances, fillers, fat augmentation, dental work, or facelift in the preceding eight months), or plans to use these substances or have these procedures during the study; the presence of any contraindication to the implant procedures, including use of platelet inhibiting agents or other anticoagulant, in a relevant period before study entry, (per the treating investigator's judgment); a history of severe allergies or multiple allergies manifested by anaphylaxis; the presence of any condition, which in the opinion of the investigator, that makes the subject unable to complete the study per protocol (e.g., subjects not likely to avoid other facial cosmetic treatments; subjects not likely to stay in the study for up to 15 months because of other commitments, concomitant conditions, or past history; subjects anticipated to be unreliable; or subjects who have a concomitant condition that might confuse or confound study treatments or assessments); the presence of known allergies or hypersensitivity reactions to local topical anesthetics or nerve blocking agents (if such products are intended to be used for that subject); the presence of cancerous or pre-cancerous lesions in the area to be treated; a history of prior surgery to the

midface; a history of prior significant trauma, such as dog bite or laceration, to the midface resulting in formation of a scar; the presence of facial hair that could interfere with MMVS evaluation; the presence of moderate or severe abnormal rating for firmness or detection of any abnormal midfacial structure, such as a scar or lump; the presence of moderate or severe abnormal rating for midface symmetry; the presence of abnormal rating in midface function, with inability to effectively puff cheeks, smile broadly, or chew; the presence of abnormal rating in midface sensation, with inability to feel a 0.4G monofilament or a cotton wisp at any site on the midface; the current use of immunosuppressive therapy; a history of connective tissue diseases such as rheumatoid arthritis, systemic lupus erythematosus, polymyositis (PM), dermatomyositis (DM) or scleroderma; participation in any interventional clinical research study within 30 days prior to randomization; or the intention to lose a significant amount of weight (≥2 BMI) during the study period.

2. Follow-up Schedule

At baseline, subjects were evaluated via the MMVS by the treating investigator (TI) and blinded evaluator (BE) before treatment. Pre-treatment photos and subject assessment via the FACE-Q metric were performed.

Subjects were randomized to *Restylane® Lyft with Lidocaine* or a no treatment control group. All patients received a subject diary for daily recording of adverse outcomes during the first two weeks after each treatment. Patient follow-up included telephone contact at 72 hours after each treatment and a clinical visit at week 2 (with touch-up if needed). Upon reaching optimal correction subjects initially randomized to *Restylane® Lyft with Lidocaine* had clinical visits at Week 4 and Months 2, 4, 6, 8, 10 and 12 (for adverse events, photography, as well as GAIS and BE MMVS assessments). Subjects initially randomized to *Restylane® Lyft with Lidocaine* were also offered retreatment at the month 12 visit with subsequent follow-up at 72 hours (by telephone) and clinical visits at week 2, 4, and 12 weeks after injection. Subjects initially randomized to no treatment (Control) were offered *Restylane® Lyft with Lidocaine* injections at the 12 Month visit with subsequent follow-ups at 72 hours (by telephone) and clinical visits at week 2, 4, and 12.

Clinical assessment**s** at week 2 were for adverse events, photography, GAIS assessment (TI and subject) and TI MMVS assessment. Other Post-Treatment evaluations were: 1) the BE MMVS assessment (at the Month 2 and all visits thereafter)*;* 2) TI assessment of safety outcomes at each visit; 3) TI assessment of patient appearance via MMVS and a Global Aesthetic Improvement Scale (GAIS); and 4) the subjects' assessment of appearance via the Global Aesthetic Improvement Scale (GAIS) and FACE-Q metric.

3. Clinical Endpoints

The primary safety objective was the incidence of all adverse events, at the 72 hour follow up and a TI assessment at 2 and 4 weeks post treatment, as well as 2, 4, 6, 8, and 12 months after treatment and 2, 4, and 12 weeks after the Month 12 retreatment. Secondary safety objectives were: Midface safety assessments of firmness, symmetry, function, sensation, product palpability, and mass formation (as evaluated by the designated study staff member) and subject diary assessments for the first 14 days following each treatment session.

The primary effectiveness endpoint was whether *Restylane® Lyft with Lidocaine* was more effective in cheek augmentation and/or contour deficiency correction than no treatment (as determined by the BE assessment) at 2 months after treatment (and compared to the baseline BE assessment) using the Medicis Midface Volume Scale (Table 1) (MMVS) for both the right and left sides of the face.

Table 1 Medicis Midface Volume Scale

1	Fairly full midface.
2	Mild loss of fullness in midface area.
3	Moderate loss of fullness with slight hollowing below malar prominence.
4	Substantial loss of fullness in the midface area, clearly apparent hollowing below malar prominence.

The following additional effectiveness endpoints were evaluated: 1) the BE assessment of whether subjects displayed at least an one grade improvement on the MMVS from baseline (on both sides of the face) at 4, 6, 8, 10, and 12 months after initial treatment and 2, 4, and 12 weeks after retreatment; 2) the TI assessment of MMVS at 2 and 4 weeks and at 2, 4, 6, 8, 10, and 12 months after treatment and 2, 4 and 12 weeks after retreatment; 3) the degree of subject satisfaction via the GAIS scale (Table 2) at 2 and 4 weeks and 2, 4, 6, 8, 10, and 12 months after treatment as well as 2, 4, and 12 weeks after retreatment; 4) the TI assessment of subject appearance via the GAIS at 2 and 4 weeks, and 2, 4, 6, 8, 10, and 12 months after treatment and 2, 4 and 12 weeks after retreatment; 5) the degree of agreement between MMVS responders (i.e., a one grade improvement) and GAIS responders (i.e., an improvement of 1 grade or more) as determined by the TI; 6) the assessment of improvement determined at 2, 6, 8, 10, and 12 months after treatment and 4 and 12 weeks after retreatment by a blinded independent photographic reviewer (IPR); and 7) the degree of improvement as determined by the subjects' FACE-Q score measured at 4 weeks and 2, 6, 8, 10, and 12 months after treatment and 4 and 12 weeks after retreatment.

Table 2 Global Aesthetic Improvement Scale (GAIS)

Score	Rating	Definition
3	Very Much Improved	Optimal aesthetic result for the implant in this subject.
2	Much Improved	Marked improvement in appearance from the initial condition, but not completely optimal for this subject.
1	Improved	Obvious improvement in appearance from the initial condition.
0	No Change	The appearance is essentially the same as baseline.
-1	Worse	The appearance is worse than the original condition.
-2	Much Worse	Marked worsening in appearance from the initial condition.
-3	Very Much Worse	Obvious worsening in appearance from the initial condition.

B. Accountability of PMA Cohort

Twelve (12) investigative sites enrolled 200 subjects who were all included in the Safety and the ITT populations for analysis. 188/200 (94%) subjects completed the study. No subject discontinued the study due to an adverse event (AE). One subject discontinued due to investigator's decision based on a diagnosis of pancreatic cancer prior to the Month 12 visit.

Table 3: Disposition of Subjects – ITT Population

Characteristic	No Treatment (N=50)	*Restylane® Lyft with Lidocaine* (N=150)	Total (N=200)
Subjects Completing Study	48 (96%)	140 (93%)	188 (94%)
Subjects That Withdrew from Study	2 (4%)	10 (7%)	12 (6%)
Primary Reason for Discontinuation			
Subject Withdrew Consent	2 (4%)	5 (3%)	7 (4%)
Lost to Follow Up	0	4 (3%)	4 (2%)
Adverse Event	0	0	0
Protocol Violation/Deviation	0	0	0
Investigator Decision	0	1 (<1%)	1 (<1%)
Other	0	0	0

Note: Percentages are based on the total number of subjects in the ITT population.
Note: Statistic = n (%)

C. Study Population Demographics and Baseline Parameters

Demographic characteristics (Table 4) were similar between the no treatment and *Restylane® Lyft with Lidocaine* treatment groups.

Table 4: Subject Demographics – Safety Population

Characteristic	No Treatment (N=50)	*Restylane® Lyft with Lidocaine* (N=150)	Total (N=200)
Age (years)			
N	50	150	200
Mean (S.D.)	53.7 (6.1)	52.6 (8.0)	52.9 (7.6)
Median	53.0	54.0	54.0
Minimum	39	25	25
Maximum	65	65	65

Characteristic	No Treatment (N=50)	*Restylane® Lyft with Lidocaine* (N=150)	Total (N=200)
Gender			
Male	5 (10%)	12 (8%)	17 (9%)
Female	45 (90%)	138 (92%)	183 (92%)
Race			
American Indian/Alaskan Native	0	1 (<1%)	1 (<1%)
Black or African American	4 (8%)	6 (4%)	10 (5%)
Native Hawaiian or other Pacific Islander	0	0	0
Asian	0	3 (2%)	3 (2%)
White	43 (86%)	135 (90%)	178 (89%)
Other	3 (6%)	5 (3%)	8 (4%)
Ethnicity			
Not Hispanic or Latino	36 (72%)	123 (82%)	159 (80%)
Hispanic or Latino	14 (28%)	27 (18%)	41 (21%)
Fitzpatrick Skin			
I	2 (4%)	2 (1%)	4 (2%)
II	12 (24%)	37 (25%)	49 (25%)
III	21 (42%)	65 (43%)	86 (43%)
IV	8 (16%)	32 (21%)	40 (20%)
V	5 (10%)	12 (8%)	17 (9%)
VI	2 (4%)	2 (1%)	4 (2%)
Height (cm)			
N	50	150	200
Mean (S.D.)	165.2 (10.0)	165.0 (7.5)	165.0 (8.1)
Median	162.6	163.4	162.8
Minimum	137.2	142.2	137.2
Maximum	188.0	189.2	189.2
Weight (kg)			
N	50	150	200
Mean (S.D.)	65.7 (10.7)	64.5 (11.4)	64.8 (11.2)
Median	63.5	63.5	63.5
Minimum	46.7	42.8	42.8
Maximum	102.1	122.1	122.1
Baseline MMVS for Blinded Evaluator (Right Midface)			
1 (Fairly full midface)	0	0	0
2 (Mild loss of fullness in midface area)	15 (30%)	34 (23%)	49 (25%)
3 (Moderate loss of fullness with slight hollowing below malar prominence)	28 (56%)	92 (61%)	120 (60%)

Characteristic	No Treatment (N=50)	*Restylane® Lyft with Lidocaine* (N=150)	Total (N=200)
4 (Substantial Loss of fullness in the midface area, clearly apparent hollowing below malar prominence)	6 (12%)	24 (16%)	30 (15%)
Baseline MMVS for Blinded Evaluator (Left Midface)			
1 (Fairly full midface)	0	0	0
2 (Mild loss of fullness in midface area)	13 (26%)	31 (21%)	44 (22%)
3 (Moderate loss of fullness with slight hollowing below malar prominence)	30 (60%)	93 (62%)	123 (62%)
4 (Substantial Loss of fullness in the midface area, clearly apparent hollowing below malar prominence)	6 (12%)	26 (17%)	32 (16%)

Note: MMVS = Medicis Midface Volume Scale

Injected Volumes of *Restylane® Lyft with Lidocaine* for Midface Treatment

Injection characteristics of *Restylane® Lyft with Lidocaine* for midface treatment are described in Table 5. The amount of *Restylane® Lyft with Lidocaine* injected for cheek augmentation of subjects with Fitzpatrick skin types IV, V, and VI was similar to the overall study population.

Table 5: Injection Characteristics of Study Treatment – Safety Population

Assessment Right and Left Midface Combined	Initial Treatment		Month 12 Treatment	
	No Treatment (N=50)	*Restylane® Lyft with Lidocaine* (1st Treatment) (N=150)	No Treatment (1st Treatment) (N=50)	*Restylane® Lyft with Lidocaine* (2nd Treatment) (N=150)
Total Volume of Injection (mL) for treatment + touch-up				
n	--	150	49	128
Mean (S.D.)	--	6.227 (2.546)	4.850 (2.141)	3.799 (2.141)
Median	--	6.000	5.200	3.250
Min, Max	--	2.00, 14.00	1.00, 10.80	0.30, 10.10
Depth of injection for treatment				
Subcutaneous	--	149 (99%)	44 (90%)	124 (97%)
Supraperiosteal	--	115 (77%)	40 (82%)	106 (83%)
Other	--	0	0	0
Depth of injection for touch-up				
Subcutaneous	--	122 (100%)	33 (92%)	77 (95%)
Supraperiosteal		85 (70%)	30 (83%)	61 (75%)
Other	--	0	0	0
Method of injection for treatment				

Assessment Right and Left Midface Combined	Initial Treatment		Month 12 Treatment	
	No Treatment (N=50)	*Restylane® Lyft with Lidocaine* (1st Treatment) (N=150)	No Treatment (1st Treatment) (N=50)	*Restylane® Lyft with Lidocaine* (2nd Treatment) (N=150)
Linear Antegrade	--	50 (33%)	17 (35%)	51 (40%)
Linear Retrograde	--	96 (64%)	34 (69%)	91 (71%)
Serial Puncture/Depot	--	124 (83%)	41 (84%)	106 (83%)
Other	--	0	0	0
Method of injection for touch-up				
Linear Antegrade	--	44 (36%)	13 (36%)	39 (48%)
Linear Retrograde	--	77 (63%)	26 (72%)	59 (73%)
Serial Puncture	--	101 (83%)	31 (86%)	65 (80%)
Other	--	0	0	0
Length of time needed (min:sec) for treatment				
n	--	150	49	128
Mean (S.D.)	--	15:11 (8:59)	12:03 (10:08)	9:40 (9:46)
Median	--	12:31	9:11	6:07
Min, Max	--	3:51, 38:55	1:35, 36:20	1:00. 37:25
Length of time needed (min:sec) for touch-up				
n	--	122	36	81
Mean (S.D.)	--	8:47 (7:02)	7:05 (5:04)	6:18 (5:22)
Median	--	6:10	6:44	5:16
Min, Max	--	0:50, 34:00	0:44, 21:20	0:35, 32:35

Note: Summary includes exposure data for all midface treatments.
Note: Subjects could have multiple depths and methods of injection for a single treatment within the same midface.
Note: Volume of Injection for Right and Left Midface combined is the sum of volumes for Right and Left Midface.
Note: Length of Time needed for Right and Left Midface combined is the total length of time for Right and Left Midface.

D. Safety and Effectiveness Results

1. Safety Results

Physician Diagnosed Adverse Events

An adverse event (AE) that occurred during the study was considered a Treatment Emergent Adverse Event (TEAE), if it was not present prior to receiving treatment; it was present prior to receiving treatment, but the intensity increased after treatment; or if it occurred after the date of initial treatment (in subjects randomized to *Restylane® Lyft with Lidocaine*) or after the Visit 2 date (in subjects randomized to no treatment).

97/199 (49%) *Restylane® Lyft with Lidocaine* and 15/50 (30%) no treatment control subjects (30%) experienced 269 and 18 TEAEs, respectively. Table 6 summarizes the number of subjects and the number of TEAEs experienced by ≥ 2% of the safety population.

Table 6: Summary of Treatment Emergent Adverse Events Occurring in ≥ 2% of Treated Subjects – Safety Population

System Organ Class *Preferred term*	Treatment Group								
	No treatment at Baseline (N=50)			First Treatment with *Restylane® Lyft with Lidocaine* (N=199)			Second Treatment with *Restylane® Lyft with Lidocaine* (N=128)		
	Events	Subjects[1]		Events	Subjects[1]		Events	Subjects[1]	
Any TEAE	18	15	(30%)	269	97	(48.7%)	77	37	(28.9%)
General Disorders and Administration Site Conditions									
Implant Site Hematoma	0	0		52	36	(18.1%)	18	10	(7.8%)
Implant Site Hemorrhage	0	0		18	10	(5.0%)	22	9	(7.0%)
Implant Site Mass	0	0		6	5	(2.5%)	1	1	(0.8%)
Implant Site Pain	0	0		36	17	(8.5%)	10	6	(4.7%)
Implant Site Swelling	0	0		36	15	(7.5%)	6	4	(3.1%)
Infections and Infestations									
Nasopharyngitis	1	1	(2.0%)	4	4	(2.0%)	0	0	
Upper Respiratory Tract Infection	0	0		4	4	(2.0%)	0	0	
Nervous System Disorders									
Headache	3	3	(6.0%)	14	13	(6.5%)	1	1	(0.8%)
Hypoaesthesia	0	0		5	4	(2.0%)	0	0	

[1] A subject with more than one treatment emergent adverse event within a system organ class and/or preferred term is only counted once.
Note: TEAE: Treatment Emergent Adverse Event
Note: For the No Treatment at Baseline group an adverse event is considered treatment emergent if the start date is on or after the Visit 2 (Day 0) date. For the First Treatment with *Restylane® Lyft with Lidocaine* group an adverse event is considered treatment emergent if the start date is on or after the date of initial treatment injection and before the date of Month 12 injection. For the Second Treatment with *Restylane® Lyft with Lidocaine* group an adverse event is considered treatment emergent if the start date is on or after the date of the Month 12 injection.
Note: Adverse events are coded using MedDRA (Version 15.0).

Table 7 presents a summary of all TEAE assessed as "Related" or "Unknown Relationship" to the device or injection procedure.

Table 7: Summary of Treatment Emergent Adverse Events Assessed by the Investigator as Related or with Unknown Relationship to either Injection Procedure or Study Device – Safety Population

System Organ Class *Preferred term*	Treatment Group								
	No treatment at Baseline (N=50)			First Treatment with *Restylane® Lyft with Lidocaine* (N=199)			Second Treatment with *Restylane® Lyft with Lidocaine* (N=128)		
	Events	Subjects[1]		Events	Subjects[1]		Events	Subjects[1]	
Any related or unknown TEAE	1	1	(2.0%)	178	67	(33.7%)	70	33	(25.8%)
Eye Disorders									
Eyes Sunken	0	0		0	0		2	1	(0.8%)
Gastrointestinal Disorders									
Nausea	0	0		1	1	(0.5%)	0	0	
General Disorders and Administration Site	0	0		7	3	(1.5%)	0	0	

Conditions								
Implant Site Erythema								
Implant Site Hematoma	0	0		51	35	(17.6%)	18	10 (7.8%)
Implant Site Hemorrhage	0	0		18	10	(5.0%)	22	9 (7.0%)
Implant Site Inflammation	0	0		2	1	(0.5%)	0	0
Implant Site Mass	0	0		5	4	(2.0%)	1	1 (0.8%)
Implant Site Pain	0	0		35	16	(8.0%)	10	6 (4.7%)
Implant Site Pruritus	0	0		5	3	(1.5%)	0	0
Implant Site Swelling	0	0		35	15	(7.5%)	6	4 (3.1%)
Implant Site Warmth	0	0		1	1	(0.5%)	0	0
Induration	0	0		3	1	(0.5%)	0	0
Injection Site Pain	0	0		0	0		2	1 (0.8%)
Infections and Infestations								
Oral Herpes	1	1	(2.0%)	0	0		0	0
Musculoskeletal and Connective Tissue Disorders								
Muscle Tightness	0	0		2	1	(0.5%)	2	1 (0.8%)
Muscle Twitching	0	0		1	1	(0.5%)	0	0
Pain in Jaw	0	0		2	1	(0.5%)	4	2 (1.6%)
Nervous System Disorders								
Headache	0	0		1	1	(0.5%)	0	0
Hypoaesthesia	0	0		5	4	(2.0%)	0	0
Presyncope	0	0		1	1	(0.5%)	0	0
VIIth Nerve Paralysis	0	0		1	1	(0.5%)	0	0
Skin and Subcutaneous Tissue Disorders								
Acne	0	0		0	0		3	1 (0.8%)
Needle Track Marks	0	0		1	1	(0.5%)	0	0
Rosacea	0	0		1	1	(0.5%)	0	0

[1] A subject with more than one treatment emergent adverse event within a system organ class and/or preferred term is only counted once.
Note: TEAE: Treatment Emergent Adverse Event
Note: For the No Treatment at Baseline group an adverse event is considered treatment emergent if the start date is on or after the Visit 2 (Day 0) date. For the First Treatment with *Restylane® Lyft with Lidocaine* group an adverse event is considered treatment emergent if the start date is on or after the date of initial treatment injection and before the date of Month 12 injection. For the Second Treatment with *Restylane® Lyft with Lidocaine* group an adverse event is considered treatment emergent if the start date is on or after the date of the Month 12 injection.
Note: Adverse events are coded using MedDRA (Version 15.0).

Severity of Adverse Events

29/199 subjects reported 48 moderate or severe adverse events with a duration longer than 7 days. None of these events were related to the device or the study procedure and all subjects recovered.

The number of TEAEs experienced by more than 2% of the safety population is summarized by severity in Table 8.

Table 8: Summary of Treatment Emergent Adverse Events Occurring in ≥ 2% of Subjects by Severity – Safety Population

System Organ	Severity	Treatment Group

Class *Preferred term*		No treatment at Baseline (N=50)			First Treatment with *Restylane® Lyft with Lidocaine* (N=199)			Second Treatment with *Restylane® Lyft with Lidocaine* (N=128)		
		Events[1]	Subjects		Events[1]	Subjects		Events[1]	Subjects	
Any TEAE	Total	18	15	(30.0%)	269	97	(48.7%)	77	37	(28.9%)
	Mild	8	8	(16.0%)	212	88	(44.2%)	70	32	(25.0%)
	Moderate	7	7	(14.0%)	55	28	(14.1%)	7	6	(4.7%)
	Severe	3	2	(4.0%)	2	2	(1.0%)	0	0	
General Disorders and Administration Site Conditions										
Implant Site Haematoma	Total	0	0		52	36	(18.1%)	18	10	(7.8%)
	Mild	0	0		49	36	(18.1%)	15	8	(6.3%)
	Moderate	0	0		3	3	(1.5%)	3	2	(1.6%)
	Severe	0	0		0	0		0	0	
Implant Site Haemorrhage	Total	0	0		18	10	(5.0%)	22	9	(7.0%)
	Mild	0	0		18	10	(5.0%)	22	9	(7.0%)
	Moderate	0	0		0			0	0	
	Severe	0	0		0			0	0	
Implant Site Mass	Total	0	0		6	5	(2.5%)	1	1	(0.8%)
	Mild	0	0		6	5	(2.5%)	1	1	(0.8%)
	Moderate	0	0		0	0		0		
	Severe	0	0		0	0		0		
Implant Site Pain	Total	0	0		36	17	(8.5%)	10	6	(4.7%)
	Mild	0	0		29	14	(7.0%)	10	6	(4.7%)
	Moderate	0	0		7	5	(2.5%)	0	0	
	Severe	0	0		0	0		0	0	
Implant Site Swelling	Total	0	0		36	15	(7.5%)	6	4	(3.1%)
	Mild	0	0		29	14	(7.0%)	5	3	(2.3%)
	Moderate	0	0		7	5	(2.5%)	1	1	(0.8%)
	Severe	0	0		0	0		0	0	
Infections and Infestations										
Nasopharyn-gitis	Total	1	1	(2.0%)	4	4	(2.0%)	0	0	
	Mild	1	1	(2.0%)	3	3	(1.5%)	0	0	
	Moderate	0	0		1	1	(0.5%)	0	0	
	Severe	0	0		0	0		0	0	
Upper Respiratory Tract Infection	Total	0	0		4	4	(2.0%)	0	0	
	Mild	0	0		4	4	(2.0%)	0	0	
	Moderate	0	0		0	0		0	0	
	Severe	0	0		0	0		0	0	
Nervous System Disorders										
Headache	Total	3	3	(6.0%)	14	13	(6.5%)	1	1	(0.8%)
	Mild	2	2	(4.0%)	13	12	(6.0%)	1	1	(0.8%)
	Moderate	1	1	(2.0%)	1	1	(0.5%)	0	0	
	Severe	0	0		0	0		0	0	
Hypo Aesthesia	Total	0	0		5	4	(2.0%)	0	0	
	Mild	0	0		5	4	(2.0%)	0	0	
	Moderate	0	0		0	0		0	0	
	Severe	0	0		0	0		0	0	

[1] All occurrences of treatment emergent adverse events are counted in each system organ class, preferred term, and/or severity
Note: TEAE: Treatment Emergent Adverse Event

Note: For the No Treatment at Baseline group an adverse event is considered treatment emergent if the start date is on or after the Visit 2 (Day 0) date. For the First Treatment with *Restylane® Lyft with Lidocaine* group an adverse event is considered treatment emergent if the start date is on or after the date of initial treatment injection and before the date of Month 12 injection. For the Second Treatment with *Restylane® Lyft with Lidocaine* group an adverse event is considered treatment emergent if the start date is on or after the date of the Month 12 injection.
Note: Adverse events are coded using MedDRA (Version 15.0).

Duration of Adverse Events

Table 9 summarizes the duration of the most commonly reported TEAEs (i.e., greater than or equal to 2% of the study population) which were assessed as "related" or "unknown relationship" to the device or procedure. Nine TEAEs assessed as unrelated to the device or injection procedure that were ongoing or with unknown outcome at study end were not included.

Table 9: Summary of Treatment Emergent Adverse Events Occurring in ≥ 2% of Treated Subjects by Duration in days - Safety population

	Treatment Group		
System Organ Class *Preferred term*	No treatment at Baseline (N=50)	First Treatment with *Restylane® Lyft with Lidocaine* (N=199)	Second Treatment with *Restylane® Lyft with Lidocaine* (N=128)
All TEAEs			
n	15	95	37
Mean (S.D.)	30.7 (87.5)	20.2 (46.3)	9.6 (8.3)
Median	8.5	8.0	7.0
Min, Max	2, 380	1, 433	1, 33
General Disorders and Administration Site Conditions			
Implant Site Haematoma			
n	-	36	10
Mean (S.D.)	-	15.0 (26.9)	12.1 (9.4)
Median	-	7.5	10.5
Min, Max	-	1, 128	1, 33
Implant Site Haemorrhage			
n	-	10	9
Mean (S.D.)	-	12.2 (6.2)	11.3 (5.2)
Median	-	11.5	11.0
Min, Max	-	4, 26	2, 19
Implant Site Mass			
n	-	5	1
Mean (S.D.)	-	39.6 (66.2)	31.0 (-)
Median	-	6.0	31.0
Min, Max	-	1, 156	31, 31
Implant Site Pain			
n	-	17	6
Mean (S.D.)	-	6.8 (6.3)	7.0 (7.4)
Median	-	4.0	2.5

Min, Max	-	1, 24	2, 18
Implant Site Swelling			
n	-	15	4
Mean (S.D.)	-	8.7 (7.3)	4.0 (2.2)
Median	-	6.0	3.5
Min, Max	-	1, 25	2, 7
Infections and Infestations			
Nasopharyngitis			
n	1	4	-
Mean (S.D.)	5.0 (-)	8.8 (5.4)	-
Median	5.0	8.0	-
Min, Max	5, 5	3, 16	-
Upper Respiratory Tract Infection			
n	-	4	-
Mean (S.D.)	-	13.3 (4.7)	-
Median	-	12.0	-
Min, Max	-	9, 20	-
Nervous System Disorders			
Headache			
n	3	13	1
Mean (S.D.)	7.7 (9.8)	2.1 (1.6)	3.0 (-)
Median	2.0	2.0	3.0
Min, Max	2, 19	1, 7	3, 3
Hypoaesthesia			
n	-	4	-
Mean (S.D.)	-	10.3 (13.2)	-
Median	-	4.5	-
Min, Max	-	2, 30	-

Note: If a subject has more than one treatment emergent adverse event within a category (overall, system organ class or preferred term), the event with the longest duration is summarized

Note: TEAE: Treatment Emergent Adverse Event, n=Number of subjects, S.D. = Standard Deviation

Note: For the No Treatment at Baseline group an adverse event is considered treatment emergent if the start date is on or after the Visit 2 (Day 0) date. For the First Treatment with *Restylane® Lyft with Lidocaine* group an adverse event is considered treatment emergent if the start date is on or after the date of initial treatment injection and before the date of Month 12 injection. For the Second Treatment with *Restylane® Lyft with Lidocaine* group an adverse event is considered treatment emergent if the start date is on or after the date of the Month 12 injection.

Note: Duration is measured in days and is calculated as the AE Stop Date - AE Start Date + 1.

Note: Adverse events are coded using MedDRA (Version 15.0).

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

30 (15%) subjects reported 48 moderate or severe adverse events with a duration longer than 7 days. Of the 48 adverse events, 1 adverse event was reported as severe (Prostatitis). This event was judged as not related to the device or the study procedure. The subject fully recovered.

There were no deaths reported during the study and no subject discontinued due to an adverse event. There were nine Serious Treatment Emergent Adverse Events reported in seven subjects during the study. The serious Treatment Emergent Adverse Events are summarized in Table 10. Five of the nine events were reported as unrelated to the study device or the injection procedure. Two subjects (1%, 2/199) reported four serious adverse events (SAEs) that were considered to be related to the device and/or the procedure. One subject reported implant site inflammation (late

onset inflammatory reactions) in both cheeks at separate times. The second subject experienced implant site hematomas in the right cheek and implant site infection. Treatment of the SAEs included NSAIDs, antibiotics, incision and drainage and, hyaluronidase. All events resolved.

Table 10: Summary of all Serious Treatment Emergent Adverse Events – Safety Population

	Treatment Group							
	No treatment at Baseline (N=50)			First Treatment with *Restylane® Lyft with Lidocaine* (N=199)			Second Treatment with *Restylane® Lyft with Lidocaine* (N=128)	
System Organ Class *Preferred term*	**Events**	**Subjects[1]**		**Events**	**Subjects[1]**		**Events**	**Subjects[1]**
Any TEAE	1	1	(2.0%)	8	6	(3.0%)	0	0
Gastrointestinal Disorders								
Colitis Ischemic	0	0		1	1	(<1%)	0	0
General Disorders and Administration Site Conditions								
Implant Site Hematoma	0	0		1	1	(<1%)	0	0
Implant Site Infection	0	0		1	1	(<1%)	0	0
Implant Site Inflammation	0	0		2	1	(<1%)	0	0
Infections and Infestations								
Pneumonia	0	0		1	1	(<1%)	0	0
Neoplasms Benign, Malignant and Unspecified (including Cysts and Polyps)								
Pancreatic Carcinoma Metastatic	0	0		1	1	(<1%)	0	0
Pregnancy, Puerperium and Perinatal Conditions								
Abortion Spontaneous	0	0		1	1	(<1 %)	0	0
Renal and Urinary Disorders								
Nephrolithiasis	1	1	(2.0%)	0	0		0	0

[1]A subject with more than one treatment emergent adverse event within a system organ class and/or preferred term is only counted once.
Note: TEAE: Treatment Emergent Adverse Event.
Note: For the No Treatment at Baseline group an adverse event is considered treatment emergent if the start date is on or after the Visit 2 (Day 0) date. For the First Treatment with *Restylane® Lyft with Lidocaine* group an adverse event is considered treatment emergent if the start date is on or after the date of initial treatment injection. For the Second Treatment with *Restylane® Lyft with Lidocaine* group an adverse event is considered treatment emergent if the start date is on or after the date of the Month 12 injection.
Note: Percentages are based on the number of Subjects in the Safety population.
Note: Adverse events are coded using MedDRA (Version 15.0).
Note: No treatment at Baseline includes subjects who did not receive an initial injection at Visit 2.

One patient reported two implant site inflammation SADEs with late onset inflammatory reaction that were judged as related to the device and the procedure. The symptoms of implant site inflammation, implant site erythema, implant site swelling, and implant site pain were treated with antibiotics, hyaluronidase injections, and aspiration of the right cheek. One other SADE was an implant site hematoma judged to be related to the procedure. This subject also reported an SADE of infection/abscess which required antibiotics and incision/drainage. The subject also reported implant site mass, VIIth nerve paralysis, and hypoaesthesia.

There were no adverse events of special interest (hyper and hypopigmentation, hypertrophic scarring, keloid formation or the appearance of granulomas) in persons of color.

Overall, a higher volume of injection did not adversely impact the device safety profile and the observed TEAEs were consistent with the commonly reported TEAEs in the study. These data reflected treatment of only five subjects who received volumes greater than 6.0 mL at a single session.

Approximately 3% of subjects had a delayed onset (> 21 days after treatment) of implant site erythema, implant site hematoma, implant site inflammation, implant site mass, implant site pain, implant site swelling, implant site warmth, induration, twitching or rosacea that occurred up to 138 days after treatment.

Subject Diary:

Subjects were asked to record and grade symptoms of erythema, swelling, bruising, pain, itching, lumps/bumps and discoloration for 14 days after each injection in a patient diary. Subjects' scores for the severity of these events after the initial treatment are presented in Table 11 and the duration of adverse outcomes is provided in Table 12. Disabling symptoms were reported in the right and left midface by 2% of subjects after their first treatment with *Restylane® Lyft with Lidocaine* and 5% of subjects after their second treatment with *Restylane® Lyft with Lidocaine*. Most of the disabling symptoms were related to swelling. For subjects that received either one or two treatments with *Restylane® Lyft with Lidocaine*, the majority of symptoms for the both the right and left midface combined resolved within 2-7 days of treatment.

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

	Treatment Group		
Location/Symptom	**No Treatment at Baseline (N=49)**	**First Treatment with *Restylane® Lyft with Lidocaine* (N=199)**	**Second Treatment with *Restylane® Lyft with Lidocaine* (N=128)**
Right and Left Midface Combined:			
Maximum Severity Reported for any Diary Symptom	49	198	127
None	47 (96%)	3 (2%)	1 (<1%)
Tolerable	2 (4%)	146 (74%)	94 (74%)
Affects Daily Activities	0	45 (23%)	26 (20%)
Disabling	0	4 (2%)	6 (5%)
Pain (Including Burning)	49	198	127
None	48 (98%)	41 (21%)	28 (22%)
Tolerable	1 (2%)	134 (68%)	84 (66%)
Affects Daily Activities	0	22 (11%)	13 (10%)
Disabling	0	1 (<1%)	2 (2%)
Tenderness	49	198	127
None	49 (100%)	9 (5%)	10 (8%)

Location/Symptom	Treatment Group: No Treatment at Baseline (N=49)	First Treatment with *Restylane® Lyft with Lidocaine* (N=199)	Second Treatment with *Restylane® Lyft with Lidocaine* (N=128)
Tolerable	0	171 (86%)	104 (82%)
Affects Daily Activities	0	17 (9%)	12 (9%)
Disabling	0	1 (<1%)	1 (<1%)
Redness	49	198	127
None	49 (100%)	43 (22%)	27 (21%)
Tolerable	0	139 (70%)	88 (69%)
Affects Daily Activities	0	16 (8%)	10 (8%)
Disabling	0	0	2 (2%)
Bruising	49	198	127
None	49 (100%)	35 (18%)	28 (22%)
Tolerable	0	130 (66%)	79 (62%)
Affects Daily Activities	0	32 (16%)	16 (13%)
Disabling	0	1 (<1%)	4 (3%)
Swelling	49	198	127
None	49 (100%)	19 (10%)	18 (14%)
Tolerable	0	145 (73%)	94 (74%)
Affects Daily Activities	0	30 (15%)	11 (9%)
Disabling	0	4 (2%)	4 (3%)
Itching	49	198	127
None	48 (98%)	131 (66%)	92 (72%)
Tolerable	1 (2%)	63 (32%)	33 (26%)
Affects Daily Activities	0	3 (2%)	1 (<1%)
Disabling	0	1 (<1%)	1 (<1%)

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

Note: For right and left combined, the overall maximum severity is taken as the maximum of overall right severity and overall left severity. The combined maximum severity within symptom category is taken as the maximum of right severity and left severity within the symptom category.

Note: Selected Adverse Events are those that were pre-listed in the diary (bruising, redness, swelling, pain, tenderness, itching) and required a recording of "none" or the presence and extent. These diary recordings were handled separately from adverse events that were elicited from an interview about any medical occurrence that meets the definition of Adverse Event.

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

Location/ Adverse Event	No Treatment at Baseline (N = 49): Any[1] n (%)	Number of Days: 1 n (%)	2-7 n (%)	8-13 n (%)	14 n (%)
Right and Left Midface Combined					
Pain (Including Burning)	1 (2%)	1 (100%)	0	0	0
Tenderness	0	0	0	0	0
Redness	0	0	0	0	0
Bruising	0	0	0	0	0
Swelling	0	0	0	0	0
Itching	1 (2%)	0	1 (100%)	0	0
Location/	**First Treatment with *Restylane® Lyft with Lidocaine* (N = 199)**				
	Number of Days				

Adverse Event	Any[1] n (%)	1 n (%)	2-7 n (%)	8-13 n (%)	14 n (%)
Right and Left Midface Combined					
Pain (Including Burning)	157 (79%)	34 (22%)	109 (69%)	12 (8%)	2 (1%)
Tenderness	189 (95%)	17 (9%)	112 (59%)	47 (25%)	13 (7%)
Redness	155 (78%)	39 (25%)	96 (62%)	18 (12%)	2 (1%)
Bruising	163 (82%)	10 (6%)	66 (40%)	70 (43%)	17 (10%)
Swelling	179 (90%)	14 (8%)	132 (74%)	26 (15%)	7 (4%)
Itching	67 (34%)	16 (24%)	42 (63%)	9 (13%)	0

Location/ Adverse Event	Second Treatment with *Restylane® Lyft with Lidocaine* (N = 128) Number of Days				
	Any[1] n (%)	1 n (%)	2-7 n (%)	8-13 n (%)	14 n (%)
Right and Left Midface Combined					
Pain (Including Burning)	99 (77%)	17 (17%)	70 (71%)	10 (10%)	2 (2%)
Tenderness	117 (91%)	9 (8%)	71 (61%)	29 (25%)	8 (7%)
Redness	100 (78%)	19 (19%)	67 (67%)	11 (11%)	3 (3%)
Bruising	99 (77%)	5 (5%)	46 (46%)	35 (35%)	13 (13%)
Swelling	109 (85%)	15 (14%)	72 (66%)	20 (18%)	2 (2%)
Itching	35 (27%)	9 (26%)	19 (54%)	5 (14%)	2 (6%)

[1] Percentages are based on the number of subjects in the Safety population.

Note: Percentages for duration categories are based on the number of subjects reporting the symptom ("Any") for the specified location, unless otherwise noted.

Note: Second Treatment with *Restylane® Lyft with Lidocaine* column only includes diary summaries from subjects who actually received a second treatment at Month 12.

Note: Selected Adverse Events are those that were pre-listed in the diary (bruising, redness, swelling, pain, tenderness, itching) and required a recording of "none" or the presence and extent. These diary recordings were handled separately from adverse events that were elicited from an interview about any medical occurrence that meets the definition of Adverse Event.

Midface safety assessments, such as firmness, symmetry, function (movement), mass formation and sensation were evaluated at the screening visit, optional touch up visit, 2 week follow up visit, 4 week follow up visit, 2, 4, 6, 8 and 10 month follow up visits, as well as the 12 month follow up visit. These midface safety assessments were also evaluated at the following month 12 post treatment visits: optional touch up visit, 2 week post-treatment visit, 4 week post-treatment visit, and the 12 week post-treatment visit. Device palpability was assessed at each scheduled visit listed above with the exception of the screening visit. One subject reported an event greater than mild for the midface safety assessments of firmness, symmetry, function, mass formation and abnormal device palpability. This subject reported a mild hematoma in the right cheek starting five days after the initial treatment that progressed to a moderate hematoma starting 26 days later and lasting 16 days. Reported treatment included antibiotics. The investigator believed that the hematoma was exacerbated by self-manipulation**.** There were no signs of inflammation in subjects reporting mild or moderate abnormality in the safety assessments of midface.

2. Effectiveness Results

The results of the primary effectiveness analysis, i.e., the proportion of MMVS responders for right and left midface combined (primary endpoint) as well as right midface, and left midface separately are presented in Table 13 for the *Restylane® Lyft with Lidocaine* and no treatment groups at Month 2 post-baseline (as assessed by the blinded evaluator). A responder was defined as a subject with an improvement of at least one grade on the MMVS scale from baseline to Month 2 as determined by the Blinded Evaluator. When left and right MMVS midface scores

were combined, the observed success rate at 2 months post treatment were 133/150 (88.7% in the *Restylane® Lyft with Lidocaine* group) and 8/50 (16.0%) in the no treatment Control group which was statistically significant (p<0.001) in favor of *Restylane® Lyft with Lidocaine*.

Table 13: Proportion of Responders Measured by the Blinded Evaluator's Assessment of Midface Fullness (MMVS) at Month 2 – ITT Population

Assessment/ Time Point	Treatment Group	# of Subjects in ITT Population	# of Responders	Proportion of Responders	95% CI	P-Value
Right and Left Midface Combined						
Month 2	*Restylane® Lyft with Lidocaine*	150	133	0.887	0.825, 0.933	--
	No Treatment	50	8	0.160	0.072, 0.291	--
	Difference	--	--	0.727	0.588, 0.837	<0.001
Right Midface						
Month 2	*Restylane® Lyft with Lidocaine*	150	137	0.913	0.856, 0.953	--
	No Treatment	50	8	0.160	0.072, 0.291	--
	Difference	--	--	0.753	0.616, 0.859	<0.001
Left Midface						
Month 2	*Restylane® Lyft with Lidocaine*	150	137	0.913	0.856, 0.953	--
	No Treatment	50	10	0.200	0.100, 0.337	--
	Difference	--	--	0.713	0.573, 0.827	<0.001

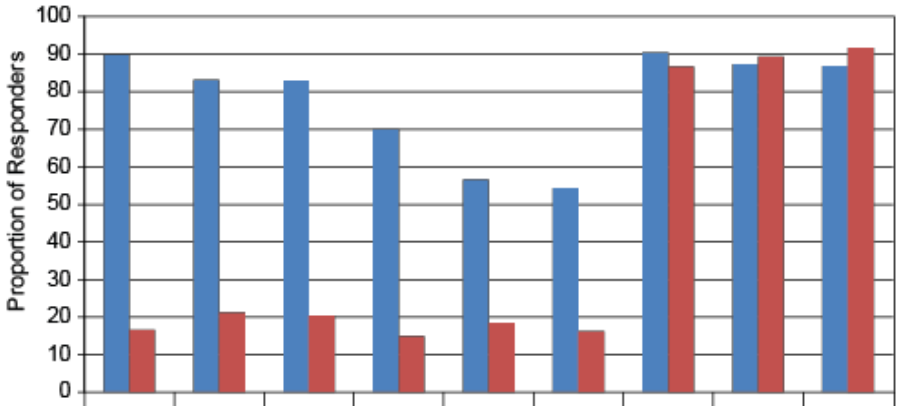
Note: Subjects with a missing Blinded Evaluator assessment at Month 2 for a midface are imputed using the hot deck method.
Note: Response is defined as an improvement of at least one grade in the Blinded Evaluator MMVS assessments from baseline to Month 2.
Note: The Proportion of Responders is calculated as the number of Responders at the visit of interest divided by the number of subjects in the ITT population for the specified treatment group.
Note: P-values for the difference in proportions in *Restylane® Lyft with Lidocaine* and No Treatment are based on the Fisher's Exact test.
Note: 95% Confidence Intervals are two-sided confidence intervals calculated using the exact binomial distribution.

Secondary Effectiveness Endpoints Outcomes

The following additional effectiveness endpoints were evaluated.

A secondary effectiveness endpoint was the proportion of responders at each visit after the 1 month visit as assessed by the blinded evaluator using the MMVS (Figure 1). A responder was defined as an improvement of at least one point on the MMVS metric compared to baseline and assessed by the BE.

Figure 1: Proportion of Responders Measured by the Blinded Evaluator's Assessment of Midface Fullness (MMVS) – ITT Population



	Month 2	Month 4	Month 6	Month 8	Month 10	Month 12	Wk 2 after 12-Mo Tx†	Wk 4 after 12-Mo Tx†	Wk 12 after 12-Mo Tx†
Restylane® Lyft with Lidocaine (n=150)	89.7* 131/146	83.2* 119/143	83.0* 117/141	70.0* 98/140	56.6* 81/143	54.3* 75/138	90.4 113/125	87.3 117/134	86.8 118/136
No Treatment (n=50)	16.7 8/48	21.3 10/47	20.4 10/49	14.9 7/47	18.4 9/49	16.3 8/49	86.7 39/45	89.4 42/47	91.7 44/48

**The difference between Restylane Lyft with Lidocaine and no treatment was statistically significant (P<.001) at each time point between month 2 and month 12 after treatment.*

†All subjects (both 'Restylane® Lyft with Lidocaine and 'No Treatment') were treated with Restylane® Lyft with Lidocaine by the Week 2 after 12-Month, Week 4 after 12-Month, and Week 12 after 12-Month visits. Wk = Week; Mo = Month; Tx = Treatment

Note: All subjects treated at the Month 12 Treatment visit received an injection with Restylane® Lyft with Lidocaine. This was the first treatment for the 'No Treatment' subjects and the second treatment for the 'Restylane® Lyft with Lidocaine' subjects.

Note: Response is defined as improvement of at least one grade in MMVS assessments from the baseline Blinded Evaluator's value to the Blinded Evaluator's assessment for the week of interest.

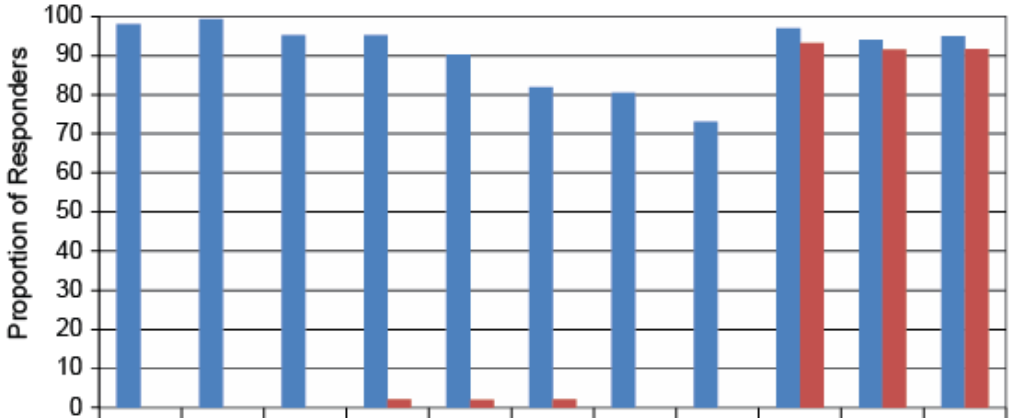
Note: The Proportion of Responders is calculated as the number of Responders at the visit of interest divided by the number of subjects in the ITT population for the specified treatment group with a non-missing assessment for the specified visit.

Note: P-values for the difference in proportions in Restylane® Lyft with Lidocaine and No Treatment are based on the Fisher's Exact test.

Note: 95% Confidence Intervals are two-sided confidence intervals calculated using the exact binomial distribution.

- The subjects assessment of improvement in Global Aesthetic appearance (GAIS) from baseline for the right and left midface combined are presented in Figure 2. A responder is defined as a subject with a one grade improvement over baseline or better on the GAIS scale at the time point of interest.

Figure 2: Right and Left Midface Combined: Proportion of Responders Measured by Subject's Assessment of GAIS by Visit – ITT Population



	Week 2	Week 4	Month 2	Month 4	Month 6	Month 8	Month 10	Month 12	Wk 2 after 12-Mo Tx†	Wk 4 after 12-Mo Tx†	Wk 12 after 12-Mo Tx†
Restylane® Lyft with Lidocaine (n=150)	98.0* 146/149	99.3* 145/146	95.2* 138/145	95.2* 138/145	90.3* 130/144	81.8* 117/143	80.4* 115/143	73.0* 103/141	96.9 123/127	94.0 125/133	95.0 134/141
No Treatment (n=50)	0 0/46	0 0/48	0 0/48	2.1 1/47	2.0 1/49	2.1 1/47	0 0/49	0 0/49	93.2 41/46	91.5 43/47	91.7 44/48

*The difference between Restylane Lyft with Lidocaine and no treatment was statistically significant (*P*<.001) at each time point between week 2 and month 12 after treatment.

†All subjects (both 'Restylane® Lyft with Lidocaine and 'No Treatment') were treated with Restylane® Lyft with Lidocaine by the Week 2 after 12-Month, Week 4 after 12-Month, and Week 12 after 12-Month visits. Wk = Week; Mo = Month; Tx = Treatment

Note: GIAS = Global Aesthetic Improvement Scale

Note: All subjects treated at the Month 12 Treatment visit received an injection with Restylane® Lyft with Lidocaine. This was the first treatment for the 'No Treatment' subjects and the second treatment for the 'Restylane® Lyft with Lidocaine' subjects.

Note: Response is defined as a score of 1 ('improved') or better on the GAIS scale at the time point of interest.

Note: The Proportion of Responders is calculated as the number of Responders at the visit of interest divided by the number of subjects in the ITT population for the specified treatment group with a non-missing assessment for the specified visit.

Note: *P*-values for the difference in proportions in Restylane® Lyft with Lidocaine and No Treatment are based on the Fisher's Exact test.

Note: 95% Confidence Intervals are two-sided confidence intervals calculated using the exact binomial distribution.

The proportion of MMVS responders from baseline as determined by the treating Independent Photographic Reviewer (IPR) at Months 2, 4, 6, 8, 10, 12 and 4 and 12 weeks after the 12 month treatment for the right and left midface combined are presented in (Table 14). For this assessment, a responder is defined as having at least a one grade increase from the IPR's baseline assessment of the MMVS for both the right and left sides of the face.

Table 14: Right and Left Midface Combined: Proportion of Responders Measured by the Independent Photographic Reviewer's Assessment of Midface Fullness by Visit – ITT Population

Assessment Time Point	Treatment Group	N	Responders n (%)	Difference (%)
Month 2	*Restylane® Lyft with Lidocaine*	146	118 (80.8)	(11.3)
	No Treatment	46	32 (69.6)	
Month 4	*Restylane® Lyft with Lidocaine*	145	116 (80.0)	(20.0)
	No Treatment	45	27 (60.0)	
Month 6	*Restylane® Lyft with Lidocaine*	145	114 (78.6)	(24.5)
	No Treatment	48	26 (54.2)	
Month 8	*Restylane® Lyft with Lidocaine*	133	106 (79.7)	(16.7)
	No Treatment	46	29 (63.0)	
Month 10	*Restylane® Lyft with Lidocaine*	142	116 (81.7)	(17.9)
	No Treatment	47	30 (63.8)	
Month 12	*Restylane® Lyft with Lidocaine*	140	106 (75.7)	(18.3)
	No Treatment	47	27 (57.4)	
Week 4 after Month 12 Treatment	*Restylane® Lyft with Lidocaine*	130	106 (81.5)	(-5.7)
	No Treatment	47	41 (87.2)	
Week 12 after Month 12 Treatment	*Restylane® Lyft with Lidocaine*	141	112 (79.4)	(-1.4)
	No Treatment	47	38 (80.9)	

Note: All subjects treated at the Month 12 Treatment visit received an injection with *Restylane® Lyft with Lidocaine*. This was the first treatment for the 'No Treatment' subjects and the second treatment for the *Restylane® Lyft with Lidocaine* subjects.

Note: The Proportion of Responders is calculated as the number of Responders at the visit of interest divided by the number of subjects in the ITT population for the specified treatment group with a non-missing assessment for the specified visit (N).

3. Subgroup Analyses

Subgroup summaries of the primary effectiveness endpoint were conducted for the following parameters: gender, total volume injected for both initial and optional touch-up treatment (<3, 3 to <6, and ≥6 cc), change in BMI from baseline to Month 2 (Decrease of >2, Decrease of 1-2, Decrease of <1, No Change, Increase of <1, Increase of 1-2, and Increase of >2 kg/m^2), as well

as Fitzpatrick Skin Type (I-III, IV-VI) (Table 15). The proportion of responders was calculated as the number of responders in that subgroup divided by the number of subjects in that subgroup and in the ITT population with non-missing data for that visit and treatment group. Analyses of these subgroups of subjects did not reveal any significant differences in product effectiveness when compared to the ITT population.

Table 15: Right and Left Midface Combined: Proportion of Responders by Parameters of Interest for the Blinded Evaluator's Assessment of Midface Fullness (MMVS) at Month 2 – ITT Population

	No Treatment (N=50)	***Restylane® Lyft with Lidocaine* (N=150)**
Right and Left Midface Combined		
Gender		
Male	2 / 5 (40%)	9 / 12 (75%)
Female	6 / 43 (14%)	122 / 134 (91%)
Total Volume of Injection		
< 3 mL	0	11 / 16 (69%)
≥ 3 mL and < 6 mL	0	38 / 47 (81%)
≥ 6 mL	0	82 / 83 (99%)
Change in BMI		
Decrease of > 2 kg/m^2	0	0
Decrease of 1-2 kg/m^2	0	1 / 1 (100%)
Decrease of <1 kg/m^2	3 / 20 (15%)	51 / 57 (89%)
No Change	1 / 7 (14%)	18 / 20 (90%)
Increase of < 1 kg/m^2	4 / 21 (19%)	54 / 59 (92%)
Increase of 1-2 kg/m^2	0	6 / 8 (75%)
Increase of > 2 kg/m^2	0	1 / 1 (100%)
Fitzpatrick Skin Type		
I, II, and III	8 / 33 (24%)	93 / 102 (91%)
IV, V, and VI	0 /15	38 / 44 (86%)

Source: Table 14.2.6.1
Note: The Proportion of Responders is calculated as the number of Responders at Month 2 divided by m, the number of subjects with a non-missing MMVS assessment in the ITT population for the specified subgroup and treatment group.
Note: Change in BMI is the change from baseline to Month 2.
Note: For Right and Left Midface Combined, the Total Volume of Initial Injection is the sum of the injection volumes for the right and left sides for the Visit 2 and Visit T (Optional Touch-Up) injections.

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 12 principal investigators and 11 sub-investigators, of which none were full-time or part-time employees of the sponsor

and 2 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: 2
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 0

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Post Market Experience:

The adverse events received from post-marketing surveillance for the use of *Restylane® Lyft with Lidocaine* when used outside the US for cheek augmentation were infrequent and included mostly reports of swelling and mass/induration. Serious adverse events which occurred ≥ 5 times were the following, in descending order of frequency: implant site swelling, implant site abscess, implant site infection, implant site erythema, implant site mass purulent discharge, implant site nodule, medical device implantation.

The incidence of post market events potentially related to treatment with *Restylane® Lyft with Lidocaine* for all indications and that occurred in greater than 5 subjects included the following, in descending order of frequency: swelling, device ineffective, accidental exposure, mass/induration, non-dermatological events, erythema, pain/tenderness, infection/abscess, bruising/abscess, bruising/bleeding, papules/nodules, inflammation, neurological symptoms, medical device implantation, injection site reactions, hypersensitivity, pruritus, discoloration, eye disorders, ischemia/necrosis, scar/scab/skin atrophy, procedural complications, herpes, device dislocation, device misuse, and rash. Reported treatments have included systemic steroids or systemic antibiotics administered intravenously, orally or by injection. Serious adverse events have been rarely reported. The most commonly reported serious adverse events (by MedDRA Preferred Term) were hypersensitivity, and implant and/ or injection site swelling, ischemia and discoloration. Serious abscess formations have also been reported.

Vision abnormalities including blindness have been reported following injection of hyaluronic acid, with and without lidocaine, into the nose, glabella, periorbital areas, and/or cheek, with a time to onset ranging from immediate to 1 week following injection. Reported treatments include anticoagulant, epinephrine, aspirin, hyaluronidase, corticosteroid treatment, hyperbaric oxygen and surgery. Outcomes ranged from resolved to ongoing at the time of last contact. Events requiring medical intervention, and events where resolution information is not available were reported after injection of hyaluronic acid with or without lidocaine. In these cases, the product was injected into the highly vascularized areas of the glabella, nose, and periorbital area, which

are outside the device indications for use (See Warnings section).

Implant and injection site reactions, mostly non-serious events, have also been reported. These include: discoloration, bruising, swelling, mass formation, erythema, pain, scarring and ischemia. Most instances of discoloration including hyperpigmentation, sometimes described as a blue or brown color and ranging from mild to severe, 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. Implant and/or injection site bruising, swelling, erythema and pain generally occurred on the same day as treatment usually resolving within 1 to 4 weeks. Some occurrences have persisted for up to 6 months. Severity for these events is generally mild to moderate although some cases have been severe.

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

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

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

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

Assessment of product effectiveness is based on the results of pivotal study MA-14-005. The submitted data provide a reasonable assurance that *Restylane® Lyft with Lidocaine* is effective for subcutaneous or supraperiosteal implantation for cheek augmentation and correction of age-related midface contour deficiencies in patients over the age of 21. The specific conclusions from the clinical study are outlined below.

- The trial was a well-designed prospective, controlled study using a validated scale and blinded, live evaluations. The data are considered to be as robust as possible for an aesthetic indication. The study met the pre-specified primary effectiveness criterion. The observed success rate at 2 months in the *Restylane® Lyft with Lidocaine* group was 88.7% (133/150) which was significantly higher than in the Control group 16.7% (8/50).

- The study met the pre-specified secondary effectiveness endpoints for cheek augmentation. The proportion of responders was numerically superior for the *Restylane® Lyft with Lidocaine* cohort in the blinded evaluators' MMVS scoring from 2 to 12 months after the initial treatment. Regarding duration of effectiveness, 75/138 (54.3%) of the *Restylane® Lyft with Lidocaine* and 8/49 (16.3%) of the no treatment subjects were responders at the Month 12 visit.

- Analysis of the primary effectiveness endpoint was performed for several subgroups (i.e., gender, total volume injected for both initial and optional touch-up treatment (<3, 3 to <6, and ≥6 cc), change in BMI from baseline to Month 2 (Decrease of >2, Decrease of 1-2,

Decrease of <1, No Change, Increase of <1, Increase of 1-2, and Increase of >2 kg/m^2), as well as Fitzpatrick Skin Type (I-III, IV-VI). The effectiveness of *Restylane® Lyft with Lidocaine* in cheek augmentation in each subgroup was similar to product effectiveness determined for the entire study population.

B. Safety Conclusions

The risks of device use are based on data collected in clinical study MA-1400-05 conducted to support PMA approval provided in P040024/S073 and a review of *Restylane® Lyft with Lidocaine* Post Market Surveillance reports. The data provide a reasonable assurance that *Restylane® Lyft with Lidocaine* is safe for subcutaneous or supraperiosteal implantation for cheek augmentation and correction of age-related midface contour deficiencies in patients over the age of 21. The specific conclusions from the clinical studies are outlined below.

- Of the 200 subjects enrolled in the study, 199 subjects received their first treatment with *Restylane® Lyft with Lidocaine* at either baseline/Day 0 or at the Month 12 visit, and 128 subjects received re-treatment at Month 12 visit. Of the 199 subjects treated with *Restylane® Lyft with Lidocaine* for the first time, 97 subjects (49%) reported at least one TEAE. A total of 269 events were reported, 212 (79%) were mild, 55 (20%) were moderate and 2 (<1%) events were severe in intensity. Of the 50 subjects in the no treatment group, 15 (30%) subjects reported at least one TEAE. A total of 18 events were reported; 8 (44%) were mild, 7 (39%) were moderate, and 3 (17%) events were severe in intensity. Of the 128 subjects treated with *Restylane® Lyft with Lidocaine* for the second time, 37 subjects (29%) reported at least one TEAE. A total of 77 events were reported, 70 (91%) were mild and 7 (9%) events were moderate. There were no severe TEAEs reported after a second treatment of *Restylane® Lyft with Lidocaine.*

- There were no deaths reported during the study and no subject discontinued due to an adverse event. There were nine serious (TEAEs) reported in seven subjects during the study. Six of the nine events were reported as unrelated to the study device or the injection procedure by the investigator. Two events of implant site inflammation (late onset inflammatory reaction) were reported as related to both the device and the procedure. An event of implant site haematoma was reported as related to the procedure by the investigator. The event of implant site infection was reported as not related to the device or the procedure by the investigator

- Three subjects became pregnant during the study. One subject had a spontaneous abortion (reported as a SADE), one subject had a normal pregnancy and normal delivery, and one subject electively terminated the pregnancy.

- Delayed onset of adverse events (i.e., more than 21 days after treatment) were observed in 12/199 *Restylane® Lyft with Lidocaine* subjects (3%). These events included implant site infection, implant site erythema, implant site hematoma, implant site hemorrhage, implant site inflammation, implant site mass, implant site pain, or implant site swelling that occurred up to 138 days after treatment. 4/12 subjects required treatment (e.g., antibiotics and

incision/drainage) for their events. All delayed onset adverse events resolved by the end of the study.

- A majority of commonly reported TEAEs were anticipated (i.e., implant site hematoma, implant site pain, and implant site swelling). The onset of these commonly reported TEAEs typically began within a day of injection and resolved in a median of 11 days or less.

- 10 subjects elected to not undergo re-treatment at Month 12. One subject was satisfied with their prior treatment and two subjects refused due to adverse events experienced with their initial treatment. One of these two subjects experienced difficulties with their *Restylane® Lyft with Lidocaine* treatment. The other subject expressed concern about the pain associated with the procedure. The decision to not receive re-treatment for the other seven subjects did not appear to be based on safety concerns. Subjects that were lost to follow-up or withdrew consent did not appear to have safety concerns that would have led to withdrawal from the study.

- While the protocol recommended that injection volumes be limited to 6 mL per treatment session (i.e., right and left midface combined), five subjects received more than 6 mL in a treatment session. When the incidence of adverse events was considered by total volume (i.e., less than 3mL, more than 3ml, but less than 6 mL, and more than 6 mL) for the initial and touch-up treatments, a correlation between injection volume and the incidence of adverse events was not observed.

- 195/198 of the subjects injected with *Restylane® Lyft with Lidocaine* reported adverse signs and symptoms in the 14 day patient diary. Most of these signs/symptoms were either 'tolerable' 146/198 (74%) or 'affects daily activities' 45/198 (23%). The most common signs and symptoms reported after the first treatment with *Restylane® Lyft with Lidocaine* were tenderness (189/199) and swelling (179/199). Of these signs and symptoms, 176/189 of the tenderness events and 172/179 of the swelling events resolved in less than 2 weeks.

- Midface safety assessments, (i.e., firmness, symmetry, function, mass formation and sensation) were evaluated at the screening visit, optional touch up visit, 2 week follow up visit, 4 week follow up visit, 2, 4, 6, 8 and 10 month follow up visits, and the 12 month follow up visit. In addition, midface safety assessments, such as firmness, symmetry, function, mass formation and sensation were evaluated at the following post treatment visits: optional touch up visit, 2 week post-treatment visit, 4 week post-treatment visit, and the 12 week post-treatment visit. Device palpability was assessed at each scheduled visit listed above with the exception of the screening visit. 43/199 (22%) subjects reported abnormal safety assessments of midface. All of these subjects reported a mild abnormality except for one subject who reported moderate midface firmness at Week 2 and Week 4, moderate abnormal symmetry at Week 4, and moderate abnormal function (broad smile) at Week 4. These events occurred after the initial treatment.

- Review of the Post Marketing Surveillance database for use of *Restylane® Lyft with Lidocaine* revealed that product use in the commercial setting did not introduce any new or different types of safety concerns.

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C. Benefit-Risk Conclusions

The probable benefits of the device are based on data collected in the MA-1400-05 clinical study conducted to support approval of this PMA supplement as described above. The primary potential benefit of the device is a perceived improvement in the visual appearance of midface fullness as assessed by BE MMVS assessment, GAIS and FACE-Q evaluations by subjects. The BE determination of the proportion of responders for cheek augmentation with *Restylane® Lyft with Lidocaine* when compared to no treatment was statistically significant ($p<0.001$) in favor of *Restylane® Lyft with Lidocaine*.

The risks with treatment for cheek augmentation and correction of age-related midface contour deficiency as observed in the clinical study are comparable to those observed with similar devices. The primary adverse events were mild implant site hematoma, implant site pain, and implant site swelling. One event of implant site infection was observed. These events can occur when a device is implanted. The incidence, severity and duration of these events were considered tolerable by a majority of subjects.

In conclusion, given the available information above, the data support that for subcutaneous or supraperiosteal implantation of *Restylane® Lyft with Lidocaine* for cheek augmentation and correction of age-related midface contour deficiencies in patients over the age of 21, the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The benefits and risks of dermal fillers are sufficiently well understood for patients to make informed decisions about their use. An improvement in the visual appearance of midface fullness was reported during the study through 12 months post-treatment for a majority of subjects. *Restylane® Lyft with Lidocaine* injection was generally well tolerated and primarily associated with mild to moderate local injection site reactions such as swelling, bruising, and pain which resolved in a median of 11 days.

XIV. CDRH DECISION

CDRH issued an approval order on July 1, 2015.

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.